Contents

COMMENTARIES

Tale of Two Fellows
Karin Purshouse, Twalib Ngoma, and David Kerr ................................................................. 431

Patient Navigation to Improve Access to Breast Cancer Care in Brazil
Alexandra Bukowski, Sandra Gioia, Yanin Chavarri-Guerra, et al ........................................... 433

Broken Machines or Broken Systems: The Road to Meaningful Global Radiotherapy Access
Shekinah Nefreteri Elmore, Roshan Vijay Sethi, Awusi Kavuma, et al .................................. 438

How Useful Are International Treatment Guidelines in Low- and Middle-Income Countries?
Stewart Kerr, Abdul-Rahman Jazieh, and David Kerr ............................................................. 441

ORIGINAL REPORTS

Cancer Prevention and Control

Acceptability of Human Papillomavirus Self-Sampling for Cervical Cancer Screening in an Indigenous Community in Guatemala
Anna Gottschlich, Alvaro Rivera-Andrade, Edwin Grajeda, et al ............................................. 444

Head and Neck Cancer

Neoadjuvant Chemotherapy With Capecitabine Plus Cisplatin in Patients With Locally Advanced Nasopharyngeal Cancer: Case Series Study
Reyad Dada, Mohamed El Sayed, and Jamal Zekri ............................................................... 455

Thoracic Oncology

Outcomes in Lung Cancer: 9-Year Experience From a Tertiary Cancer Center in India
Aditya Navile Murali, Venkatraman Radhakrishnan, Trivadi S. Ganesan, et al ............................ 459

Health Services and Outcomes

Awareness and Perception About Cancer Among the Public in Chennai, India
Vidhubala Elangovan, Swaminathan Rajaraman, Barsha Basumalik, et al ................................. 469

continued on next page
Breast Cancer

Breast Cancer Knowledge, Behaviors, and Preferences in Malawi: Implications for Early Detection Interventions From a Discrete Choice Experiment
Racquel E. Kohler, Satish Gopal, Clara N. Lee, et al ................................................................. 480

Developing a Breast Cancer Screening Program in Nigeria: Evaluating Current Practices, Perceptions, and Possible Barriers
Olalekan Olasehinde, Carla Boutin-Foster, Olusegun I. Alatise, et al ........................................ 490

Factors Relating to Late Presentation of Patients With Breast Cancer in Area 2 KwaZulu-Natal, South Africa
Sharon R. Cačala and José Gilart ......................................................................................... 497

Pilot Educational Intervention and Feasibility Assessment of Breast Ultrasound in Rural South Africa
Lindsay K. Dickerson, Anne F. Rositch, Susan Lucas, et al...................................................... 502

Knowledge and Attitudes About Breast Cancer in Limpopo, South Africa
Lydia A. Trupe, Anne Rositch, Lindsay Dickerson, et al ........................................................ 509

Melanoma

Ipilimumab in Pretreated Patients With Advanced Malignant Melanoma: Results of the South African Expanded-Access Program
Bernardo L. Rapoport, Daniel A. Vorobiof, Lydia M. Dreosti, et al ........................................ 515

Gynecologic Cancer

Systematic Review and Meta-Analysis of Individual Patient Data to Assess the Sensitivity of Cervical Cytology for Diagnosis of Cervical Cancer in Low- and Middle-Income Countries
Alejandra Castanon, Rebecca Landy, Dimitrios Michalopoulos, et al .................................. 524

Use of Palliative Cisplatinum for Advanced Cervical Cancer in a Resource-Poor Setting: A Case Series From Kenya
Elkanah Orang’o, Peter Itsura, Philip Tonui, et al ................................................................. 539

Pediatric Oncology

Pediatric Hodgkin Lymphoma Treated at Cancer Institute, Chennai, India: Long-Term Outcome
Venkatraman Radhakrishnan, Manikandan Dhanushkodi, Trivadi S. Ganesan, et al ................ 545

Wilms Tumor Treatment Outcomes: Perspectives From a Low-Income Setting
Festus Njuguna, Hugo A. Martijn, Robert Tenge Kuremu, et al ............................................. 555

Radiation Oncology

Model for Estimating Power and Downtime Effects on Teletherapy Units in Low-Resource Settings
Rachel McCarroll, Bassem Youssef, Beth Beadle, et al ......................................................... 563

REVIEW ARTICLES

Barriers and Challenges to Treatment Alternatives for Early-Stage Cervical Cancer in Lower-Resource Settings
Emily S. Wu, Jose Jeronimo, and Sarah Feldman ................................................................. 572

Managing Pain in Patients With Cancer: The Chinese Good Pain Management Experience
Shi-Ying Yu, Jie-Jun Wang, Yu-guang Huang, et al .............................................................. 583

Improving Access to Cancer Treatments: The Role of Biosimilars
Rakesh Chopra and Gilberto Lopes .................................................................................. 596
SPECIAL ARTICLES

Primary Prevention of Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Guideline
Silvina Arrossi, Sarah Temin, Suzanne Garland, et al ........................................................................................................ 611

Jose Jeronimo, Philip E. Castle, Sarah Temin, et al ........................................................................................................ 635

Project ECHO: A Telementoring Program for Cervical Cancer Prevention and Treatment in Low-Resource Settings
Melissa S. Lopez, Ellen S. Baker, Andrea M. Milbourne, et al .......................................................................................... 658

Multidisciplinary Gynecologic Oncology Clinic in Botswana: A Model for Multidisciplinary Oncology Care in Low- and Middle-Income Settings
Surbhi Grover, Sebathu Philip Chiyapo, Priya Puri, et al ................................................................................................. 666

QOPI International, or How to Globalize Quality
Evangelia D. Razis ......................................................................................................................................................... 671

CASE REPORTS

Atypical T1 Hyperintense Neurocysticercosis Masquerading As Cystic Brain Metastases
Abhishek Mahajan, Mehul Patel, Nilesh Sable, et al ...................................................................................................... 673

Refractory Choriocarcinoma: Complete Response With Oral Etoposide
Manikandan Dhanuskodi, Trivadi Ganesan, and Tenali Gnana Sagar ............................................................................ 678

CORRESPONDENCE

Breast Course for Nurses: Educating Health Care Workers to Perform Clinical Breast Screening
Jenny Edge, Lieske Wegelin, and Dave Woods ............................................................................................................... 680

Also in This Issue

Editorial Roster
Current Abstracts

Supplementary information available

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EDITORIAL CORRESPONDENCE (manuscript-related inquiries):
Gilberto Lopes, MD, MBA, Editor-in-Chief
Journal of Global Oncology
Phone: 703-797-1900; Fax: 703-684-8720
E-mail: jgo@asco.org; Internet: ascopubs.org/journal/jgo

AMERICAN SOCIETY OF CLINICAL ONCOLOGY (membership-related inquiries):
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Acceptability of Human Papillomavirus Self-Sampling for Cervical Cancer Screening in an Indigenous Community in Guatemala

**Purpose** Cervical cancer rates in Latin America are higher than those in developed countries, likely because of the lower prevalence of screening. Specifically, less than 40% of women in Guatemala are regularly screened and even fewer women are screened in indigenous communities. Current screening strategies—Pap smears and visual inspection with acetic acid—might not be the most effective methods for controlling cancer in these settings. We thus investigated the potential of self-collection of cervical samples with testing for human papillomavirus (HPV) to help prevent cervical cancer in an indigenous community in Guatemala.

**Patients and Methods** A community representative random sample of 202 indigenous women age 18 to 60 years residing in Santiago Atitlan, Guatemala, were surveyed to assess knowledge of and risk factors for HPV and cervical cancer. Women were then invited to self-collect a cervical sample using HerSwab collection kits to assess the prevalence of HPV and the acceptability of self-sampling.

**Results** Of 202 women who completed the survey, 178 (89%) provided a self-sample. In all, 79% of these women found the test comfortable, 91% found the test easy to use, and 100% reported they were willing to perform the test periodically as a screening method. Thirty-one samples (17%) were positive for at least one of 13 high-risk HPV types, and eight (4.5%) were positive for HPV 16/18.

**Conclusion** HPV testing by using self-collected samples was well accepted, suggesting that it is a plausible modality for cervical cancer screening in indigenous communities. Further studies are needed to assess rates of follow-up after a positive test and to determine whether these findings extend to other indigenous and nonindigenous communities in Guatemala and Latin America.

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Neoadjuvant Chemotherapy With Capecitabine Plus Cisplatin in Patients With Locally Advanced Nasopharyngeal Cancer: Case Series Study

Purpose Capecitabine, an oral fluorouracil (5-FU) derivative, has replaced 5-FU in many chemotherapy regimens used in various GI tract cancers. The experience with capecitabine in nasopharyngeal carcinoma (NPC) is limited.

Patients and Methods We report on eight patients with locally advanced NPC treated with neoadjuvant chemotherapy with capecitabine and cisplatin.

Results All eight patients responded well to the chemotherapy combination and achieved complete remission after definitive chemoradiotherapy. No grade 3/4 toxicities were observed. Five patients experienced a relapse after 6, 8, 9, 12, and 17 months.

Conclusion In the patients studied, capecitabine (in combination with cisplatin) was a safe and effective substitution for 5-FU for the neoadjuvant treatment of locally advanced NPC. Larger prospective clinical studies are required to confirm these results.

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continued
Outcomes in Lung Cancer: 9-Year Experience From a Tertiary Cancer Center in India

Purpose Lung cancer is the most common cause of cancer mortality in the world. There are limited studies on survival outcomes of lung cancer in developing countries such as India. This study analyzed the outcomes of patients with lung cancer who underwent treatment at Cancer Institute (WIA), Chennai, India, between 2006 and 2015 to determine survival outcomes and identify prognostic factors.

Patients and Methods In all, 678 patients with lung cancer underwent treatment. Median age was 58 years, and 91% of patients had non–small-cell lung cancer (NSCLC). Testing for epidermal growth factor receptor mutation was performed in 132 of 347 patients and 61 (46%) were positive.

Results Median progression-free survival was 6.9 months and overall survival (OS) was 7.6 months for patients with NSCLC. Median progression-free survival was 6 months and OS was 7.2 months for patients with small-cell lung cancer. On multivariable analysis, the factors found to be significantly associated with inferior OS in NSCLC included nonadenocarcinoma histology, performance status more than 2, and stage. In small-cell lung cancer, younger age and earlier stage at presentation showed significantly better survival.

Conclusion Our study highlights the challenges faced in treating lung cancer in India. Although median survival in advanced-stage lung cancer is still poor, strategies such as personalized medicine and use of second-line and maintenance chemotherapy may significantly improve the survival in patients with advanced-stage lung cancer in developing countries.

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Awareness and Perception About Cancer Among the Public in Chennai, India

**Purpose** Cancer-related stigma influences the way people perceive cancer, which renders cancer control—beginning with prevention and proceeding to palliation—a challenging task. This study aimed to assess the current levels of awareness and perceptions about cancer among people with various socioeconomic status and diverse backgrounds in the city of Chennai, India.

**Patients and Methods** The sample population (N = 2,981; 18 to 88 years of age) was stratified into four groups: patients (n = 510), caregivers (n = 494) consulting at the Cancer Institute (Women Indian Association), college students (n = 978), and general public (n = 999). Fourteen statements related to cancer stigma or myths were identified and categorized by awareness (10 items) or perception (4 items). Responses to those statements were recorded by using a Likert scale (yes, no, and don’t know). The data were described by frequency analysis and χ² test using SPSS Version 13 (SPSS, Chicago, IL).

**Results** More than 70% of the study participants were aware that cancer is curable, that cancer is not contagious, and that cancer is not a curse or a death sentence. However, only approximately half believed that surgery or biopsy do not cause cancer to spread to other organs or that radiation therapy does not consist of receiving an electric shock. Higher education, younger age, male sex, personal experience with cancer (either as a patient or caregiver), and high socioeconomic status were the categories of people with increased awareness about cancer.

**Conclusion** These factors need to be taken into consideration in tailoring information, education, and communication campaigns. Resource allocation for these campaigns is an investment in cancer control.
Purpose Breast cancer is the most common female cancer in Africa and leading cause of death resulting from cancer; however, many countries lack early detection services. In Malawi, women are frequently diagnosed with large tumors after long symptomatic periods. Little is known about local cancer knowledge.

Methods We administered a cross-sectional survey with a discrete choice experiment to a random sample in urban and rural areas of Lilongwe district. Bivariable and multivariable analyses determined factors associated with knowledge. Preference utilities for early detection interventions were estimated using a hierarchical Bayesian model in Sawtooth software.

Results Of 213 women recruited, fewer than half were aware of breast cancer. In multivariable analysis, electricity at home and knowing someone with cancer increased the odds of awareness. Women were more knowledgeable about symptoms than treatment or risk factors; more than 60% erroneously believed local misconceptions. Seventeen percent were aware of breast self-examination, and 20% were aware of clinical breast examination (CBE); few reported either behavior. Common barriers included not knowing where to access CBE and transportation difficulties. Discrete choice experiment results indicated the detection strategy (breast health awareness, CBE, or both) was the most important attribute of an intervention, followed by the encounter setting and travel time.

Conclusion Addressing misconceptions in health messages and engaging survivors to promote early detection may help improve breast cancer knowledge in Malawi. Program designs accounting for women’s preferences should provide breast health education and CBEs in convenient settings to address transportation barriers, particularly for women with low socioeconomic position.

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Developing a Breast Cancer Screening Program in Nigeria: Evaluating Current Practices, Perceptions, and Possible Barriers

**Purpose** In low- and middle-income countries like Nigeria, women present with advanced breast cancer at an earlier age. Given the limited resources, development of screening programs that parallel resource capabilities of low- and middle-income countries is imperative. The objective of this study was to evaluate the perceptions, practices, and barriers regarding clinical breast examination (CBE) screening in a low-income community in Nigeria.

**Materials and Methods** A cross-sectional survey of women age 40 years or older in Ife, Nigeria, using multistaged sampling was performed. Information on sociodemographics, knowledge of breast cancer, screening practices, and willingness to participate in CBE screening was obtained using an interviewer-administered questionnaire.

**Results** A total of 1,169 women whose ages ranged from 40 to 86 years (mean age, 47.7 years; standard deviation, 8.79 years) were interviewed. The majority of women (94%) knew about breast cancer, whereas 27.5% knew someone who had had breast cancer, the majority of whom (64.5%) had died of the disease. Of the 36% of women who had breast screening recommended to them, only 19.7% had an actual CBE. Of these, only 6% had it in the last year. The majority of women (65.4%) were willing to have regular CBEs and did not care about the sex of the examiner in most instances. Lack of perceived need was the reason cited by women unwilling to participate.

**Conclusion** The majority of women were aware of breast cancer and knew it as a fatal disease. With the relatively encouraging number of those willing to be examined, a carefully designed CBE program coupled with advocacy to correct uneducated beliefs seems promising.
Factors Relating to Late Presentation of Patients With Breast Cancer in Area 2 KwaZulu-Natal, South Africa

**Purpose** Patients with breast cancer (BC) in Area 2 KwaZulu-Natal, South Africa, often present with advanced disease. We performed a review of the patients' sociodemographic characteristics and their reasons for late presentation to identify what changes could be made to improve time to presentation.

**Patients and Methods** Fifty women with T1, T2, T3, or T4 BC were assessed for sociodemographic data. Patients in T3 and T4 groups were asked to provide reasons for late presentation.

**Results** Of 172 patients, 50 had T2, T3, or T4 BC, and 22 had T1. Age ranged from 23 to 100 years (average, 56 years). There was no significant difference in age for different tumor sizes. The average size of a T1 tumor was 1.8 cm; T2, 3.6 cm; T3, 11.4 cm; and T4, 14.8 cm. Regarding education, 19% of patients had never attended school (T1, 5%; T2, 12%; T3, 22%; T4, 32%), and 19% had completed their education (finished 12th grade). The average education level was 6th grade. Patients with larger tumors had less education ($P < .05$). Of the patients who lived in rural areas, 41% had T1, 52% had T2, 66% had T3, and 78% had T4 tumors ($P < .01$). Patients with larger tumors were associated with having less electricity in their homes than patients with smaller tumors ($P < .05$). Patients presented with a variety of symptoms. A breast lump was the presenting complaint in 96% of T1 and T2, 68% of T3 and 32% of T4; with a nipple or skin change, 2% of T3 and 8% of T4; because their families insisted, 6% of T3 and 8% of T4; because of pain, 24% of T3; and because of pain with malodorous smell, 50% of T4. Patients' reasons for late presentation were fear (40%), not aware of disease severity (40%), fear of losing a breast (40%), referral problems (34%), financial problems (8%), and transportation problems (6%). Approximately 33% sought medical help from traditional healers, and 65% regularly attended clinics.

**Conclusion** Patients who presented late often lived in rural areas with fewer amenities (such as having no electricity in their homes), less education, and poor understanding of BC. Pictorial information about BC needs to be introduced to people who live in rural communities, and opportunistic screening needs to be provided at local clinics.

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Pilot Educational Intervention and Feasibility Assessment of Breast Ultrasound in Rural South Africa

**Purpose** Breast cancer is the leading cause of cancer death in women worldwide, with high mortality in low- and middle-income countries because of a lack of detection, diagnosis, and treatment. With mammography unavailable, ultrasound offers an alternative for downstaging. The literature reports successful training in various domains, but a focus on the breast is novel. We assessed the feasibility (knowledge acquisition, perceived usefulness, and self-efficacy) of breast ultrasound training for nonphysician providers.

**Methods** Training was implemented for 12 providers at Hlokomela Clinic in Hoedspruit, South Africa, over 3 weeks. Didactic presentations and example cases were followed by a presurvey and test (n = 12). All providers received hands-on training with nurses as models; five providers trained with patients. A post-test (n = 12) assessed knowledge acquisition and a postsurvey (n = 10) assessed perceived program usefulness and provider self-efficacy.

**Results** The pre- to post-test averages improved by 68% in total and in four competencies (foundational knowledge, descriptive categories, benign v malignant, and lesion identification). On the postsurvey, providers expressed that ultrasound could significantly influence breast cancer detection (9.1 out of 10), treatment (7.9 out of 10), and survival (8.7 out of 10) in their community and endorsed moderate confidence in their scanning (6.3 out of 10) and interpreting abilities (5.6 out of 10).

**Conclusion** Our research supports the feasibility of breast ultrasound training as part of a breast education program in low- and middle-income countries. Pre- and post-test results and observed proficiency indicate that training nonphysician providers is achievable; postsurvey responses indicate program acceptance, community-based ownership, and provider self-efficacy with ultrasound. Future work may show that breast ultrasound is viable for early detection where mammography is unavailable.
Knowledge and Attitudes About Breast Cancer in Limpopo, South Africa

Purpose Breast cancer survival is unacceptably low in many low-resource settings, including rural South Africa, where access to screening and treatment services is limited. To describe the context for implementing an early detection program, we assessed knowledge and attitudes toward breast cancer risk, early detection, and treatment.

Methods We conducted a cross-sectional survey among 243 women presenting to Hlokomela Clinic in Hoedspruit, South Africa, during April and May 2016. We used quantitative and qualitative analyses to determine levels of knowledge of risk factors, symptoms, and treatment of breast cancer, as well as experience with and attitudes toward detection and treatment methods.

Results Thirty-one percent of women correctly identified at least six of 12 risk factors for breast cancer, and 53.1% identified breast lumps as an important symptom. Although >97% of women stated that self-breast examination and early detection were highly important and that they would seek care for changes in their breasts, only 33.3% of women reported performing self-breast examination, and only 24.3% reported receiving a clinical breast examination. Age and education were not associated with knowledge, and level of knowledge did not predict care-seeking behaviors or attitudes.

Conclusion Although women demonstrated moderate levels of knowledge of breast cancer symptoms and risk factors and the importance of early detection, few women reported seeking services. These data demonstrate sufficient levels of knowledge and positive attitudes toward care seeking and suggest both a need and readiness for increased access to cost-effective services to facilitate early diagnosis and improved outcomes.

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Ipilimumab in Pretreated Patients With Advanced Malignant Melanoma: Results of the South African Expanded-Access Program

Purpose The primary objective of this study was to evaluate 1- and 2-year survival rates and durable remissions in pretreated patients with advanced (unresectable or metastatic) malignant melanoma treated with ipilimumab in a South African expanded-access program (SA-EAP).

Patients and Methods This multicenter, retrospective study obtained data from pretreated patients with advanced malignant melanoma who were eligible for the ipilimumab SA-EAP. Ipilimumab was administered at a dose of 3 mg/kg intravenously every 3 weeks for four cycles to adults with advanced melanoma for whom at least one line of treatment for metastatic disease had failed. Data from the medical records of 108 patients treated within the SA-EAP were collected and statistically analyzed to determine overall (OS) and progression-free survival (PFS) at 1 and 2 years.

Results In the population of 108 patients, a median OS of 8.98 months (95% CI, 7.47 to 10.79 months) was observed. One-year OS was 36% (95% CI, 26% to 45%), and 2-year survival was observed as 20% (95% CI, 12% to 27%). The median survival without progression (ie, PFS) was 3.44 months (95% CI, 2.98 to 4.16 months), and 1- and 2-year PFS were 22% (95% CI, 14% to 29%) and 14% (95% CI, 8% to 21%), respectively. The longest recorded survival was 3.4 years. No independent prognostic variables were identified to predict for OS by multivariate Cox proportional hazards model.

Conclusion In this multicenter South African setting, ipilimumab at a dose of 3 mg/kg was an effective treatment with long-term OS in a subset of patients with pretreated advanced malignant melanoma.

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continued
Systematic Review and Meta-Analysis of Individual Patient Data to Assess the Sensitivity of Cervical Cytology for Diagnosis of Cervical Cancer in Low- and Middle-Income Countries

Purpose To assess the sensitivity of cervical cytology to cancer by pooling individual patient cytology results from cancers diagnosed in studies that assessed cervical screening in low- and middle-income countries.

Methods Two authors reviewed studies identified through PubMed and Embase databases. We included studies that reported cervical cytology in which at least one woman was diagnosed with cervical cancer and in which abnormal cytology results were investigated at colposcopy and through a histologic sample (if appropriate). When cytology results were not reported in the manuscript, authors were contacted. Stratified analyses and meta-regression were performed to assess sources of heterogeneity between studies.

Results We included 717 cancers from 23 studies. The pooled sensitivity of cytology to cancer at a cutoff of a high-grade squamous intraepithelial lesion (HSIL) or worse was 79.4% (95% CI, 67.7% to 86.0%). Results from stratified analyses did not differ significantly, except among studies that recruited symptomatic women or women referred because of abnormal cytology, when the sensitivity of cytology was much higher (95.9%; 95% CI, 86.5% to 99.9%). The cutoff of an HSIL or worse detected 85% of the cancers that would have been detected at a cutoff of atypical squamous cells of undetermined significance or worse (relative sensitivity, 85.2%; 95% CI, 80.7% to 89.7%).

Conclusion Cytology at a high cutoff could be an excellent tool for targeted screening of populations at high risk of cervical cancer with a view to diagnose cancer at an earlier stage.
Use of Palliative Cisplatinum for Advanced Cervical Cancer in a Resource-Poor Setting: A Case Series From Kenya

**Purpose** To evaluate the effectiveness and feasibility of cisplatinum for palliative treatment of advanced cervical cancer in a resource-poor setting.

**Methods** An observational case series is reported from a university teaching hospital in Kenya. All women presenting with advanced cervical cancer and planned for palliative cisplatinum therapy from 2010 to 2014 were included. Women were treated with cisplatinum 50 mg/m² every 4 weeks in an outpatient setting. Data on tumor stage and symptoms control were prospectively collected in an electronic database. The main outcome measure was control of symptoms such as bleeding, discharge, and pain.

**Results** Of the women who originally presented with bleeding, 62% reported improvement in this symptom, 31.3% reported the bleeding completely stopped, 58% had improvement of their vaginal discharge, and 20.5% reported complete resolution. Of the women who presented with pain, 54% reported improvement; 30.9% reported pain had completely resolved. After each treatment cycle, approximately 30% of patients did not return for their next treatment.

**Conclusion** Cisplatinum as palliative treatment of advanced cervical cancer is feasible in a resource-poor setting and leads to effective symptom control. However, unknown barriers may inhibit women from returning for regular treatment.

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Pediatric Hodgkin Lymphoma Treated at Cancer Institute, Chennai, India: Long-Term Outcome

**Purpose** Pediatric Hodgkin lymphoma (HL) is a highly curable malignancy. Outcomes for pediatric HL may vary between developed and developing countries for multiple reasons. This study was conducted to ascertain the outcomes of children with HL at our center and to identify risk factors for recurrent disease.

**Methods** We analyzed the outcomes of 172 consecutive, previously untreated patients with pediatric HL presenting at our center from 2001 to 2010. Patients were treated with either adriamycin, bleomycin, vinblastine, and dacarbazine or adriamycin, bleomycin, vinblastine, cyclophosphamide, vincristine, prednisone, and procarbazine chemotherapy initially, and radiation to bulky sites or a single site of residual disease when appropriate.

**Results** The median duration of follow-up was 77 months. The median age of the patients was 10 years; 127 (74%) of the 172 patients were male. The extent of disease was stage I and II in 59% of the patients. B symptoms were present in 32% of the patients, and 27% had bulky disease. The most common histologic subtype was mixed cellularity (45%). The 5-year overall survival (OS) and progression-free survival (PFS) of the entire cohort were 92.9% and 83.1%, respectively. The 5-year OS rates for patients with stage I, II, III, and IV were 96%, 94.7%, 84%, and 69.8%, respectively. On univariate analysis, advanced stage, response on interim radiologic assessment, and presence of B symptoms significantly predicted inferior PFS and OS. On multivariate analysis, only interim radiologic response significantly predicted PFS ($P < .001$) and OS ($P < .001$).

**Conclusion** Overall, the outcomes of patients treated at our center are comparable to those observed in other centers in India and globally.

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Wilms Tumor Treatment Outcomes: Perspectives From a Low-Income Setting

Purpose Wilms tumor is the commonest renal malignancy in childhood. Survival in high-income countries is approximately 90%, whereas in low-income countries, it is less than 50%. This study assessed treatment outcomes of patients with Wilms tumor at a Kenyan academic hospital.

Patients and Methods We conducted a retrospective medical record review of all children diagnosed with Wilms tumor between 2010 and 2012. Data on treatment outcomes and various sociodemographic and clinical characteristics were collected.

Results Of the 39 patients with Wilms tumor, 41% had event-free survival, 31% abandoned treatment, 23% died, and 5% had progressive or relapsed disease. Most patients presented at an advanced stage: stage I (0%), II (7%), III (43%), IV (40%), or V (10%). The most likely treatment outcome in patients with low-stage (I to III) disease was event-free survival (67%), whereas in those with high-stage (IV to V) disease, it was death (40%). No deaths or instances of progressive or relapsed disease were recorded among patients with low-stage disease; their only reason for treatment failure was abandonment of treatment. Stage of disease significantly affected treatment outcomes (P = .014) and event-free survival estimates (P < .001). Age at diagnosis, sex, duration of symptoms, distance to hospital, and health insurance status did not statistically significantly influence treatment outcomes or event-free survival estimates.

Conclusion Survival of patients with Wilms tumor in Kenya is lower compared with that in high-income countries. Treatment abandonment is the most common cause of treatment failure. Stage of disease at diagnosis statistically significantly affects treatment outcomes and survival.

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Model for Estimating Power and Downtime Effects on Teletherapy Units in Low-Resource Settings

**Purpose** More than 6,500 megavoltage teletherapy units are needed worldwide, many in low-resource settings. Cobalt-60 units or linear accelerators (linacs) can fill this need. We have evaluated machine performance on the basis of patient throughput to provide insight into machine viability under various conditions in such a way that conclusions can be generalized to a vast array of clinical scenarios.

**Materials and Methods** Data from patient treatment plans, peer-reviewed studies, and international organizations were combined to assess the relative patient throughput of linacs and cobalt-60 units that deliver radiotherapy with standard techniques under various power and maintenance support conditions. Data concerning the frequency and duration of power outages and downtime characteristics of the machines were used to model teletherapy operation in low-resource settings.

**Results** Modeled average daily throughput was decreased for linacs because of lack of power infrastructure and for cobalt-60 units because of limited and decaying source strength. For conformal radiotherapy delivered with multileaf collimators, average daily patient throughput over 8 years of operation was equal for cobalt-60 units and linacs when an average of 1.83 hours of power outage occurred per 10-hour working day. Relative to conformal treatments delivered with multileaf collimators on the respective machines, the use of advanced techniques on linacs decreased throughput between 20% and 32% and, for cobalt machines, the need to manually place blocks reduced throughput up to 37%.

**Conclusion** Our patient throughput data indicate that cobalt-60 units are generally best suited for implementation when machine operation might be 70% or less of total operable time because of power outages or mechanical repair. However, each implementation scenario is unique and requires consideration of all variables affecting implementation.

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*continued*
Barriers and Challenges to Treatment Alternatives for Early-Stage Cervical Cancer in Lower-Resource Settings

Cervical cancer is one of the most common cancers among women worldwide, and approximately 85% of new diagnoses occur in less-developed regions of the world. Global efforts in cervical cancer to date have focused on primary and secondary prevention strategies of human papillomavirus vaccination and cervical cancer screening. Cervical cancer screening is effective to reduce the incidence of cervical cancer and can result in diagnosis at earlier stages, but it will take time to realize its full impact. With expansion of screening programs, there is now a greater imperative to increase access to treatment for women who have cervical cancer, particularly in earlier stages of disease, when it is still curable. Resources for multimodality treatment can be limited—or even absent—in many less-developed regions of the world and may be associated with geographic, social, and financial barriers for the patient. However, there is evidence that, in many cases, less-invasive and less-resource-intensive treatment options are still effective. To this end, the National Comprehensive Cancer Network and American Society of Clinical Oncology have published guideline adaptations for specific resource constraints, and research about more conservative approaches to the treatment of cervical cancer continues. This review focuses on potential barriers and challenges to provision of safe and effective treatment of early-stage cervical cancer in lower-resource settings, and it suggests future directions for expansion of access to cervical cancer treatment around the world.

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continued
Managing Pain in Patients With Cancer: The Chinese Good Pain Management Experience

**Purpose** The number of cancer cases in China has increased rapidly from 2.1 million in 2000 to 4.3 million in 2015. As a consequence, pain management as an integral part of cancer treatment became an important health care issue. In March 2011, the Good Pain Management (GPM) program was launched to standardize the treatment of cancer pain and improve the quality of life for patients with cancer. With this work, we will describe the GPM program, its implementation experience, and highlight key lessons that can improve pain management for patients with cancer.

**Methods** We describe procedures for the selection, implementation, and assessment procedures for model cancer wards. We analyzed published results in areas of staff training and patient education, pain management in practice, analgesic drugs administration, and patient follow-up and satisfaction.

**Results** Pain management training enabled medical staff to accurately assess the level of pain and to provide effective pain relief through timely dispensation of medication. Patients with good knowledge of treatment of pain were able to overcome their aversion to opioid drugs and cooperate with nursing staff on pain assessment to achieve effective drug dose titration. Consumption of strong opioid drugs increased significantly; however, there was no change for weaker opioids. Higher pain remission rates were achieved for patients with moderate-to-severe pain levels. Proper patient follow-up after discharge enabled improved outcomes to be maintained.

**Conclusion** The GPM program has instituted a consistent and high standard of care for pain management at cancer wards and improved the quality of life for patients with cancer.

Improving Access to Cancer Treatments: The Role of Biosimilars

Biologics play a key role in cancer treatment and are principal components of many therapeutic regimens. However, they require complex manufacturing processes, resulting in high cost and occasional shortages in supply. The cost of biologics limits accessibility of cancer treatment for many patients. Effective and affordable cancer therapies are needed globally, more so in developing countries, where health care resources can be limited. Biosimilars, which have biologic activity comparable to their corresponding reference drugs and are often more cost effective, have the potential to enhance treatment accessibility for patients and provide alternatives for decision makers (ie, prescribers, regulators, payers, policymakers, and drug developers). Impending patent expirations of several oncology biologics have opened up a vista for the development of corresponding biosimilars. Several countries have implemented abbreviated pathways for approval of biosimilars; however, challenges to their effective use persist. Some of these include designing appropriate clinical trials for assessing biosimilarity, extrapolation of indications, immunogenicity, interchangeability with the reference drug, lack of awareness and possibly acceptance among health care providers, and potential political barriers. In this review, we discuss the potential role and impact of biosimilars in oncology and the challenges related to their adoption and use. We also review the safety and efficacy of some of the widely used biosimilars in oncology and other therapeutic areas (eg, bevacizumab, darbepoetin, filgrastim, rituximab, and trastuzumab).

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Primary Prevention of Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Guideline

**Purpose** To provide resource-stratified (four tiers), evidence-based recommendations on the primary prevention of cervical cancer globally.

**Methods** The American Society of Clinical Oncology convened a multidisciplinary, multinational panel of oncology, obstetrics/gynecology, public health, cancer control, epidemiology/biostatistics, health economics, behavioral/implementation science, and patient advocacy experts. The Expert Panel reviewed existing guidelines and conducted a modified ADAPTE process and a formal consensus-based process with additional experts (consensus ratings group) for one round of formal ratings.

**Results** Existing sets of guidelines from five guideline developers were identified and reviewed; adapted recommendations formed the evidence base. Five systematic reviews, along with cost-effectiveness analyses, provided evidence to inform the formal consensus process, which resulted in agreement of ≥ 75%.

**Recommendations** In all resource settings, two doses of human papillomavirus vaccine are recommended for girls age 9 to 14 years, with an interval of at least 6 months and possibly up to 12 to 15 months. Individuals with HIV positivity should receive three doses. Maximal and enhanced settings: if girls are age ≥ 15 years and received their first dose before age 15 years, they may complete the series; if no doses were received before age 15 years, three doses should be administered; in both scenarios, vaccination may be through age 26 years. Limited and basic settings: if sufficient resources remain after vaccinating girls age 9 to 14 years, girls who received one dose may receive additional doses between age 15 and 26 years. Maximal, enhanced, and limited settings: if ≥ 50% coverage in the priority female target population, sufficient resources, and cost effectiveness, boys may be vaccinated to prevent other noncervical human papillomavirus–related cancers and diseases. Basic settings: vaccinating boys is not recommended.

It is the view of the American Society of Clinical Oncology that health care providers and health care system decision makers should be guided by the recommendations for the highest stratum of resources available. The guideline is intended to complement but not replace local guidelines.

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**Purpose** To provide resource-stratified, evidence-based recommendations on the secondary prevention of cervical cancer globally.

**Methods** ASCO convened a multidisciplinary, multinational panel of oncology, primary care, epidemiology, health economic, cancer control, public health, and patient advocacy experts to produce recommendations reflecting four resource-tiered settings. A review of existing guidelines, a formal consensus-based process, and a modified ADAPTE process to adapt existing guidelines were conducted. Other experts participated in formal consensus.

**Results** Seven existing guidelines were identified and reviewed, and adapted recommendations form the evidence base. Four systematic reviews plus cost-effectiveness analyses provided indirect evidence to inform consensus, which resulted in \( \geq 75\% \) agreement.

**Recommendations** Human papillomavirus (HPV) DNA testing is recommended in all resource settings; visual inspection with acetic acid may be used in basic settings. Recommended age ranges and frequencies by setting are as follows: maximal: ages 25 to 65, every 5 years; enhanced: ages 30 to 65, if two consecutive negative tests at 5-year intervals, then every 10 years; limited: ages 30 to 49, every 10 years; and basic: ages 30 to 49, one to three times per lifetime. For basic settings, visual assessment is recommended as triage; in other settings, genotyping and/or cytology are recommended. For basic settings, treatment is recommended if abnormal triage results are present; in other settings, colposcopy is recommended for abnormal triage results. For basic settings, treatment options are cryotherapy or loop electrosurgical excision procedure; for other settings, loop electrosurgical excision procedure (or ablation) is recommended. Twelve-month post-treatment follow-up is recommended in all settings. Women who are HIV positive should be screened with HPV testing after diagnosis and screened twice as many times per lifetime as the general population. Screening is recommended at 6 weeks postpartum in basic settings; in other settings, screening is recommended at 6 months. In basic settings without mass screening, infrastructure for HPV testing, diagnosis, and treatment should be developed.

Additional information can be found at [www.asco.org/rs-cervical-cancer-secondary-prev-guideline](http://www.asco.org/rs-cervical-cancer-secondary-prev-guideline) and [www.asco.org/guidelineswiki](http://www.asco.org/guidelineswiki).

It is the view of of ASCO that health care providers and health care system decision makers should be guided by the recommendations for the highest stratum of resources available. The guideline is intended to complement, but not replace, local guidelines.

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Project ECHO: A Telementoring Program for Cervical Cancer Prevention and Treatment in Low-Resource Settings

Cervical cancer incidence and mortality rates are significantly higher in low- and middle-income countries compared with the United States and other developed countries. This disparity is caused by decreased access to screening, often coupled with low numbers of trained providers offering cancer prevention and treatment services. However, similar disparities are also found in underserved areas of the United States, such as the Texas-Mexico border, where cervical cancer mortality rates are 30% higher than in the rest of Texas. To address these issues, we have adopted the Project ECHO (Extension for Community Healthcare Outcomes) program, a low-cost telementoring model previously proven to be successful in increasing local capacity, improving patient management skills, and ultimately improving patient outcomes in rural and underserved areas. We use the Project ECHO model to educate local providers in the management of cervical dysplasia in a low-resource region of Texas and have adapted it to inform strategies for the management of advanced cervical and breast cancer in Latin America and sub-Saharan Africa. This innovative approach, using ECHO, is part of a larger strategy to enhance clinical skills and develop collaborative projects between academic centers and partners in low-resource regions.

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continued
Multidisciplinary Gynecologic Oncology Clinic in Botswana: A Model for Multidisciplinary Oncology Care in Low- and Middle-Income Settings

**Purpose** Cervical cancer is a major cause of mortality in low- and middle-income countries (LMICs) and the most common cancer diagnosed in women in Botswana. Most women present with locally advanced disease, requiring chemotherapy and radiation. Care co-ordination requires input from a multidisciplinary team (MDT) to deliver appropriate, timely treatment. However, there are limited published examples of MDT implementation in LMICs.

**Methods** In May 2015, a weekly MDT clinic for gynecologic cancer care was initiated at Botswana's national referral facility. The MDT clinic served as a forum for discussion and coordination of patients with gynecologic cancer and consisted of a gynecologist, pathologist, medical oncologist, radiation oncologist, palliative care specialist, and nurse coordinator.

**Results** Between May 2015 and December 2015, 135 patients were seen in the MDT clinic. The mean age of the patients was 49 years. Most (60%) of the patients were HIV positive. The most common diagnosis was cervical cancer (60%), followed by high-grade cervical intraepithelial neoplastic lesions (12%) and vulvar cancer (11%). Only data up to September 2015 were assessed for treatment delays. It was found that only 38% of patients needed more than one visit for care coordination before treatment initiation. Among patients with cervical cancer, the median delay from date of biopsy to start of radiation treatment was 39 days (interquartile range, 34 to 57 days) for patients treated after MDT initiation, compared with 108 days (interquartile range, 71 to 147 days) for patients treated before MDT initiation ($P < .001$).

**Conclusion** Implementation of MDT clinics in LMICs is feasible and can help reduce delays in treatment initiation, as demonstrated by a gynecologic MDT clinic in Botswana. Streamlining care through MDT clinics can enhance care coordination and improve clinical outcomes. This model can apply to cancer care in other LMICs.

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The Scots have a saying, “When friends meet, hearts warm.” And such has been the friendship between Twalib Ngoma and David Kerr since they met as Fellows at Glasgow’s Beatson Cancer Institute in the 1980s, where Twalib showed data suggesting that the majority (80%) of Tanzanians presented with late stage 4 cancer. In conversation in Dar es Salaam some 30 years later, despite the significant downward stage shifts and improvements in cancer survival seen in Europe and the United States, it was apparent that there have been no such steps forward in most sub-Saharan African nations. It remains true that although the continent of Africa as a whole has a relatively low overall incidence rate of cancer, patients in less-developed countries also unfortunately have the poorest prognosis with the highest numbers of deaths. Much of this can be attributed to late-stage diagnosis.

These sorts of anecdotes prompted *Journal of Global Oncology* to conduct a survey of ASCO members who practiced in low- and middle-income countries (LMICs) to ask them to list the factors that hindered their ability to deliver high-quality cancer care to their citizens. Apart from the generic complaint of lack of resources (financial, human, and infrastructural), late presentation of disease and tumor burden were cited as the greatest barrier to improving the outcome for their patients. Tumor volume and stage correlate with prognosis for a variety of reasons—metastasis leading to multiorgan failure, reduction in performance status and cachexia, and increased tumor heterogeneity, with an associated increase in the likelihood of anticancer drug resistance. In short, the opportunity to diagnose, treat, and potentially cure cancer early in LMICs is being lost.

The benefits of screening for cervical, breast, and colorectal cancer in the West have been demonstrated, but the costs of establishing and maintaining conventional screening infrastructure is high and places these interventions at the margins of cost effectiveness, even in wealthy countries where cancer incidence is relatively high. Given this, we wanted to challenge the wider oncology community that, rather than adopt a one-size-fits-all approach to earlier disease detection or downstaging on the basis of Western screening models, was it possible to identify, develop, and deliver simpler, effective methods that could be used in prospective trials to demonstrate a population shift in tumor burden at presentation?

Some have proposed turning the problem on its head: rather than getting patients to come to a medical center for screening, take screening to them. Training female village-based volunteers to perform a clinical breast examination was just one pilot intervention that demonstrated potential in increasing awareness and pick-up rate of early-stage breast cancer.¹ Cervical cancer rates have declined significantly since the introduction of cervical smear screening programs, but the logistic and cultural challenges surrounding this also required an alternative approach. Using the Visual Inspection with Acetic Acid test, whereby a see-and-treat approach is used to treat abnormal areas, has resulted in a notable reduction in cervical cancer incidence.² More technological advances include the development of a microendoscope with a build-it-yourself computer and dye kit, which allows the cervix to be visualized and assessed in the same sitting.³ Geography is a key problem that any downstaging program must overcome. In Tanzania, there is only one tertiary cancer center (the Ocean Road Cancer Institute) to manage the estimated 20,000 new diagnoses of all cancers nationwide each year. This means screening for cancer must be feasible in smaller hospitals and medical centers across the country and must be acceptable to the population it is serving. Screening acceptability is just one of the issues identified by the African Research Group for Oncology (ARGO), a collective that aims to learn from the development and maintenance of a cancer research consortium in Nigeria.⁴ The key messages are of different population expectations, a different oncology management structure that is surgically centered, and the challenges of accessing, say, stool testing and colonoscopy services if colorectal cancer screening was to be implemented, although this is a controversial theme in LMICs.⁵ To this end, we have commissioned a special issue of *Journal of Global Oncology* as a call to arms: we must identify novel screening tools that are cheap,
Immediate, and effective. Existing screening tools cannot be relied on to address this pressing need in LMICs with the logistic, financial, and cultural limitations they present. Diagnosing cancer early is vital to improve patient outcomes and health care efficiencies, particularly with the significant predicted increase in cancer incidence on the horizon. We hope that we can stimulate a debate and action beyond the conventional readership of our journal to engage not only physicians, front-line health workers, and public health specialists but also social and technology entrepreneurs and existing high-tech companies to consider this problem and, from this, research laterally useful methodologies. Let us invent a hand-held, solar-powered ultrasound machine that is digitally interpretable and could be used by two old friends: Kerr and Ngoma.

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Karin Purshouse
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Twalib Ngoma
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David Kerr
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Affiliations
Karin Purshouse and David Kerr, University of Oxford, Oxford, United Kingdom; and Twalib Ngoma, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania.

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Patient Navigation to Improve Access to Breast Cancer Care in Brazil

Noncommunicable diseases, such as cancer, are surpassing infectious diseases as the most pressing health care threat in low- and middle-income countries (LMICs).1 By 2025, 59% of new cancer cases and 68% of all cancer deaths will occur in LMICs,2 and health care systems in these countries are struggling to respond to this changing landscape.3 In Brazil, breast cancer is the most common cancer and the leading cause of cancer death among women, with 14,206 deaths in 20134 and 57,960 new cancer diagnoses estimated for the year 2016.5

Recognizing the need for cancer control strategies, the Brazilian government issued Ministry of Health Law No. 12.732/12, also called the Law of 60 Days, in 2012. This law states that treatment of any cancer for patients in the public health system must start within 60 days of definitive diagnosis.6 Shortly after the Law of 60 Days was enacted, the Cancer Information System (or SISCAN, the Brazilian acronym) was instituted to monitor the implementation of the law by tracking patient treatment times, appointments, diagnostic tests, and targets and indicators for future cancer control actions.7 However, even years after the institution of the law, a large proportion of patients still do not receive timely treatment, and SISCAN has not been effectively used. Innovative solutions are needed to ensure that the law is properly implemented. In this context, an intervention such as patient navigation (PN) could potentially allow for appropriate implementation of the law.8 Although PN programs have shown demonstrable success among underserved populations in the United States, their global implementation has been limited. Here, we discuss the potential role of PN in alleviating health system barriers and supporting adherence to the Law of 60 Days in Brazil, which in turn could improve the outcomes of women with breast cancer throughout the country.

HEALTH SYSTEM DELAY IN BRAZIL

A delay in breast cancer care leads to more advanced stages at presentation and worse survival.5 Delay can be divided into the following two intervals: a patient interval and a health system interval. The health system interval—the time between first consultation and treatment initiation—is significantly longer in LMICs compared with high-income countries (HICs; Fig 1).10 For example, whereas HICs report a median health system interval of 10 to 42 days for patients with breast cancer, the median interval reported in Mexico City is 5 months.11 Other studies from Brazil and Mexico show that it takes a patient with breast cancer between 6 and 7 months to receive a definitive diagnosis after her first consultation with a physician.3 A study from Rio de Janeiro, Brazil, found that the median time from first consultation to diagnosis was 6.5 months and that 80% of patients experienced a health system delay of more than 3 months.12

In LMICs, long delays frequently result in clinical upstaging. In the United States, 60% of breast cancers are diagnosed at an early stage of disease, whereas in Brazil, this is true for only 20% of breast cancer diagnoses.8 In a study of 87,969 Brazilian women with breast cancer, 53.5% were considered to have advanced-stage disease (= stage IIB).13 In another study cohort, 78.8% of women had stage II to IV breast cancer.14 The latest report from the Breast Health Global Initiative highlighted the importance of clinical downstaging and developed guidelines for the early detection, diagnosis, and treatment of breast cancer to ultimately reduce mortality.15

Even within Brazil, staging and survival statistics vary according to sociodemographic characteristics, such as type of health insurance.16-19 There are two insurance modalities within the Brazilian health care system; insurance can be obtained through the public system, Sistema Único de Saúde, or through private providers. Approximately 75% of Brazilians receive coverage solely through Sistema Único de Saúde, and although progress toward universal health coverage has been made throughout the country, large disparities affecting cancer care remain.20 Women treated in the public system present with more advanced disease than women in the private sector, and public sector patients have worse cancer-specific, disease-free, and overall survival (which can be partially attributed to longer delays...
The negative impact of delays on the prognosis of patients with cancer within the public sector is so relevant that the Brazilian Ministry of Health enacted the aforementioned Law of 60 Days. Although this law is an important and well-intentioned effort to begin to reduce health system delays, surveillance of its implementation has been deficient.

To monitor the law’s application, the Ministry of Health in Brazil created the cancer database SISCAN. However, a survey of representatives from 59 public health institutions throughout Brazil showed that SISCAN is being used in only one quarter of Brazilian municipalities and that only approximately 1% of all patients with cancer had been registered in the system as of July 2014, almost 2 years after the announcement of the law. In addition, a 2015 study that collected data from 239 hospitals throughout Brazil showed that approximately 40% of patients with breast cancer failed to initiate treatment within the mandated 60-day period. This statistic varies widely by region, with the state of Rio de Janeiro reporting more than 70% of women failing to initiate treatment within the 60-day mandate.

POTENTIAL ROLE OF PN IN BRAZIL

PN is designed to address health disparities and alleviate institutional, socioeconomic, and personal barriers to timely cancer care. Patient navigators are trained health care workers who facilitate a patient’s passage through the health care system by providing services such as scheduling diagnostic and follow-up appointments, facilitating health system referrals, and coordinating communication between patients and health care professionals.

First pioneered in New York City’s Harlem district in the 1990s, PN was designed to improve timely access to cancer care among African American, Hispanic, and poor patients with low educational levels. The program achieved impressive results, improving the 5-year survival rate for breast cancer from 39% to 70% in the target population. Subsequent studies have proven that PN can improve times to diagnostic resolution and treatment, reduce loss to follow-up rates and health disparities, and improve patient education. For instance, in one study, PN programs reduced no-show rates for cancer follow-up screening by providing targeted education to patients. In another study, patients receiving PN were more likely to attend all regular medical visits compared with those who did not receive PN and had significantly shorter times to screening and diagnostic resolution. Additionally, PN results in significantly lower rates of missed appointments, shorter follow-up times, and a decrease in the severity of cervical abnormalities, as well as increased screening rates and improved equity in vulnerable patients. Finally, studies have also shown a decrease in time to diagnosis for women navigated because of an abnormal Pap smear and shorter times from an abnormal cancer screen to a definitive diagnosis for underserved patients with breast and cervical cancer.

Despite the great success of PN among underserved populations in the United States, PN has not been widely studied in LMICs. Patients in LMICs face structural barriers that are similar to those faced by underserved patients in the United States. In LMICs, urban poor, rural, remote, and indigenous populations often cannot access timely cancer care because of lack of awareness, complex and fragmented health care systems, low socioeconomic status, cultural barriers, and limited funding and human resources in public
institutions. PN has already proven to be a valuable tool for tackling these barriers in the United States, and it could potentially be tailored and implemented to do the same in LMICs.

An ongoing study by our group, the Global Cancer Institute, in the Mexico City metropolitan area aims to establish proof of implementation of PN for patients with cancer within the public health system in Mexico. Mexico City is a large metropolis with a fragmented health care system, which makes referrals between centers complex. As a result of this fragmentation, patients often experience long health system delays, with one study finding the median interval from breast cancer identification to start of treatment to be 7 months. In our study, a navigator is located at a secondary-level hospital and navigates patients with a suspected or confirmed diagnosis of cancer through the health care system, helping the patients to arrive at a tertiary care center for appropriate diagnosis and treatment. Results and lessons from this study in Mexico City will help us understand the feasibility and acceptability of PN in Latin America and guide the creation and adaptation of future PN sites throughout the region.

We previously proposed an action agenda aimed at successfully implementing PN in LMICs in general, and this same agenda could be applied in the Brazilian context to guide implementation of PN in the country:

1. Target gaps in infrastructure. The timely initiation of treatment after a diagnosis of cancer is a major gap in cancer care delivery in Brazil. The Ministry of Health has already acknowledged this issue by passing the Law of 60 Days, but the impact of the law has been low. The aforementioned survey of 59 Brazilian public health institutions revealed that nearly half of all responders cited difficulties in the referral and follow-up of patients within the public health system. Local PN programs should be designed to target delays in the health system interval of breast cancer care and promote total adherence to the Law of 60 Days.

2. Use a customizable protocol and training program. By using a template protocol designed in accordance with PN studies in the United States and implemented in our Mexico City site, the Brazilian PN program could be customized to address gaps in diagnosis and treatment pathways for public patients in Brazil. As one responder to the Brazilian survey stated: “One law does not alter the care and treatment of cancer; (the law’s implementation) requires training, resources, and knowledge of the reality of each location.” We have also designed a customizable training program aimed at providing local navigators and health care workers with knowledge of both the general principles of PN and site-specific issues. Both the protocol and the training program include tools to collect data specific to the study’s goals.

3. Engage policymakers. Because one of the goals of proof-of-implementation PN programs is to influence health care authorities and hospital administrators to integrate PN into the existing health system infrastructure, policymakers are engaged in our PN programs during the planning and implementation phases. This is essential, because PN should not be seen as an additional expense for health care systems, but as an opportunity for the reallocation of funds, focusing on use of scarce resources in prevention and early treatment, rather than late-stage disease. Within the Brazilian context, PN could represent an opportunity to implement the existing legislation appropriately, and as such, it would have a great potential for integration into the federal, state, and local health systems.

Implementing a breast cancer PN program in Brazil, which would reflect the lessons learned in studies from the United States and in our pilot project in Mexico City, has great potential to alleviate the barriers faced by patients in the public sector. By promoting adherence to the Law of 60 Days, PN could shorten the time to the start of cancer treatment, reduce loss to follow-up, and improve the outcomes of women with breast cancer in Brazil.

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Alexandra Bukowski
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Sandra Gioia
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Affiliations

Alexandra Bukowski, Jessica St. Louis, and Paul E. Goss, Avon International Breast Cancer Research Program, Massachusetts General Hospital; Alexandra Bukowski, Sandra Gioia, Yanin Chavarri-Guerra, Enrique Soto-Perez-de-Celis, Jessica St. Louis, Eduardo Paulino, Angelica Nogueira-Rodrigues, and Paul E. Goss, The Global Cancer Institute, Boston, MA; Sandra Gioia and Eduardo Paulino, Instituto Nacional de Cancer José Alencar Gomes da Silva; Rio de Janeiro; Angelica Nogueira-Rodrigues, Federal University of Minas Gerais, Belo Horizonte, Brazil; and Yanin Chavarri-Guerra and Enrique Soto-Perez-de-Celis, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

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Uganda has no radiotherapy. The sole workhorse machine, installed in 1995 at the country’s national hospital, stopped functioning in April 2016 and is beyond repair, a fact that rose to international attention.1 The absence of this machine means that hundreds of patients who were in the middle of cancer treatment were not able to complete it and many patients who could have lived with their cancers will now die of them.

Yet, lack of access to radiation therapy is a daily reality for most patients with cancer in low- and middle-income countries (LMICs) across the globe. Nowhere is this dearth of access greater than in Africa. Nearly 30 African countries do not have a single radiotherapy unit. An additional eight have fewer than 0.1 machines per million people.2 The International Atomic Energy Association recommends between four and eight machines per million people; North America has 14.89 machines per million.2 Before this month, Uganda had one machine serving its 37 million people, in addition to referrals from Burundi, Rwanda, and further afield.

Machine number does not always equate to practical access. Although neighboring Kenya has eight machines, only two serve public-sector patients at low cost. Both of these machines have been repeatedly out of service throughout 2015 and early 2016, a fact that reached national news outlets but did not rise to international attention.3,4 Uganda’s single external-beam radiation machine operated on a radioactive cobalt source that was last exchanged in 2002. Because the half-life of cobalt-60 is roughly 5 years, patient treatments would take four to five times longer than a younger source would have required. There has also been an increase in the number of patients with cancer seeking radiotherapy treatment, from approximately 250 in 1995 to nearly 2,000 in 2015. In part because of the dying cobalt source and in part because of the relentless patient volume, Uganda’s machine ran for more than 20 hours per day, in three shifts, straining against the impossible demand. A team of radiation oncologists, physicists, technicians, and nurses all worked these hours, striving to provide the best possible care in adverse circumstances. The work was just too important to stop—this one machine was the only hope for tens of thousands of patients in the region.

The loss of Uganda’s only machine is an unequivocal tragedy, albeit a predictable one. Jackson Orem, MMed, PhD, Director of the Uganda Cancer Institute (UCI), reported 2 years ago that logistic concerns, and not funding, were the primary issues in ensuring a new, reliable radiotherapy machine. The asking price of a machine is an all-too-common way to start and end the discussion on providing radiotherapy to those who need it.

Radiotherapy facilities require a complex support system, so complex that people are often intimidated by the magnitude of the task. Early in the HIV/AIDS crisis, antiretroviral medications were also deemed too complex to deliver in low-resource settings, even as the epidemic raged across the subcontinent. But people who believed it was possible made it possible on a broad scale. If there is anything to learn from this situation, it is not that radiotherapy in LMICs is too difficult to sustain. In East Africa alone, Mulago and Kenyatta, Nairobi’s public hospitals, have treated hundreds of thousands of patients with minimal foreign assistance for decades, whereas the rest of the world has argued about the feasibility of radiotherapy in LMICs.

There is a current action to revive radiotherapy services in the country. The government of Uganda, in collaboration with the UCI, has embarked on building six new radiotherapy bunkers at the UCI site adjacent to Mulago Hospital. There are also plans to formally decommission the non-functional cobalt machine and replace it with a
modern cobalt unit. In addition, a new cobalt-60 high-dose-rate brachytherapy unit and a computed tomography simulator were commissioned in March and April and are fully functional.

Uganda’s radiotherapy facility was an inspiring place, and its successors will be even more so. The lesson from Uganda is not that machines break, but that systems do. We are in need of more robust mechanisms to ensure that radiotherapy is a part of planning for cancer care and control in all LMIC settings.

There are several essential steps. The International Atomic Energy Association’s Programme of Action for Cancer Therapy needs a bigger budget, staff, and mandate to ameliorate the numerous logistical complexities of acquiring and maintaining radiotherapy machines. Currently, they rely primarily on volunteers with varying experience in the LMIC context to conduct their national assessments and follow-up. Furthermore, the numerous North American and European academic and nongovernmental organizations that have taken up the mantle of global cancer care must prioritize radiotherapy as part of their work with national programs.

Common malignancies in LMICs—including head and neck and cervical cancers—are incurable without radiation therapy, especially in the absence of highly specialized surgical care. Furthermore, patients with painful, large masses often benefit from palliative radiotherapy; these patients also suffer because of a profoundly limited supply of opiates. Yet, many international partnerships that attempt to strengthen cancer care in LMIC focus preferentially on chemotherapy.

Above all, we need more brains and bodies—doctors, physicists, and radiation therapists from across the globe who are dedicated to this mission. There are many hopeful national and international strides toward broader access to radiotherapy. This has been particularly true over the last few years, with the Union for International Cancer Control’s Global Task Force on Radiotherapy for cancer control publishing a comprehensive assessment of what is needed to set up a basic radiotherapy service. Furthermore, Datta et al provide a compelling road map of how these services can be established, improved, and maintained.

Radiotherapy was functional in Uganda and will be again, and it is support for partnership and systems of care that are bringing this to bear, not simply machines. Machines will break. Downtime and decommissioning are a part of the process of radiotherapy in radiation oncology departments across the globe. We should expect them to be and should have better support and strategies from national and international bodies to address these realities. Uganda provides us with a sobering reality and a ray of hope. Uganda’s machine is broken, but so is our system for ensuring access to radiotherapy for patients with cancer across the globe.

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Shekinah Nefreteri Elmore
No relationship to disclose
Roshan Vijay Sethi
No relationship to disclose
Awusi Kavuma
No relationship to disclose
Daniel Mukasa Kanyike
No relationship to disclose

Affiliations
Shekinah Nefreteri Elmore and Roshan Vijay Sethi, Harvard Radiation Oncology Program, Boston, MA; and Awusi Kavuma and Daniel Mukasa Kanyike, Mulago Hospital, Kampala, Uganda.

REFERENCES


One of the recent growth industries and, one might add, great successes in global oncology has been the rise of international treatment guidelines. The most prominent of these guidelines include those by ASCO,1 the National Comprehensive Cancer Network (NCCN),2 and the European Society of Medical Oncology (ESMO),3 which provide timely, evidence-based recommendations for the multi-disciplinary management of most cancer types. They provide an international gold standard in a fairly user-friendly format, tend not to be overly prescriptive when evidence favors neither one nor another regimen, and are backed by well-respected experts who provide additional data on the depth of evidence to support a particular recommendation. International treatment guidelines are updated regularly, which is important when the standard of care may change from quarter to quarter and can provide a point of reference for hard-pressed clinicians. Until recently, only the gold standard existed, with no mention of silver, bronze, or tin! One wonders what fraction of the world’s cancer community might be supported by a health care system that could afford full and undiluted access to gold standard care, perhaps on the order of 10%?

An African health minister might have $10 per head of his or her population to spend on all of health care, let alone cancer, whereas a conservative estimate of cancer spending is approximately $150 million per million population in the developed world.4 How then can these trusted guidelines serve oncologists who work in low- and middle-income countries (LMICs)?

We conducted an online survey of oncologic practice with respect to the treatment of lung and breast cancer in LMICs including India, China, Thailand, the Philippines, Malaysia, Vietnam, Indonesia, Argentina, Brazil, Chile, and Mexico. The majority of survey respondents were consultants (44%) or oncology department chiefs (31%) from university hospitals (48%) and general private hospitals (35%); the other respondents were from community hospitals. These respondents, therefore, represent a senior and influential group of oncologists who are likely considered key opinion leaders in their countries. The full data set will be published, but significant international differences in the use of specific regimes in defined disease settings exist.

Of the 139 respondents, 58% claimed to always use guidelines (often different ones for different diseases) to support their clinical decisions. The guidelines used vary, with some referring to more than one set of guidelines. Ninety-two percent use NCCN guidelines, 55% ASCO guidelines, 55% ESMO guidelines, and 40% national guidelines. All respondents mainly rely on NCCN guidelines, predominantly for private and self-pay patients, because national health care systems and insurance coverage are not sufficiently funded to support particular cancer treatment protocols. Of the respondents who use national guidelines, their stated reason for not relying on the international guidelines is that the treatments specified in international guidelines are not easily accessible within their countries. Seventy-five percent of respondents who use international guidelines modify them in some way to treat their patients, which contrasts with only 50% who rarely have to modify national guidelines.

We do not have a one-size-fits-all single set of guidelines of universal applicability but rather a pick-and-mix approach that dips into various guidelines according to disease, stage, affordability, and whether the oncologist was trained in the United States or Europe. At one level, this approach is not surprising: Can uniformity of cancer treatment reside as a universal verity, as argued by Plato, or, rather, as shades of opinion and interpretation?

These data suggest that the international guidelines groups could take two utilitarian steps to increase their usefulness outside the United States or western Europe, namely by consulting with clinicians within a geographic region on how...
their guidelines might be better adapted to serve the local community of physicians and their patients and to introduce an element of resource stratification derived from the concept of affordability. ESMO and ASCO both have international input into their clinical guideline committees, but NCCN has taken a step farther to globalize its advice by hosting regional conferences in which invited senior clinicians modify, adapt, and customize the parent guideline set. Because the majority of clinical trial evidence that supports guidelines is still generated in the West in predominantly white patients, these data probably will always be borrowed until a sufficient regional clinical trials infrastructure permits stronger regional trial recruitment. Nevertheless, this experiential approach suffices as a temporary bridge across continents, cultures, and ethnicities.

Medicine affordability is a major barrier to cancer drug access, and cancer generally is acknowledged as the most common disease associated with medical bankruptcy. The term financial toxicity is frequently used by the public and policymakers with regard to cancer treatment, which has led both ASCO and NCCN to include some estimates of affordability in their guidance.

The NCCN Evidence Blocks are an easily accessible visual representation of five key components of value that provide important information about specific recommendations contained within the NCCN Clinical Practice Guidelines. These five components are efficacy, safety, quality and quantity of evidence, consistency of evidence, and affordability. ASCO’s Value Framework has been constructed as a conceptual model that incorporates the elements of clinical benefit, toxicity, and symptom palliation as derived from a comparative clinical trial and combines these elements into a score termed the net health benefit. Information on the cost of the regimens also will be presented so that the patient can consider the relative financial impact of the treatment options, an essential component of delivering cancer care in LMICs.

Many would argue that a single, global, evidence-based standard of care for patients with cancer should exist and that to detract or divert from this standard is a breach of human rights. Such an argument accepts that the world will always be riven by inequity between the haves and have-nots and that to support cancer treatment with anything less than ideal is to promulgate this base philosophy. We regard this argument as wholly specious and subscribe to the philosophy that the perfect is the enemy of the good. Guidance should not be prevented from being offered where certain diagnostic tests and treatment approaches are unavailable, and NCCN has taken the lead to define appropriate treatment pathways that are based on available resources. Basic, Core, and Enhanced Resources and NCCN Guidelines identify treatment options that will provide the best possible outcomes given specific resource constraints. The NCCN Framework resources are defined as follows:

Basic Resources: essential services needed to provide a minimal standard of care.

Core Resources: resources provided in the Basic Resources Framework plus services that provide major improvements in disease outcomes (eg, survival) and that are not cost prohibitive.

Enhanced Resources: resources provided in the Core Resources Framework plus services that provide lesser improvements in disease outcomes and/or services that provide major improvements in disease outcomes but are cost prohibitive in lower-resource settings.

NCCN Guidelines: resources provided in the Enhanced Resources Framework plus services that provide minor improvements in disease outcomes, interventions that are cost prohibitive in lower-resource settings, and/or services that do not provide improvement in disease outcomes but are desirable.

ASCO has published two resource-stratified guidelines in the Journal of Global Oncology for cervical cancer screening and treatment. A multidisciplinary, multinational panel of cancer control, medical and radiation oncology, health economics, obstetric and gynecologic, and palliative care experts produced recommendations that reflect resource-tiered settings. Existing sets of guidelines were identified and reviewed, and adapted recommendations form the evidence base for clinicians and patients in relatively impoverished situations.

Everyone involved in guideline production believes that the best available resources should be delivered. However, if basic resources for cancer treatment are unavailable, palliative and best supportive care should be provided. These tiered guidelines can also be used to inform health policy and national cancer plans in that they define a minimal baseline of resources required to establish foundation levels of cancer treatment.

In summary, good evidence suggests that several of the issues highlighted in our survey of colleagues who work in LMICs are being addressed by the major professional societies and guidelines groups, namely, adaptation for local use by
engaging with clinicians in specific geographic regions, stratifying resources and defining minimal treatment standards, engaging with the concept of value, and providing tools to enable the often difficult discussion about treatment affordability between the patient and the physician.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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Stewart Kerr
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Abdul-Rahman Jazieh
No relationship to disclose

David Kerr
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Patents, Royalties, Other Intellectual Property: Patent on chemotoxicity single nucleotide polymorphisms (Inst)

Affiliations
Stewart Kerr and David Kerr, Africa Oxford Cancer Foundation, Oxford, United Kingdom; and Abdul-Rahman Jazieh, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Kingdom of Saudi Arabia.

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REFERENCES
Acceptability of Human Papillomavirus Self-Sampling for Cervical Cancer Screening in an Indigenous Community in Guatemala

Purpose Cervical cancer rates in Latin America are higher than those in developed countries, likely because of the lower prevalence of screening. Specifically, less than 40% of women in Guatemala are regularly screened and even fewer women are screened in indigenous communities. Current screening strategies—Pap smears and visual inspection with acetic acid—might not be the most effective methods for controlling cancer in these settings. We thus investigated the potential of self-collection of cervical samples with testing for human papillomavirus (HPV) to help prevent cervical cancer in an indigenous community in Guatemala.

Patients and Methods A community representative random sample of 202 indigenous women age 18 to 60 years residing in Santiago Atitlan, Guatemala, were surveyed to assess knowledge of and risk factors for HPV and cervical cancer. Women were then invited to self-collect a cervical sample using HerSwab collection kits to assess the prevalence of HPV and the acceptability of self-sampling.

Results Of 202 women who completed the survey, 178 (89%) provided a self-sample. In all, 79% of these women found the test comfortable, 91% found the test easy to use, and 100% reported they were willing to perform the test periodically as a screening method. Thirty-one samples (17%) were positive for at least one of 13 high-risk HPV types, and eight (4.5%) were positive for HPV 16/18.

Conclusion HPV testing by using self-collected samples was well accepted, suggesting that it is a plausible modality for cervical cancer screening in indigenous communities. Further studies are needed to assess rates of follow-up after a positive test and to determine whether these findings extend to other indigenous and nonindigenous communities in Guatemala and Latin America.
detect lesions. This procedure is less costly and invasive than Pap smears and can be performed by trained laypersons in low-resource health facilities. In addition, VIA gives the option to treat women with cervical lesions immediately. Thus VIA is often called a “see/screen-and-treat” or “one-visit” approach. Previous studies have shown that VIA screening helps reduce CC incidence and mortality in low-resource settings. However, VIA shares some of the same barriers associated with Pap smears, so despite these efforts, CC incidence and mortality remain high in many LMICs, presumably because of persistent low rates of screening with either approach.

Human papillomavirus (HPV) infections are responsible for more than 90% of CC cases. There are 13 types of high-risk HPV associated with development of CC. Of these, types 16 and 18 account for approximately 70% of all cases. Cervical HPV tests have high sensitivity (approximately 90%) and specificity (greater than 80%). Women who test positive for high-risk HPV should follow up with a Pap smear and/or VIA or treatment, depending on each country’s setting and resources, but a negative test means the risk of developing CC in the next few years is minimal, lower than the risk after a negative Pap smear. Furthermore, when Pap smears are performed only on women who have tested positive for HPV, the relatively low sensitivity of screening by using Pap smears is significantly improved. Thus, primary screening for high-risk HPV before referral for Pap smear or VIA has been proposed as an alternative CC screening method. Unfortunately, HPV testing is expensive and requires infrastructure not readily available in many LMICs. Nonetheless, research is underway to develop low-cost HPV tests that can be used with minor infrastructure requirements.

Self-collection HPV kits have been developed to allow women to collect their own cervicovaginal samples at home and send these to a testing facility through the mail or by other means. Studies in several countries have compared the accuracy of HPV self-collection samples with samples obtained by a physician and have assessed the acceptability of self-collection in different populations. Some studies have provided women with self-collection kits, but at medical facilities before collection by a physician rather than at the woman’s home. In these studies, self-collection has been shown to have sensitivity similar to that of physician-collected samples, and self-collection has been found to be highly acceptable in many settings. This suggests that self-collection could be helpful to increase CC screening rates in LMICs, once cost- and infrastructure-efficient HPV tests have been developed. However, few studies have provided participants with the opportunity to try these in community settings outside of medical facilities; thus, it is not clear whether they would be an accepted form of primary CC screening.

Guatemala has one of the highest levels of CC morbidity and mortality in the region. Age-standardized annual incidence and mortality rates are 22.3 and 12.5 per 100,000 women, respectively, largely because less than 40% of Guatemalan women (who have a relatively high prevalence of HPV) have ever been screened for CC. There have been self-collection studies conducted in Latin America, a region in which CC morbidity and mortality are particularly high, although few have tested the acceptability of HPV self-collection in community rather than clinical settings. Moreover, HPV self-collection has not been studied in indigenous populations in Latin America, who tend to have less access to health facilities and higher levels of stigma associated with physician-administered vaginal and STD tests. Thus, it is important to assess the acceptability of HPV self-collection kits and tests and determine the potential of HPV testing as a screening modality in these settings. We thus conducted a cross-sectional study in an indigenous population in Lake Atitlan, Guatemala, to assess knowledge of HPV and CC, provide women with the opportunity to collect a self-sample in their home and report their feelings and experiences, and assess HPV prevalence in indigenous populations.

**PATIENTS AND METHODS**

We conducted a cross-sectional study in Santiago Atitlan, an indigenous community of 45,000 residents in Guatemala. Data were collected by using electronic surveys and self-collection kits.

**Study Population**

This community is almost exclusively Tz’utujil, a Mayan indigenous group. We sampled 212 women age 18 to 60 years from nine neighborhoods that encompass 85% of the population of Santiago Atitlan. Population data were obtained from the local municipality. We followed a stratified sampling approach by first allocating samples of size \( N_c \) to each neighborhood according to its relative population size \( (c = 1, \ldots, 9) \) and then randomly selecting a sample of \( N_c \) blocks. One house was randomly selected per block, in which one woman was interviewed.
If more than one woman in a house was eligible, the woman who had the next upcoming birthday was selected. Only women ages 25 to 54 years were eligible to provide a self-collected sample for HPV testing because women outside these ages are not eligible to receive screening using Pap smears or VIA according to Guatemalan CC screening guidelines. Menstruating and pregnant women were also excluded from self-collection. We chose to interview women outside the screening range because, although the focus of the study was on acceptability, we were interested in learning about the health practices and risk factors for all adult women.

Survey

The survey component was designed by using the Qualtrics application. It included 143 questions about demographics, preventive health care practices, and HPV and CC knowledge and risk factors. The survey also assessed the acceptability of and feelings toward HPV self-collection. Questions were developed by using the STEPwise Approach to Surveillance (STEPS) survey, The University of North Carolina’s Family Health Study Survey, and the University of Michigan’s Michigan HPV and Oropharyngeal Cancer study. Four trained community health workers (CHWs) fluent in Tz’utujil and Spanish conducted the surveys. The survey was written in English and then translated to Spanish by native speakers from the study team. After each pilot, surveyor notes were reviewed and appropriate revisions were made. At the end of each day, surveys were uploaded to the server, ensuring that the participant’s data could no longer be accessed, except by members of the study team.

HPV Self-Collected Samples

We used Eve Medical HerSwab self-collection HPV kits. Each kit came with an instructions card written in Spanish with step-by-step infographs explaining the collection process. The CHWs were trained on the procedure and on how to explain the instructions to the participants in their native language. Upon interview completion, each eligible participant was asked about her interest in collecting a sample for HPV testing. If the participant agreed, the CHWs explained the instructions, and the participant collected a sample in a private room in the household. The collection kit comprised a plastic handle and brush. The woman inserted the brush into her vagina and then turned a crank on the handle to extend the brush. The woman then removed the brush and cranked it back by using

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<th>No.</th>
<th>%</th>
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<th>SD</th>
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<td>Mammogram</td>
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<td>3.5</td>
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<td>134</td>
<td>66.3</td>
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<tr>
<td>&lt; 6 months</td>
<td>16</td>
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<tr>
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<td>Use condom</td>
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</tr>
<tr>
<td>Always</td>
<td>3</td>
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<tr>
<td>Almost always</td>
<td>5</td>
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<td></td>
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</tr>
<tr>
<td>No. of children</td>
<td>2.9</td>
<td>1.9</td>
<td></td>
<td></td>
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<tr>
<td>Age at first pregnancy, years</td>
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<td>4.0</td>
<td></td>
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</tr>
<tr>
<td>Family member with cervical cancer</td>
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<td>6.4</td>
<td></td>
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<td>3.9</td>
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<td>No. of lifetime partners</td>
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<td></td>
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<tr>
<td>Knowledge of HPV</td>
<td>30</td>
<td>14.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed with cervical cancer</td>
<td>0</td>
<td></td>
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<tr>
<td>Urban</td>
<td>165</td>
<td>81.7</td>
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</tbody>
</table>
the handle. She then returned the kit to the CHWs.

Afterward, each participant completed a five-question survey assessing the level of ease and comfort associated with the collection and her willingness to self-collect periodically as a form of CC screening. Finally, CHWs encouraged participants to attend free VIA screening clinics at their local public hospital.

Samples were sent to an independent, nonprofit laboratory in Guatemala City (Asociación de Salud Integral) for testing and were tested by using the Anyplex II HPV-28 kit, which tests for 13 high-risk HPV types according to the International Agency for Research on Cancer classification, as well as 15 low-risk types (Data Supplement).

To ensure the privacy and confidentiality of the participant’s information, given the sensitivity of the survey questions and the HPV test, no contact information was collected in this pilot study; thus, participants could not be contacted by the study team with their results. Instead, participants were told to call for their results 10 days after collection by using an identification number. Announcements were made daily on the local radio for 1 month after the end of recruitment that reminded women to call for their results. Participants were informed only if they tested positive for one of the 13 high-risk types.

Statistical Analyses

Post–self-collection survey questions were analyzed to determine the acceptability of HPV self-collection as a form of CC screening. Two additional outcomes were analyzed: positive HPV results and previous Pap smear or VIA results. Crude comparisons between these and relevant covariates were run by using log-binomial regression, and then models were run adjusting for other covariates. Statistical analyses were conducted by using SAS software Version 9.4 (SAS Institute, Cary, NC).

Human Subjects Approval

The University of Michigan Institutional Review Board approved study protocols (HUM00096559). All participants gave oral, informed consent before participation. The consent was documented by signature from one of the CHWs.

RESULTS

Of 481 women who were asked to participate through door-to-door recruitment, 212 women enrolled (44% acceptance rate), with 202 (95%) completing the survey. Ten women chose to withdraw, and their data were destroyed. Participants’ mean age was 34.5 years, and more than 80% had primary education at most (Table 1). One hundred thirty-five women (67%) reported previous CC screening with Pap smears and/or VIA (Table 1). Women with previous Pap smear and/or VIA testing tended to be older, married, and with a higher number of children and pregnancies, suggesting that access to screening is strongly tied to reproductive care. Whereas only 31 participants (15%) reported previous knowledge of HPV, 188 (93%) were interested in and willing to collect a self-sample for HPV testing (Table 2). Of these, 178 (88%) were eligible and provided a sample.

<table>
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<th>Characteristic</th>
<th>No.</th>
<th>%</th>
<th>Mean</th>
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<tbody>
<tr>
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<td></td>
</tr>
<tr>
<td>Not</td>
<td>2</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A little</td>
<td>3</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>69</td>
<td>34.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very</td>
<td>35</td>
<td>17.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremely</td>
<td>93</td>
<td>46.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CC, cervical cancer; HPV, human papillomavirus; IUD, intrauterine device; Q, quetzal; VIA, visual inspection with acetic acid.
Self-Collection Acceptability

Of these 178 women, 79% found the kit comfortable to use, and 91% found it easy to use. Upon collection, 100% reported that they were willing to use the test periodically as a form of CC screening, and more than 80% said they preferred to screen themselves at home rather than with a physician in a doctor’s office (Tables 2 and 3). Because identifying information was not collected, the study team was unable to actively return results; however, more than 90% of participants called to receive their own results.

HPV Prevalence

Thirty-seven (21%) of 178 women tested positive for one of 28 types of HPV, and 31 (17%) tested positive for a high-risk type (Table 3). HPV 16 had the highest prevalence with seven women testing positive, followed by HPV 53 and 56 (six women tested positive for each), and HPV 59 (five women tested positive). Of the four strains with the highest prevalence, all except HPV53 are high risk. Figure 1 shows the HPV type distribution in the study population.

HPV Infection

The number of lifetime sexual partners was significantly higher in women who tested positive for HPV. Characteristics comparing women by HPV test results can be found in Table 4; characteristics comparing women by their number of sexual partners can be found in the Data Supplement. Exposure covariates in the final model include current age, level of education, age at first pregnancy, and age at first sexual encounter. Other covariates were also explored, including age at marriage and other demographic factors.

After adjustment, the association became statistically nonsignificant, but it did show a prevalence ratio (PR) greater than 1 (crude PR, 2.18; 95% CI, 1.07 to 4.43; \( P = .03 \); adjusted PR, 1.42; 95% CI, 0.68 to 2.97; \( P = .34 \); regression tables are provided in the Data Supplement).

Previous Screening

The use of health services was statistically significantly higher in women who had a previous Pap smear or VIA. Characteristics of women with and without a history of screening are presented in Table 5, and characteristics of women categorized by use of health services are presented in the Data Supplement. The final adjusted model included age and education level, as well as the HPV test results. The participants’ use of alcohol, as well as other demographic factors, were considered but not included in the final model.

After adjustment, the association between use of health services and having had a previous Pap smear or VIA remained greater than 1 but was no longer significant (crude PR, 2.49; 95% CI, 1.26 to 4.93; \( P = .009 \); adjusted PR, 1.24; 95% CI, 0.93 to 1.66; \( P = .15 \); regression tables are provided in the Data Supplement).

DISCUSSION

We assessed the acceptability of HPV self-collection as an alternative to screening by using Pap smears or VIA in an indigenous community in Latin America. We found that self-collection kits had high acceptability and were preferred to physician screenings; a majority of women found the test kit comfortable and easy to use. We found a 17.4% prevalence of high-risk HPV, which is consistent with previous studies reporting a...
16.1% prevalence for Latin America. We also investigated risk factors for HPV infection and previous Pap smears or VIAs, associations that became statistically nonsignificant after adjustment for other covariates. This could be the result of inconsistencies with self-reporting or perhaps because their partner’s sexual history (which was not assessed) might be a stronger determinant of HPV risk in this community.

This study was intended to serve as a first step to determine the potential of HPV screening in indigenous populations and also to provide baseline data for future longitudinal studies assessing the efficacy of HPV testing versus other screening modalities. Perhaps the most relevant finding is the high acceptability of self-collection and the willingness of the participants to engage in the study. In fact, 95% of participants completed the survey, 93% were interested in collecting self-samples, and more than 90% called to receive their results, numbers higher than expected. The study was very well received in the community, with strong support from local and health authorities, suggesting the potential to eventually implement HPV screening programs in this and other similar settings.

Strengths of the study include the multiclustered community design, which allowed us to obtain a representative sample of the population, provided an opportunity for participants to try self-collection in their homes rather than at a clinic, and allowed local CHWs to perform recruitment and interviews. Because of the latter, interviews were conducted in the participants’ native language, potentially making them more comfortable answering sensitive questions. In addition, data were collected electronically.

### Table 4. Characteristics of HR HPV-Positive and HPV-Negative Participants in Guatemala (N = 178)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR HPV-Positive</th>
<th>HR HPV-Negative</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>Mean</td>
</tr>
<tr>
<td>No. of patients</td>
<td>31</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>Age, years*</td>
<td>35.4</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>Education†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No formal</td>
<td>12</td>
<td>38.7</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>17</td>
<td>54.8</td>
<td></td>
</tr>
<tr>
<td>More than primary</td>
<td>2</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Pap/VIA†</td>
<td>26</td>
<td>83.9</td>
<td></td>
</tr>
<tr>
<td>Daily income (Q)*</td>
<td>33.1</td>
<td>19.0</td>
<td></td>
</tr>
<tr>
<td>Lifetime sexual partners*</td>
<td>1.3</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Age at marriage, years*</td>
<td>17.4</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Literate†</td>
<td>18</td>
<td>58.1</td>
<td></td>
</tr>
<tr>
<td>Married/united†</td>
<td>26</td>
<td>83.9</td>
<td></td>
</tr>
<tr>
<td>Use health services†</td>
<td>31</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Use alcohol†</td>
<td>2</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Use Depo-Provera</td>
<td>21</td>
<td>67.7</td>
<td></td>
</tr>
<tr>
<td>Use birth control pill†</td>
<td>7</td>
<td>22.6</td>
<td></td>
</tr>
<tr>
<td>Use IUD†</td>
<td>2</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Use condom†</td>
<td>3</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>No. of pregnancies*</td>
<td>4.0</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>No. of children*</td>
<td>3.1</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Age at first pregnancy, years*</td>
<td>18.8</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Age at first sexual relation, years*</td>
<td>17.2</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Knowledge of HPV†</td>
<td>5</td>
<td>16.1</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. P values at <.05 significance level.
Abbreviations: HPV, human papillomavirus; HR, high risk; IUD, intrauterine device; Q, quetzal; SD, standard deviation; VIA, visual inspection with acetic acid.
* P value obtained by using independent t test.
† P value obtained by using χ² test.
which eliminated the risk of errors from manual data entry. However, there are also important limitations. Given the cross-sectional design, participants might have misreported their history of screening and other risk factors, especially if there had been community educational programs or interventions that suggested that women should be screened for CC. Women may not have accurately remembered whether they had previously had a Pap smear or VIA (recall bias) or may not even be aware of whether

Table 5. Characteristics of Participants Who Had or Had Not Received Previous Screening (N = 202)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Previous Pap/VIA</th>
<th>No Previous Pap/VIA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>135</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Age, years*</td>
<td>36.3 8.3</td>
<td>30.9 8.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Education†</td>
<td></td>
<td></td>
<td>.0486</td>
</tr>
<tr>
<td>No formal</td>
<td>53 39.3</td>
<td>27 40.3</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>63 46.7</td>
<td>22 32.7</td>
<td></td>
</tr>
<tr>
<td>More than primary</td>
<td>19 14.1</td>
<td>18 26.9</td>
<td></td>
</tr>
<tr>
<td>HR HPV positive†</td>
<td>26 20.47</td>
<td>5 9.8</td>
<td>.0897</td>
</tr>
<tr>
<td>Daily income (Q)*</td>
<td>33.6 19.9</td>
<td>31.2 19.5</td>
<td>.43</td>
</tr>
<tr>
<td>Lifetime sexual partners*</td>
<td>1.2 0.5</td>
<td>1.2 0.4</td>
<td>.61</td>
</tr>
<tr>
<td>Age at marriage, years*</td>
<td>18.8 3.4</td>
<td>20.1 4.3</td>
<td>.05</td>
</tr>
<tr>
<td>Literate†</td>
<td>80 59.3</td>
<td>43 64.2</td>
<td>.4999</td>
</tr>
<tr>
<td>Married/united†</td>
<td>132 91.9</td>
<td>51 76.1</td>
<td>.0065</td>
</tr>
<tr>
<td>Use health services†</td>
<td>129 95.6</td>
<td>52 77.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Frequency of health visits†</td>
<td></td>
<td></td>
<td>.142</td>
</tr>
<tr>
<td>Once a month or more</td>
<td>29 21.5</td>
<td>12 17.9</td>
<td></td>
</tr>
<tr>
<td>Every 3-6 months</td>
<td>51 37.8</td>
<td>18 26.9</td>
<td></td>
</tr>
<tr>
<td>Once a year or less</td>
<td>55 40.8</td>
<td>37 55.2</td>
<td></td>
</tr>
<tr>
<td>Time since last visit to health services, years†</td>
<td></td>
<td></td>
<td>.208</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>98 72.5</td>
<td>42 62.7</td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>23 17.1</td>
<td>12 17.9</td>
<td></td>
</tr>
<tr>
<td>&gt; 5</td>
<td>7 5.2</td>
<td>4 6.0</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>7 5.2</td>
<td>9 13.4</td>
<td></td>
</tr>
<tr>
<td>Breast examination†</td>
<td>9 6.7</td>
<td>1 1.5</td>
<td>.17</td>
</tr>
<tr>
<td>Mammogram†</td>
<td>7 5.2</td>
<td>0 0</td>
<td>.10</td>
</tr>
<tr>
<td>Use alcohol†</td>
<td>11 8.2</td>
<td>17 25.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Use Depo-Provera†</td>
<td>92 68.2</td>
<td>17 25.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Use birth control pill†</td>
<td>32 23.7</td>
<td>8 11.9</td>
<td>.0482</td>
</tr>
<tr>
<td>Use condom†</td>
<td>18 13.3</td>
<td>8 12</td>
<td>.78</td>
</tr>
<tr>
<td>No. of pregnancies*</td>
<td>3.7 2.5</td>
<td>2.1 4.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of children*</td>
<td>3.1 2.0</td>
<td>2.4 1.5</td>
<td>.0138</td>
</tr>
<tr>
<td>Age at first pregnancy, years*</td>
<td>20.1 4.1</td>
<td>21.0 3.8</td>
<td>.1878</td>
</tr>
<tr>
<td>Family member with CC†</td>
<td>8 5.9</td>
<td>5 7.5</td>
<td>.6951</td>
</tr>
<tr>
<td>Age at first sexual relation, years*</td>
<td>18.6 3.3</td>
<td>20.2 4.8</td>
<td>.0201</td>
</tr>
<tr>
<td>Knowledge of HPV†</td>
<td>23 17.0</td>
<td>7 10.5</td>
<td>.2150</td>
</tr>
</tbody>
</table>

NOTE. P values at <.05 significance level.
Abbreviations: CC, cervical cancer; HPV, human papillomavirus; HR, high risk; Q, quetzal; SD, standard deviation; VIA, visual inspection with acetic acid.
* P-value obtained by using independent t test.
† P-value obtained by using χ² test.
these procedures had been performed on them. Another limitation is that we were unable to assess whether HPV-positive women followed up on their results. This is the topic of our current work in multiple communities in Guatemala with a new study population that will be followed up after 6 months and 1 year.

In addition, this community has been exposed to prior health interventions and studies from multiple institutions.44-46 Although these studies did not specifically discuss HPV and CC, the exposure to health interventions could be reflected in the women’s knowledge of health issues and their willingness to try self-collection. In the future, it will be important to assess the acceptability of these tests in other indigenous communities with less exposure to studies and interventions.

The study results are consistent with those of previous studies conducted in Asia and Africa on the acceptability of self-screening for HPV.25,27,29 However, to the best of our knowledge, this is the first study to assess self-collection in indigenous populations in Latin America. This is also one of the first studies to provide an opportunity for participants to collect a sample in a community setting rather than simply sharing their feelings toward self-collection or collecting at a clinic.

This work assessed the acceptability of HPV self-screening in one community in Guatemala. Guatemala is a country with 23 languages and even more distinct communities, so our findings cannot be generalized to the whole population. It will be important to attempt to replicate the study in other parts of Guatemala and Latin America. Although it does seem that HPV self-collection screening could be a useful alternative to Pap smear or VIAs in these settings, this information alone does not allow us to make any determinations about whether this method of screening will reduce CC rates in developing countries. Women who tested positive for HPV should follow up with a doctor to receive Pap smears or VIAs or treatment. Hence, a logical next step would be to conduct longitudinal studies that compare rates of follow-up care among women who have tested positive with rates for those who have not been screened for HPV, as well as head-to-head comparisons between HPV-based versus Pap smear and VIA screening programs.47 It is also important to continue developing new affordable and easy-to-use tests that could readily be implemented in low-income settings.20-22

The Ministry of Health in Guatemala is in the process of refining the National Cervical Cancer Prevention and Control program.48 Following Pan-American Health Organization and WHO guidelines, the ministry has compiled a list of screening programs, some including HPV testing, that could be adopted. It will be the responsibility of each province (department) to determine which program best fits their needs and resources. We hope that our study, along with future evidence,49 will help local and regional authorities identify the best CC screening alternative for their own settings.

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AUTHOR CONTRIBUTIONS
Conception and design: Anna Gottschlich, Alvaro Rivera-Andrade, Christian Alvarez, Carlos Mendoza Montano, Rafael Meza
Collection and assembly of data: Anna Gottschlich, Alvaro Rivera-Andrade, Edwin Grajeda
Data analysis and interpretation: Anna Gottschlich, Rafael Meza
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF
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Anna Gottschlich
No relationship to disclose
Alvaro Rivera-Andrade
No relationship to disclose
Edwin Grajeda
No relationship to disclose
Christian Alvarez
No relationship to disclose
Carlos Mendoza Montano
No relationship to disclose
Rafael Meza
No relationship to disclose

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Affiliations
Anna Gottschlich, Christian Alvarez, and Rafael Meza, University of Michigan, Ann Arbor, MI; Alvaro Rivera-Andrade and Carlos Mendoza Montano, Institute of Nutrition of Central America and Panama; Carlos Mendoza Montano, Universidad Mariano Galvez de Guatemala; Edwin Grajeda, Universidad Rafael Landivar, Guatemala City, Guatemala; and Alvaro Rivera-Andrade, The Hebrew University, Jerusalem, Israel.

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REFERENCES


Neoadjuvant Chemotherapy With Capecitabine Plus Cisplatin in Patients With Locally Advanced Nasopharyngeal Cancer: Case Series Study

Purpose  Capecitabine, an oral fluorouracil (5-FU) derivative, has replaced 5-FU in many chemotherapy regimens used in various GI tract cancers. The experience with capecitabine in nasopharyngeal carcinoma (NPC) is limited.

Patients and Methods  We report on eight patients with locally advanced NPC treated with neoadjuvant chemotherapy with capecitabine and cisplatin.

Results  All eight patients responded well to the chemotherapy combination and achieved complete remission after definitive chemoradiotherapy. No grade 3/4 toxicities were observed. Five patients experienced a relapse after 6, 8, 9, 12, and 17 months.

Conclusion  In the patients studied, capecitabine (in combination with cisplatin) was a safe and effective substitution for 5-FU for the neoadjuvant treatment of locally advanced NPC. Larger prospective clinical studies are required to confirm these results.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a chemotherapy-sensitive cancer and more common in Asia, with a reported annual incidence in Far Asia of approximately 25-fold higher than in the Western world.1 Epstein-Barr virus plays an important role in the pathogenesis of NPC and induces tumor metastasis.2 Concurrent chemoradiotherapy (CCRT) is the standard for locally advanced NPC (LANPC). However, neoadjuvant chemotherapy (NAC) with cisplatin and 96 hours of infusional fluorouracil (5-FU) may reduce the radiotherapy field, and thus toxicity, and may improve long-term outcomes in select high-risk patients.3 Conventional infused 5-FU is an essential part of many chemotherapy regimens used to treat patients with head and neck cancer. At many institutions, it requires central venous access and hospitalization or the use of an ambulatory portable chemotherapy pumps (APCP), which causes substantial inconvenience to patients. Furthermore, central venous catheters can cause immediate and long-term complications, including pneumothorax, thrombosis, and sepsis.4 Capecitabine is an oral fluoropyrimidine carbamate that is metabolized to 5-FU through three steps of enzymatic reactions. It has replaced 5-FU in many chemotherapy regimens used to treat patients with various GI tract cancers. Several trials have demonstrated in patients with metastatic colorectal cancer that adjuvant capecitabine is well tolerated and has much of the same antitumor activity as 5-FU.5-7 Capecitabine is incorporated in chemotherapy regimens for many other tumor types, such as esophageal,8 gastric,9 and breast.10 Single-agent and combination regimens have also shown advantage in other cancer types, such as prostate, pancreatic, renal cell, and ovarian.11 The efficacy, safety, and convenience of the oral formulation make capecitabine an attractive option for patients with NPC.

PATIENTS AND METHODS

Cisplatin and 96 hours of infusional 5-FU is the standard regimen for the neoadjuvant treatment of patients with LANPC at our hospital. The treatment is administered intravenously in an inpatient setting or through an outpatient APCP. Intravenous 5-FU is substituted with oral capecitabine twice per
day on days 1 to 14 every 3 weeks for patients who refuse hospital admission, the placement of a central venous catheter, and the APCP. Patients who achieve excellent clinical response after the second cycle undergo early radiologic examination to confirm their response and are referred for radical CCRT and not undergoing the third cycle of NAC. Thereafter, all patients receive radical combined-modality chemotherapy (cisplatin 100 mg/m² once every 3 weeks) and radiation with the intensity-modulated radiation therapy administered according to standard hospital practice guidelines.

The follow-up protocol includes clinical examination with endoscopy every 2 to 3 months during the first year, every 4 to 6 months the second year, and every 6 to 12 months thereafter. Radiologic examination starts 2 to 3 months after the end of radiotherapy and is repeated every 6 months for the first 2 years.

We performed a retrospective case series study to analyze the outcome of patients with LANPC treated with neoadjuvant capecitabine and cisplatin followed by definitive CCRT.

RESULTS

Between March 2013 and June 2016, neoadjuvant capecitabine (with cisplatin) was administered to eight patients (six male and two female) with LANPC. Mean age was 47.8 years. All patients completed the neoadjuvant and combined-modality treatment. As a result of excellent clinical response in four patients, the induction therapy was stopped after two cycles. Computed tomography scans showed 25% complete and 85% partial remissions after NAC. Treatment was well tolerated without grade 3 to 4 toxicities. Furthermore, no dose reduction or delay of NAC cycles was necessary. No toxicity-related hospitalization occurred during NAC. All patients started radical combined-modality chemoradiotherapy (intensity-modulated radiation therapy) within 4 to 6 weeks after NAC. Radiologic response assessment was carried out 2 to 3 months after completion of the therapy. All patients achieved clinical and radiologic complete remission by the end of the planned treatment approach (NAC and CCRT). At the last follow-up (August 2016), three patients remained disease free and five experienced a relapse 6, 8, 9, 12, and 17 months after completing CCRT. All patients were alive at the last follow-up. Table 1 lists the patient characteristics and relevant adverse effects.

DISCUSSION

The patients treated with capecitabine had an excellent outcome with an acceptable adverse effect profile. There was no grade 3 to 4 toxicity. Although the drug is used in many GI tract chemotherapy protocols instead of 5-FU, it has not yet replaced 5-FU in chemotherapy regimens used in patients with head and neck cancer. Several phase II studies confirmed the effectiveness and tolerance of capecitabine combination in head and neck cancer.12-16 The recommended dose range of capecitabine in these studies was 825 to 1,250 mg/m². In addition, in the concurrent setting with radiotherapy, capecitabine seems to be effective with a manageable adverse effects profile.17,18,19 A randomized study in 153 patients with locally advanced squamous cell head and neck cancer showed a significantly better rate of complete response and better overall survival with concurrent cisplatin and capecitabine plus radiotherapy compared with cisplatin and 5-FU plus radiotherapy, with similar progression-free and overall survival.20

Data on capecitabine in NPC are scarce and mostly limited to patients with metastatic and refractory disease. These data from four small phase II studies examined the outcome and tolerance to capecitabine in metastatic/refractory NPC. The efficacy results were similar to conventional 5-FU but with better patient acceptance and, in general, a similar tolerability profile.21-24 To our knowledge, no data in the literature describe the use of capecitabine in neoadjuvant treatment of NPC apart from preliminary results of one recently reported study from China. In this randomized study in patients with LANPC, capecitabine and cisplatin were better tolerated than 5-FU and cisplatin (neutropenia and electrolyte disturbance) and were associated with better overall survival (hazard ratio, 0.57; 95% CI, 0.34 to 0.97).25

Some patients with head and neck cancer can present with dysphagia, which may preclude the routine use of oral formulation drugs. In patients without dysphagia, capecitabine oral treatment is considered an attractive and practical substitute to a long course of intravenous 5-FU infusion. The patients in this study expressed satisfaction with this treatment because it was well tolerated and allowed them more time away from the hospital. This approach relieves the burden on already-stretched health care resources by reducing bed occupancy. Furthermore, the treatment is
more convenient and safe for patients because it avoids the need for a central line that may be associated with complications.

In conclusion, capecitabine is an active and safe substitute for 5-FU in patients with LANPC treated in a neoadjuvant setting. Further validation in randomized clinical studies in patients with LANPC and metastatic NPC is required.

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AUTHOR CONTRIBUTIONS
Conception and design: All authors
Administrative support: Reyad Dada
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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Reyad Dada
No relationship to disclose
Mohamed El Sayed
No relationship to disclose
Jamal Zekri
No relationship to disclose

Affiliations
Reyad Dada, Mohamed El Sayed, and Jamal Zekri, King Faisal Specialist Hospital and Research Center, Jeddah; Reyad Dada and Jamal Zekri, Al-Faisal University, Riyadh, Kingdom of Saudi Arabia; and Mohamed El Sayed, Cairo University, Cairo, Egypt.

REFERENCES

Table 1. Patient Characteristics and Capecitabine-Related Adverse Effects During NAC

<table>
<thead>
<tr>
<th>Characteristic</th>
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<th>2</th>
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Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; NAC, neoadjuvant chemotherapy.


Purpose Lung cancer is the most common cause of cancer mortality in the world. There are limited studies on survival outcomes of lung cancer in developing countries such as India. This study analyzed the outcomes of patients with lung cancer who underwent treatment at Cancer Institute (WIA), Chennai, India, between 2006 and 2015 to determine survival outcomes and identify prognostic factors.

Patients and Methods In all, 678 patients with lung cancer underwent treatment. Median age was 58 years, and 91% of patients had non–small-cell lung cancer (NSCLC). Testing for epidermal growth factor receptor mutation was performed in 132 of 347 patients and 61 (46%) were positive.

Results Median progression-free survival was 6.9 months and overall survival (OS) was 7.6 months for patients with NSCLC. Median progression-free survival was 6 months and OS was 7.2 months for patients with small-cell lung cancer. On multivariable analysis, the factors found to be significantly associated with inferior OS in NSCLC included nonadenocarcinoma histology, performance status more than 2, and stage. In small-cell lung cancer, younger age and earlier stage at presentation showed significantly better survival.

Conclusion Our study highlights the challenges faced in treating lung cancer in India. Although median survival in advanced-stage lung cancer is still poor, strategies such as personalized medicine and use of second-line and maintenance chemotherapy may significantly improve the survival in patients with advanced-stage lung cancer in developing countries.

INTRODUCTION
Lung cancer is one of the most common causes of cancer-related deaths worldwide. In India, lung cancer accounts for 9.3% of all cancer-related deaths in both sexes.1 There are few studies on survival outcomes of lung cancer in India. This study analyzed outcomes in patients with lung cancer treated at our center and identified prognostic factors.

PATIENTS AND METHODS
Clinical and treatment details of all consecutive patients with lung cancer who underwent treatment at our center between January 2006 and June 2015 were collected and analyzed retrospectively. The study was approved by the Institute Ethics Committee. Never-smokers were defined as those who had smoked fewer than 100 cigarettes during their lifetime; ever smokers were defined as those who had smoked 100 cigarettes or more during their lifetime.2 Diagnosis was established by core needle biopsy or fine-needle aspiration cytology. Histopathologic examination and immunohistochemistry were performed to classify non–small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC was further categorized as adenocarcinoma, squamous cell carcinoma, or poorly differentiated carcinoma. Molecular testing for epidermal growth factor receptor (EGFR) mutation was begun in our center in 2012, and testing for anaplastic lymphoma kinase (ALK) translocation was begun in 2014. EGFR mutation analysis was performed by using reverse transcriptase polymerase chain reaction, and ALK translocation analysis was performed by immunohistochemistry using an anti-ALK rabbit monoclonal antibody (Ventana Medical Systems, Tucson, AZ).3 Molecular testing was performed only in patients who had adequate tissue material for analysis. For staging, patients underwent contrast-enhanced computed tomography (CT) scanning of the chest, ultrasound scan of the abdomen and pelvis, and bone scan or whole-body positron emission tomography (PET)/CT scanning. In addition, patients with SCLC underwent bone marrow trephine biopsy.
Treatment was based on physician discretion and patient choice. Responses were assessed by using chest x-ray, contrast-enhanced CT, or PET/CT after four cycles of intravenous chemotherapy. Assessments were performed at the physician’s discretion between 3 and 6 months after the start of tyrosine kinase inhibitors (TKIs) and repeated again at the same intervals. Radiologic assessment was also performed if the patient had signs and symptoms of disease progression at any time during follow-up. Response Evaluation Criteria in Solid Tumors (RECIST) was used for assessment of response.4 Patients who were started on treatment and were followed up for at least one visit or those whose outcome was known were included in the survival analysis. Patients who were started on treatment and died before response assessment were also included. Patients who did not complete the first follow-up visit and those whose survival status was not known were not included.

Progression-free survival (PFS) was calculated from date of initiation of treatment to date of disease progression or relapse. Overall survival (OS) was calculated from date of initiation of treatment to date of last follow-up or date of death. For survival analysis, all patients were censored at date of last follow-up or date of contact by telephone or mail if they were lost to follow-up or on December 31, 2015, whichever was earlier. PFS and OS were analyzed by the Kaplan-Meier method, and risk factors were compared by using the log-rank test for univariable analysis and a Cox proportional hazards model for multivariable analysis. SPSS version 17.0 (SPSS, Chicago, IL) was used for statistical analysis.

RESULTS

During the study period, 1,039 patients were registered in the hospital with a diagnosis of lung cancer. Records were available for 1,006 patients. Of these, 866 patients had histologically proven lung cancer. One hundred twenty-six of 866 patients did not receive any treatment because of either poor performance status (PS) or patient preference. Sixty-two patients began treatment but had no follow-up details and thus were excluded from the survival analysis. A total of 678 patients underwent treatment for lung cancer and had at least one follow-up visit; they were included in the outcome analysis.

Baseline Characteristics

The median age was 58 years (range, 20 to 83 years). Males constituted 516 (76%) of 678 patients. Cough was the most common presenting complaint seen in 302 (44.5%) of 678 patients. Lung cancer was incidentally detected in nine (1.3%) of 678 patients (Table 1). History of smoking was present in 362 (53.4%) of 678 patients, and the median number of pack-years was 20 (range, 3 to 80 pack-years). Thirty (4.5%) of 678 patients had a previous history of tuberculosis. The majority of the patients had a PS of 1 or 2.

Diagnosis and Pathology

Diagnosis of lung cancer was confirmed by using excision or guided core needle biopsy in 497 (74%) of 678 patients or by using fine-needle aspiration cytology in 181 (26%) of 678 patients. NSCLC was diagnosed in 616 (91%) of 678 patients and SCLC was diagnosed in 62 (9%) of 678 patients. The most common histologic subtype among patients with NSCLC was adenocarcinoma, which was recorded in 347 (56.3%) of 616 patients followed by squamous cell carcinoma in 109 (17.7%) of 616 patients. A total of 132 samples were tested for EGFR mutation, of which 61 (46.2%) were positive. Exon 19 was the most common type of EGFR mutation and was observed in 20 (33%) of 61 patients. Exact type of EGFR mutation was not known in 19 patients. Testing for ALK mutation was performed in 32 patients with adenocarcinoma of whom two (6.25%) were found to be positive.

Staging and Treatment

NSCLC. NSCLC was diagnosed in 616 (91%) of 678 patients. The majority of patients presented with disseminated disease: 411 (67%) of 616 were stage IV, and the most common site of metastasis was bone in 126 (31%) of 411. Ninety-seven patients (23.2%) had more than one site of metastasis. Among patients with stage III disease, 12 (7%) of 169 received oral gefitinib empirically because they were not eligible for surgery or radiotherapy. Of the remaining 34 patients, 19 underwent only surgical resection, nine received adjuvant chemotherapy after surgical resection, two received neoadjuvant chemotherapy followed by surgery, and four received definitive radiotherapy only. Among 169 patients with stage IV disease, 12 (7%) of 169 received oral TKIs, and two (1%) of 169 underwent surgery followed by adjuvant chemotherapy. Thirty-six (21%) of 169 patients received concurrent chemotherapy and radiotherapy, and 39 (23%) of 169 received chemotherapy followed by sequential radiotherapy. The remaining 80 patients received either intravenous or oral chemotherapy only. Among 411 patients with stage IV disease, 169
of 411 received intravenous chemotherapy, and 179 (43.5%) of 411 received oral EGFR TKIs such as gefitinib or erlotinib as first-line therapy. Sixty-one patients received only oral etoposide because they were deemed ineligible for intravenous chemotherapy, and two received only radiotherapy for the same reason. Among patients with metastatic disease who received intravenous chemotherapy, 70 (42%) of 169 received gemcitabine and platinum doublet. Fifty-eight (35%) of 169 patients received pemetrexed and platinum doublet, which was used mostly after 2012 when generic medications became available. Twenty-six patients received maintenance pemetrexed chemotherapy after completing four or six cycles of initial chemotherapy.

SCLC. Sixty-two patients (9%) were diagnosed with SCLC, and 51 (82%) of 62 were ever smokers. The majority of patients presented with disseminated disease: 36 (58%) of 62 were stage IV, and the most common site of metastasis at presentation was bone in 15 (42%) of 36 patients. Seven patients (19%) had more than one site of metastasis. Among 26 patients with stage III disease, one patient received intravenous chemotherapy only, and three patients received only oral etoposide because of poor general condition. Thirteen (50%) of 26 patients received concurrent chemotherapy and radiotherapy, and nine (35%) of 26 received chemotherapy followed by sequential radiation. Among 36 patients with stage IV disease, 22 (61%) of 36 received intravenous chemotherapy and 14 (39%) of 36 received oral etoposide only because they were deemed ineligible for intravenous chemotherapy. Among patients with metastatic disease who received intravenous chemotherapy, 14

<table>
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<th>Table 1. Baseline Characteristics</th>
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Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer; PS, performance status; SCLC, small-cell lung cancer.

(Continued in next column)
(67%) of 22 received cisplatin and etoposide doublet and eight (23%) of 22 received carboplatin and etoposide doublet.

Survival Outcomes in NSCLC

Of the 678 patients with lung cancer in our study, 616 were found to have NSCLC, and survival outcomes were analyzed for that group. Median duration of follow-up was 6.3 months (range, 0.1 to 108.1 months). Median PFS for patients with all stages of NSCLC was 6.9 months, and median OS was 7.6 months (Fig 1). Survival status was not known for 91 patients because they could not be contacted by telephone or mail. Thus, they were censored to be alive for survival analysis. On univariable analysis, smoking, alcohol consumption, histologic subtype of NSCLC, PS, disease stage, and sex were significant predictors of OS (Table 2). On multivariable analysis, histology, stage, and PS were significant predictors of OS (Data Supplement). Disease stage and PS were significant predictors of PFS on univariable analysis (Table 2) and multivariable analysis.

The 1-year survival for patients with stage I disease (n = 19) was 83%, and it was 76% for those with stage II disease (n = 17; Data Supplement). Patients with stage IV disease (n = 411) had a median PFS of 5.7 months and a median OS of 6.5 months (P < .001). In patients with stage IV NSCLC who received first-line intravenous chemotherapy, the median OS had not yet been reached in those who received pemetrexed combinations (n = 58). Patients with stage III NSCLC who received concurrent chemotherapy and radiotherapy (n = 36) had better PFS (31% vs 8%; P = .29) and OS (30% vs 0%; P = .51) compared with those who received chemotherapy followed by sequential radiotherapy (n = 39). Patients with stage IV NSCLC who received maintenance chemotherapy (n = 26) had a median PFS of 9.6 months and a median OS of 24.9 months.

Second-line treatment was given to 107 (26%) of 411 patients with stage IV disease on progression, among whom 63 of 107 received intravenous chemotherapy and 44 of 107 received oral TKIs. The median PFS was 3.6 months for second-line treatment, 4.1 months for oral TKIs, and 3.46 months for intravenous chemotherapy.

Survival Outcomes in SCLC

Sixty-two of 678 patients with lung cancer were found to have SCLC. Median duration of follow-up was 6.1 months (range, 0.7 to 54 months). Median PFS for all stages was 6.0 months, and median OS for all stages was 7.2 months (Fig 2; Table 3).

Age and stage at presentation were the only two factors that were significantly associated with survival in patients with SCLC (Table 3). Patients with SCLC who presented with stage III disease and received concurrent chemotherapy and radiotherapy had better PFS (46.2% vs 33.3%; P = .53) and OS (24% vs 0%; P = .43) compared with those who received sequential chemotherapy and radiotherapy, but it was not statistically significant. Second-line chemotherapy was given to 16 of 62 patients, and the median PFS was 2.9 months.

DISCUSSION

Treatment of advanced lung cancer in India is accompanied by a unique set of challenges. Access to quality oncologic care is limited because of the scarcity of resources and qualified professionals. The cost of mutation analysis for patients with lung cancer in India is still substantial. With the advent of generic drugs, the cost of EGFR TKIs has substantially decreased making them...
Table 2. Univariable Analysis of Prognostic Factors for NSCLC for All Stages (n = 616 except where noted)

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<th>P*</th>
<th>Median OS (months)</th>
<th>P*</th>
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Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer; NR, not reached; OS, overall survival; PFS, progression-free survival; PS, performance status.
*Log-rank test.
affordable for a wider patient population. However, ALK inhibitors are still prohibitively expensive and are expected to remain so for the foreseeable future. There are only a few studies in India that have reported outcome data in patients with advanced-stage NSCLC (Table 4).

In our study, the median age of presentation was 58 years, which is a decade younger compared with the European population, but it is comparable to that in other reports from India. The majority of patients (53.4%) in our study were smokers. This is a lower rate than in other studies.

**Table 3.** Univariable Analysis of Prognostic Factors for SCLC (n = 62)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>%</th>
<th>Median PFS (months)</th>
<th>P</th>
<th>Median OS (months)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>40</td>
<td>64.5</td>
<td>8.2</td>
<td>.008</td>
<td>8.3</td>
<td>.132</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>22</td>
<td>35.5</td>
<td>4.8</td>
<td></td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54</td>
<td>87</td>
<td>6</td>
<td>.42</td>
<td>6.1</td>
<td>.1</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>13</td>
<td>5.5</td>
<td></td>
<td>15.6</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51</td>
<td>82.2</td>
<td>5.3</td>
<td>.846</td>
<td>6.2</td>
<td>.405</td>
</tr>
<tr>
<td>No</td>
<td>11</td>
<td>17.8</td>
<td>6</td>
<td></td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36</td>
<td>58.1</td>
<td>6</td>
<td>.94</td>
<td>6.8</td>
<td>.86</td>
</tr>
<tr>
<td>No</td>
<td>26</td>
<td>41.9</td>
<td>5</td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>History of tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>4.8</td>
<td>4.3</td>
<td>.64</td>
<td>8</td>
<td>.23</td>
</tr>
<tr>
<td>No</td>
<td>59</td>
<td>95.2</td>
<td>5.9</td>
<td></td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>33</td>
<td>53.2</td>
<td>9.2</td>
<td>.061</td>
<td>9.2</td>
<td>.059</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>43.5</td>
<td>4.9</td>
<td></td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>3.3</td>
<td>2.1</td>
<td></td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
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</tr>
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<td>1</td>
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<td></td>
<td></td>
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<tr>
<td>2</td>
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<td></td>
</tr>
<tr>
<td>3</td>
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<td></td>
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</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Abbreviations: ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression-free survival; PS, performance status; SCLC, small-cell lung cancer. 

*Log-rank test.
in North India but is comparable to that in other studies in South India. This may reflect the variations in tobacco consumption practices among different geographic regions in India. In our study, 76% of the patients were males which may be a result of decreased smoking habits among women. This is lower compared with the distribution of the sexes in other international studies, but it is comparable to data from other Indian centers.

The majority of the patients in our study had adenocarcinoma histology (51%). This is consistent with other Indian studies in the current era and indicates a shift from predominantly squamous histology as was observed earlier and may reflect changes in smoking practices and the increasing use of filtered cigarettes. Most of our patients presented with advanced lung cancer with 66% having stage IV disease at diagnosis. However, this is comparable to other Indian studies and indicates a delay in seeking treatment.

Most of the patients in this study (89.7%) had a PS of 1 or 2. This was higher than what has been observed in other Indian studies, probably because our study included only those patients who received some form of treatment. Patients with poor PS were referred for best supportive care at a nearby palliative care center. However, none of our patients had a PS of 0 at presentation.

Evaluation of tumors for EGFR mutation was started in 2012; at that time, 132 patients were examined and 46% of tumors were positive for an EGFR mutation. This is higher than in other studies performed in India by Doval et al (33%) and Bhatt et al (31.3%), possibly as a result of selection bias because the testing was aimed more at female patients and never-smokers. In the study titled “First Line IRETTA Versus Carboplatin/Paclitaxel in Asia (IPASS)” in East Asia in which only a selected population of nonsmokers with adenocarcinoma of the lung were included, EGFR mutations were present in 59.7%. In our study, the most common sites of EGFR mutation were deletion in exon 19 and mutation at exon 21 (L858R). Together, these accounted for 62% of the mutations. These two mutations were also the predominant mutations in the IPASS study. Approximately 6% of the patients in our study tested positive for ALK translocation. This is higher compared with results from other centers (2.7% to 3%) in India. This might be a result of the use of immunohistochemistry rather than fluorescent in situ hybridization for detecting translocations.

Although the survival outcomes in this study are similar to those in another study from South India, they are inferior to the outcomes from other studies in North India. The median PFS was 6.9 months for patients with NSCLC in our study and 7.8 months in the study by Malik et al. We analyzed the patients in our study from date of treatment initiation, unlike

### Table 4. Comparison of Demographics, Clinical Profiles, and Survival Outcomes in Various Studies of Lung Cancer in India

<table>
<thead>
<tr>
<th>Factor</th>
<th>Behera et al⁶ (Chandigarh)</th>
<th>Malik et al⁸ (Delhi)</th>
<th>Rajappa et al⁷ (Hyderabad)</th>
<th>Bhatt et al⁹ (Mumbai)</th>
<th>This Study (Chennai)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>1,009</td>
<td>434</td>
<td>194</td>
<td>1,385</td>
<td>678</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>54.3</td>
<td>55</td>
<td>58</td>
<td>57</td>
<td>58</td>
</tr>
<tr>
<td>Males: females</td>
<td>—</td>
<td>4.2:1</td>
<td>4.1</td>
<td>1.96:1</td>
<td>3.16:1</td>
</tr>
<tr>
<td>Ever smokers: never-smokers</td>
<td>2.7:1</td>
<td>2.1</td>
<td>1.45:1</td>
<td>1:1.6</td>
<td>1.14:1</td>
</tr>
<tr>
<td>Histology (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>25.9</td>
<td>45.4</td>
<td>—</td>
<td>86.7</td>
<td>51.1</td>
</tr>
<tr>
<td>Squamous carcinoma</td>
<td>34.3</td>
<td>29.4</td>
<td>—</td>
<td>—</td>
<td>16</td>
</tr>
<tr>
<td>Poorly differentiated carcinoma</td>
<td>12.2</td>
<td>26.54</td>
<td>—</td>
<td>—</td>
<td>23.5</td>
</tr>
<tr>
<td>Small-cell carcinoma</td>
<td>—</td>
<td>14.7</td>
<td>—</td>
<td>—</td>
<td>9.4</td>
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<tr>
<td>Stage (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>—</td>
<td>2.67</td>
<td>—</td>
<td>0</td>
<td>2.8</td>
</tr>
<tr>
<td>II</td>
<td>—</td>
<td>8</td>
<td>—</td>
<td>0.2</td>
<td>2.5</td>
</tr>
<tr>
<td>III</td>
<td>—</td>
<td>28.91</td>
<td>58</td>
<td>7.7</td>
<td>28.7</td>
</tr>
<tr>
<td>IV</td>
<td>—</td>
<td>56.75</td>
<td>42</td>
<td>92.1</td>
<td>66</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>—</td>
<td>7.8</td>
<td>6</td>
<td>—</td>
<td>6.9</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>—</td>
<td>12.8</td>
<td>7</td>
<td>19.7</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Abbreviations: OS, overall survival; PFS, progression-free survival.
Malik et al who analyzed patients from date of presentation to the hospital; assessment of response was also performed earlier in our study compared with theirs. These factors could account for the improvement of 1 month in PFS in their study. Our median OS was 7.6 months, whereas Malik et al reported a median OS of 12.8 months; however, the majority of our patients with stage IV disease (74%) did not receive second-line chemotherapy. Details about second-line or maintenance treatment were not available in the article by Malik et al. Bhatt et al did not report on median PFS, second-line treatment, or response assessment in their study.

In patients who had EGFR-positive stage IV NSCLC, the median PFS was 11.1 months and median OS was 14.1 months, which is comparable to those in other studies performed worldwide. Patients who had EGFR-negative stage IV NSCLC had a significantly better PFS and OS with pemetrexed-based chemotherapy regimens. The combination of cisplatin and etoposide showed a better OS (8.4 months) compared with all other regimens; thus, use of this regimen is still a reasonable option in a resource-challenged setting.

Concurrent chemotherapy and radiotherapy was associated with better OS compared with chemotherapy followed by sequential radiation in both SCLC and NSCLC, although this was not statistically significant. Thus, in all eligible patients, concurrent chemotherapy and radiotherapy should be considered as the treatment modality of choice.

Use of maintenance pemetrexed in stage IV NSCLC led to a better OS, which demonstrates the role of maintenance chemotherapy in stage IV NSCLC. In our study, patients who received maintenance chemotherapy had a median PFS of 9.6 months and median OS of 24.9 months. In a study by Pandey et al of maintenance pemetrexed for 188 patients, the median PFS was 8 months and median OS was 20 months. However, the retrospective nature of this study precludes us from making conclusions.

There is a paucity of data on SCLC in India. In SCLC, on univariable analysis, only stage of disease was shown to significantly affect OS in this study. The study by Malik et al included 64 patients with SCLC. Median PFS (6.8 v 6 months) and OS (9.1 v 7.2 months) were higher compared with those in this study.

Our results are limited by their retrospective nature and the fact that widely heterogeneous treatment modalities were used over a period of 9 years. Mutation testing was not performed in many patients for economic reasons. The final survival analysis did not include 62 of 866 patients who received treatment but did not have any follow-up and 126 of 866 patients who did not receive any treatment because of poor PS or patient preference. About 14% of patients were lost to follow-up (91 of 616). The above issues related to data are confounding factors in our analysis and may have a significant impact on projected survival for patients with lung cancer in India. However, unlike controlled conditions in a trial, these data reflect circumstances in the field.

Lung cancer is a common cause of cancer-related mortality in India, and the majority of patients do not receive adequate therapy. This could be improved by early diagnosis, appropriate treatment, and subsequent second-line therapy if required. The ability to select patients for detection of EGFR mutations in their tumors has improved, thus allowing them to have optimal treatment. Really making an impact on mortality resulting from lung cancer in India requires strong public health measures to control tobacco use. Fortunately, this is now being increasingly recognized by the government and provides hope for the future.

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Aditya Navile Murali  
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Venkatraman Radhakrishnan  
No relationship to disclose  

Trivadi S. Ganesan  
No relationship to disclose  

Rejiv Rajendranath  
Consulting or Advisory Role: Bristol-Myers Squibb, Eli Lilly  

Prasanth Ganesan  
No relationship to disclose  

Ganesarajah Selvaluxmy  
No relationship to disclose  

Rajaraman Swaminathan  
No relationship to disclose  

Shirley Sundersingh  
No relationship to disclose  

Arvind Krishnamurthy  
No relationship to disclose  

Tenali Gnana Sagar  
No relationship to disclose  

Affiliations  
All authors: Cancer Institute (WIA), Adyar, Chennai, India.

REFERENCES  

Awareness and Perception About Cancer Among the Public in Chennai, India

**Abstract**

**Purpose** Cancer-related stigma influences the way people perceive cancer, which renders cancer control—beginning with prevention and proceeding to palliation—a challenging task. This study aimed to assess the current levels of awareness and perceptions about cancer among people with various socioeconomic status and diverse backgrounds in the city of Chennai, India.

**Patients and Methods** The sample population (N = 2,981; 18 to 88 years of age) was stratified into four groups: patients (n = 510), caregivers (n = 494) consulting at the Cancer Institute (Women Indian Association), college students (n = 978), and general public (n = 999). Fourteen statements related to cancer stigma or myths were identified and categorized by awareness (10 items) or perception (4 items). Responses to those statements were recorded by using a Likert scale (yes, no, and don’t know). The data were described by frequency analysis and \( \chi^2 \) test using SPSS Version 13 (SPSS, Chicago, IL).

**Results** More than 70% of the study participants were aware that cancer is curable, that cancer is not contagious, and that cancer is not a curse or a death sentence. However, only approximately half believed that surgery or biopsy do not cause cancer to spread to other organs or that radiation therapy does not consist of receiving an electric shock. Higher education, younger age, male sex, personal experience with cancer (either as a patient or caregiver), and high socioeconomic status were the categories of people with increased awareness about cancer.

**Conclusion** These factors need to be taken into consideration in tailoring information, education, and communication campaigns. Resource allocation for these campaigns is an investment in cancer control.

**INTRODUCTION**

Cancer has long been one of the most feared diseases, widely regarded to be synonymous with death.\(^1\)-\(^5\) In India, the annual burden for new cancers is approximately one million, and the mortality rate is 67.2 per 100,000,\(^6\) which is primarily the result of late diagnosis. Lack of awareness fuels many myths and misconceptions related to cancer, which perpetuates the stigma associated with it.\(^7\),\(^8\) This stigma influences the way people perceive cancer, which renders cancer control—beginning with prevention and proceeding to palliation—a challenging task. This study aimed to assess the current levels of awareness and perceptions about cancer among people with various socioeconomic status (SES) and diverse backgrounds in the city of Chennai, India.

**PATIENTS AND METHODS**

The study was conducted in Chennai, which is a metropolitan city that is transitioning into a cosmopolitan city. The residents come from different strata of society ranging from the slums to posh areas. The population sample (N = 2,981) was stratified into four groups: patients (n = 510), caregivers (n = 494), college students (n = 978), and general public (n = 999); a total of 2,981 responses were elicited. The responses were stratified to adjust for possible variability in the level of understanding and sociocultural aspects. The sample size was determined under each category to ensure adequate representation of even the rarest subcategories within the four major groups of respondents.

The patients consulting with physicians at the Cancer Institute (Women Indian Association [WIA]) were randomly sampled from both nonpaying (n = 246) and paying (n = 264) categories. Persons accompanying patients (caregivers), at the Cancer Institute (WIA), were randomly chosen from nonpaying (n = 250) and paying (n = 244) categories. Four administrative zones of the city and streets of Chennai that included slum (n = 513) and nonslum (n = 486) populations were defined; members of the general public were randomly chosen from those areas. Because it was difficult to obtain uniform and
reliable information on family income from all the categories of people, their SES was categorized as lower SES (LSES) and higher SES (HSES). The LSES group included people living in urban informal settlements (slums), and patients and caregivers from no paying category. The HSES group included patients and caregivers from the paying category and the general public from nonslum areas. Fields of study for college students were arts and science (n = 320), polytechnic subjects (n = 327), or engineering (n = 321). Respondents were chosen alternately to achieve equal sex distribution.

A list of statements related to cancer stigma or myths were identified and presented to six experts. On the basis of their inputs, 14 items were shortlisted and categorized under awareness or perception. Responses associated with definite knowledge or information were categorized under awareness (10 items) and those not associated with a definite answer were categorized under perception (four items). The responses were recorded by using a Likert scale (yes, no, and don’t know). The items were printed in both Tamil and English. Written consent was obtained from all participants. The participants who were conversant in either language were given the form for self-administration. For those without any formal education, the items were read aloud by trained social workers or psychologists. The responses for the 10 items relating to awareness were categorized into two groups—correct responses (aware), and incorrect responses or a response of don’t know (unaware). The responses for the four items categorized under perception were yes, no, and don’t know.

The data were described by using frequency analysis, and the χ² test was used to find the association between cancer awareness and perception across age, sex, SES, and categories of people. SPSS Version 13 (SPSS, Chicago, IL) was used for analyses.

**RESULTS**

**Sample Details**

The median age of participants was 28 years of age (range, 18 to 88 years), with almost equal representation of men (50.5%) and women (49.5%).

The median age, excluding the student category, was 38 years. A majority of responders were literate (94%) and had completed primary school (10.1%) or secondary school (27.8%) or had earned a diploma (12.8%) along with college undergraduates (13%) and postgraduates (30.3%). Age was categorized into four groups: younger than 25 years of age (44.6%), 25 to 39 years of age (26%), 40 to 59 years of age (12.1%), and 60 years of age or older (17.2%). All the participants were categorized into one of the following categories: general public (33.5%), students (32.8%), patients with cancer (17.1%), and caregivers (16.6%).

**Awareness Among Respondents Overall**

More than half of the respondents (53.5%) believed that radiation treatment means receiving an electric shock; this item showed the lowest level of awareness among all items. The maximum level of awareness (90%) was elicited from the item that only poor people get cancer. A majority of respondents (83.5%) were aware that cancer is not contagious, that it is not a curse (83.3%), that it can be cured (79.5%), and that it is not a death sentence (74.6%). About one fifth of respondents (22.9%) believed that herbal and expensive tobacco products do not cause cancer.

**Education**

The proportion of respondents with awareness was observed to increase with education level for almost all the items studied (Table 1). Awareness of the following items was greater among college students compared with the participants who had only some schooling and did not have any formal education: Cancer can spread from one person to another (χ² [2, N = 2,981] = 100.869; P < .000); cancer is a curse (χ² [2, N = 2,981] = 33.733; P < .000); only poor people get cancer (χ² [2, N = 2,981] = 25.918; P < .000); and surgery or biopsy causes the spread of cancer (χ² [2, N = 2,981] = 28.799; P < .000). Regarding the item about the curability of cancer, participants in both the school and college categories had more awareness than those who did not have formal education (χ² [2, N = 2,981] = 7.345; P = .025). This was similar regarding the item that only old people get cancer; participants with no formal education had less awareness (χ² [2, N = 2,981] = 33.733; P = .044). Participants who were literate were more aware than those who did not have formal education that expensive cigarettes also cause cancer (χ² [2, N = 2,981] = 13.356; P = .001); radiation therapy does not mean that an electric shock is given (χ² [2, N = 2,981] = 55.377; P < .000); and cancer patients can lead a normal life after treatment (χ² [2, N = 2,981] = 17.150; P < .000).

**Sex**

Men showed more awareness than women on most items (Table 1): cancer is contagious
Table 1. Cancer-Related Awareness Among Respondents With Different Levels of Education and Different Sex

<table>
<thead>
<tr>
<th>Item No.</th>
<th>Item</th>
<th>No Formal Education</th>
<th>School</th>
<th>College</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>1</td>
<td>Cancer can spread from one person to another</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aware</td>
<td>128</td>
<td>71.9</td>
<td>865</td>
<td>76.5</td>
<td>1,498</td>
</tr>
<tr>
<td></td>
<td>Unaware</td>
<td>50</td>
<td>28.1</td>
<td>265</td>
<td>23.5</td>
<td>176</td>
</tr>
<tr>
<td>2</td>
<td>Cancer is a curse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aware</td>
<td>124</td>
<td>69.7</td>
<td>922</td>
<td>81.7</td>
<td>1,437</td>
</tr>
<tr>
<td></td>
<td>Unaware</td>
<td>54</td>
<td>30.3</td>
<td>207</td>
<td>18.3</td>
<td>237</td>
</tr>
<tr>
<td>3</td>
<td>Cancer can be cured</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aware</td>
<td>134</td>
<td>75.3</td>
<td>924</td>
<td>81.9</td>
<td>1,312</td>
</tr>
<tr>
<td></td>
<td>Unaware</td>
<td>44</td>
<td>24.7</td>
<td>204</td>
<td>18.1</td>
<td>362</td>
</tr>
<tr>
<td>4</td>
<td>Cancer is a death sentence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aware</td>
<td>115</td>
<td>64.4</td>
<td>804</td>
<td>71.2</td>
<td>1,305</td>
</tr>
<tr>
<td></td>
<td>Unaware</td>
<td>63</td>
<td>35.6</td>
<td>325</td>
<td>28.8</td>
<td>309</td>
</tr>
<tr>
<td>5</td>
<td>Only poor people get cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aware</td>
<td>144</td>
<td>80.9</td>
<td>1,007</td>
<td>89.2</td>
<td>1,542</td>
</tr>
<tr>
<td></td>
<td>Unaware</td>
<td>34</td>
<td>19.1</td>
<td>122</td>
<td>10.8</td>
<td>132</td>
</tr>
<tr>
<td>6</td>
<td>Surgery or biopsy causes cancer to spread to other parts of the body</td>
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\(\chi^2 [1, N = 2,981] = 23.470; P < .000\); cancer is a curse \(\chi^2 [1, N = 2,981] = 17.493; P < .000\); cancer is incurable \(\chi^2 [1, N = 2,981] = 7.017; P = .008\); cancer is a death sentence \(\chi^2 [1, N = 2,981] = 5.332; P = .021\); surgery or biopsy causes cancer to spread to other organs \(\chi^2 [1, N = 2,981] = 12.730; P < .000\); and patients with cancer can never
return to a normal life ($\chi^2 [1, N = 2,981] = 4.502; P = .034$).

Age
Awareness was the lowest among those 60 years of age or older than those in other age groups for most items (Table 2): cancer is contagious ($\chi^2 [3, N = 2,981] = 21.106; P < .000$); cancer is a curse ($\chi^2 [3, N = 2,981] = 45.893; P < .000$); cancer can be cured ($\chi^2 [3, N = 2,981] = 15.567; P = .001$); cancer is a death sentence ($\chi^2 [3, N = 2,981] = 8.283; P = .041$); only poor people get cancer ($\chi^2 [3, N = 2,981] = 13.949; P = .003$); surgery or biopsy causes cancer to spread to other parts of the body ($\chi^2 [3, N = 2,981] = 24.613; P < .000$); current treatment means giving the patient electric shocks to destroy cancer cells ($\chi^2 [3, N = 2,981] = 45.439; P < .000$); and patients with cancer can never return to a normal life ($\chi^2 [3, N = 2,981] = 11.071; P = .011$).

SES
The differences in awareness between participants with LSES and HSES were statistically significant for only four items (Table 2): cancer is contagious ($\chi^2 [1, N = 2,003] = 66.002; P > .000$); cancer is curable ($\chi^2 [1, N = 2,003] = 5.086; P > .024$); only poor people get cancer ($\chi^2 [1, N = 2,003] = 4.673; P > .031$); and current treatment means giving the patient electric shocks to destroy cancer cells ($\chi^2 [1, N = 2,003] = 11.399; P > .001$). Awareness about cancer was generally greater among the HSES group than the LSES group.

Categories of People
Awareness was generally the greatest among caregivers compared with patients, students, and general public, the differences being statistically significant for eight items (Table 3). However, awareness that radiation therapy does not mean giving the patient an electric shock was observed in only 47% of caregivers, the lowest across all categories. The two items for which no differences existed across categories were cancer is not a curse ($\chi^2 [3, N = 2,981] = 3.824; P = .281$) and expensive tobacco causes cancer ($\chi^2 [3, N = 2,981] = 1.802; P = .614$).

Cancer-Related Perception
Four items that were categorized as cancer-related perception in the study were analyzed separately by using $\chi^2$ test to examine their association with age, sex, education level, and SES, and across different categories of people (Table 4 and Table 5).

**Item 11: Patients should not be informed of their diagnosis and treatment.** More women (71.7%), those 25 to 59 years of age (69%), and college students (73.5%) perceived that patients should be told about their disease; the differences among the rest of the respondent groups was statistically significant ($P < .05$). No statistically significant difference was observed with respect to sex and SES ($P > .05$).

**Item 12: Cancer tumors will be painful.** The majority of respondents, including patients with cancer, perceived that cancer tumors are not painful. Those older than 60 years of age (74%), those educated up to the school level (74%), and the general public (75%) had greater perception of this than other respondent groups and the differences were statistically significant ($P < .05$). No differences existed with respect to sex and SES ($P > .05$).

**Item 13: Cancer is a hereditary disease.** Education and category of people were found to have an association with the perception that cancer is a hereditary disease. Students who had completed school compared with others perceived that cancer is not a hereditary disease ($\chi^2 [4, N = 2,981] = 13.655; P = .008$). Participants in the HSES group ($\chi^2 [2, N = 2,981] = 13.814; P = .001$) and the general public ($\chi^2 [1, N = 2,981] = 21.791; P = .001$) were more likely to perceive that cancer is not a hereditary disease.

**Item 14: It is better not to inform family and friends when diagnosed with cancer.** More men than women perceived that disclosing the diagnosis to relatives and friends was acceptable ($\chi^2 [2, N = 2,981] = 11.630; P = .003$). Middle-age participants (25 to 40 years of age; $\chi^2 [6, N = 2,981] = 38.257; P < .000$); college students ($\chi^2 [4, N = 2,981] = 29.660; P < .000$); and caregivers were more likely to perceive that cancer disclosure to others is acceptable compared with other respondents in respective groups ($\chi^2 [6, N = 2,981] = 48.408; P < .000$).

**DISCUSSION**
Knowledge about cancer and perception toward cancer varied across different categories.
People with higher education, younger age, male sex, personal experience with cancer (as either a patient or a caregiver), and HSES had increased awareness about cancer. More than 70% of the study participants were aware that cancer can be cured, that cancer is not contagious, and that cancer is not a curse or a death sentence. However, only approximately half the participants were aware that cancer can spread from one person to another, cancer is a death sentence, or that only poor people get cancer.

Table 2. Cancer-Related Awareness in the Study Sample by Age Group and Socioeconomic Status

<table>
<thead>
<tr>
<th>Item No.</th>
<th>Items</th>
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<th>Socioeconomic Status</th>
<th>P</th>
<th>P</th>
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<td>25-40 (n = 775)</td>
<td>41-60 (n = 362)</td>
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<td>Cancer can spread from one person to another</td>
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<td>Cancer can be cured</td>
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participants believed that surgery or biopsy do not cause cancer to spread to other organs, and that radiation therapy does not involve giving the patient an electric shock.

In a study conducted by Rai et al. in a hospital setting in Varanasi among patients with breast or cervical cancer, 63.3% of the patients with breast cancer and 41.1% of the patients with cervical...
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cancer considered their disease curable. In our study, 85.7% of the patients and 86.2% of the caregivers reported that they believed that cancer can be cured. A qualitative study conducted with a population from the United Kingdom revealed that although participants expressed profound fear of cancer and perceived cancer as synonymous to death, they acknowledged improved outcomes. Both positive and negative responses were noted in the same sentence.1

The reason a person gets cancer was perceived as a result of witchcraft and karma.7,8 Moreover, the origin of the disease was perceived by 98.3% as being from the patient’s gods or goddesses, and the patients consulted religious counselors (71.3%) or occultists.7 In our study, more than 80% of the participants believed that cancer is not a curse; however, those with no formal education and those in older age groups (older than 60 years of age) had lower awareness compared with those in other groups. A majority of the study participants in the study by Rai et al7 had minimal or no formal education, were housewives (87.7%), and had LSES (64.4%), which could be the reason for the lower level of awareness among those participants.

Similarly, in a study conducted by Ray and Mandal,9 in Kolkata, education, SES, and social participation were found to be associated with the knowledge index. Education is a significant factor that helps create awareness.9-11 A study by Brokalaki et al12 revealed that patients in younger age groups had more information-seeking behavior, and the patient’s education level was linked to increased requests for additional information. In our study, awareness levels were greater among those who were literate than among those who did not have any formal education. Moreover, men had greater awareness than women. Despite being educated, women have less exposure to the outside world compared with men, the reason being the culture, which limits their knowledge.7

Moreover, in the study by Ray and Mandal,9 21% of the participants reported that cancer is an infectious disease.7 In our study, 30% of the participants reported that cancer is contagious; of the participants in that sample, people who were literate, male, in a younger age group, patients and caregivers, and those with HSES had 80% to 90% awareness that cancer is not contagious.

Table 5. Cancer-Related Perception Among Respondents by Socioeconomic Status and Category

<table>
<thead>
<tr>
<th>Item No.</th>
<th>Responses</th>
<th>Socioeconomic Status</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low (n = 1,009)</td>
<td>General Public (n = 999)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High (n = 994)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Patients should not be informed of their diagnosis and treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>256 25.4 241 24.2 248 24.8 204 20.9 118 23.1 131 26.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>691 68.5 708 71.3 689 69.0 708 72.4 371 72.7 339 68.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>62 6.1 45 4.5 62 6.2 66 6.7 21 4.2 24 4.9</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Cancer tumor will be painful</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>345 34.2 331 33.3 187 18.7 182 18.6 102 20.0 98 19.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>481 47.7 497 50.0 752 75.3 682 69.7 366 71.8 346 70.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>183 18.1 166 16.7 60 6.0 114 11.7 42 8.2 50 10.1</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Cancer is a hereditary disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>166 16.5 221 22.2 231 23.1 141 14.4 93 18.2 85 17.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>774 76.7 690 69.4 723 72.4 757 77.4 402 78.8 391 79.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>69 6.8 83 8.4 45 4.5 80 8.2 15 2.9 18 3.6</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>It is better not to inform family and friends when diagnosed with cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>207 20.5 202 20.3 321 32.1 344 35.2 172 33.7 183 37.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>768 76.1 748 75.3 429 42.9 450 46.0 304 59.6 245 49.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Don’t know</td>
<td>34 3.4 44 4.4 249 24.0 184 18.8 34 6.7 66 13.4</td>
<td></td>
</tr>
</tbody>
</table>
In India, the concept of multimodal treatment of cancer emerged three decades ago, which increased the overall cancer survival rates. Cancer awareness programs from governmental and non-governmental organizations have evolved in the past few years. The National Cancer Control Program in India used media campaigns to educate people about cancer and to encourage them to undergo screening. In addition, the Government of Tamil Nadu initiated awareness campaigns as part of the Tamil Nadu Health System Project supported by the World Bank for noncommunicable diseases including cancers. Although the impact of these initiatives was not systematically studied, in this study, younger people had more awareness of cancer-related facts, which could be a reflection of these recent initiatives.

In India, communication with the patient regarding the diagnosis and prognosis of cancer is not commonly practiced, and caregivers ask doctors not to inform patients about their diagnosis, fearing that the patient would not be able to handle the situation emotionally. In a study by Chittem et al, 51% of the patients with cancer were not aware of their diagnosis. The need for information about the diagnosis and treatment of cancer was expressed by 94% of the patients with cancer, and 92% wanted information about the prognosis, as revealed in a study by Laxmi and Khan. However, awareness about the disease leads to increased psychiatric morbidity among patients with cancer in India. Per the notification of the Medical Council of India on the Code of Medical Ethics Regulations, 2002, it is essential to disclose the diagnosis and prognosis to the patient. In this study, approximately one in four patients and caregivers perceived that patients should not be informed of their diagnosis, whereas informing relatives and friends about the diagnosis was perceived as unacceptable by one in five patients and caregivers.

Rapid urbanization and Westernization have resulted in fast-changing dietary patterns and lifestyle in India. Tobacco-related cancers have reached a new peak, and the consumption of alcohol and fatty and preserved food, low intake or no intake of fiber-rich food, and sedentary lifestyles are on the rise. This rise is expected to increase the burden of alcohol- and diet-related cancers in the coming decades in India. Lack of awareness about the onset and prevention of cancer may be the major challenge in cancer control. The perception of cancer as a curse or as the consequence of doing bad deeds prevents people from maintaining a healthier lifestyle. People also tend to argue saying, “Do all tobacco users get cancer? I have seen people who use tobacco and alcohol and still have a healthy life; I don’t have any bad habits, so how did I get this disease?” They thus attribute cancer to fate or karma. These statements are also widely used by tobacco industries as arguments to counter and dilute efforts to control use of tobacco.

Empowering people about the role of lifestyle in controlling or preventing cancer will gradually dispel this stigma. The yardstick for measuring the success of awareness campaigns is achieving downstaging of common cancers at presentation for treatment. In India, a major proportion of patients with cancer present with advanced-stage disease and do not get the required symptom relief. Much criticism has been raised regarding the underuse of morphine. Although India produces 99% of the world’s supply of morphine, only 3% of patients with cancer in India are benefitting. When a community perceives cancer as a curse or a death sentence, they tend to presume that pain and suffering are inevitable, thereby preventing patients from having a dignified death. Furthermore, witnessing this suffering reiterates and strengthens their belief and perception that cancer is a dreadful and deadly disease and it is acquired by doing bad deeds. Hence, addressing fatalistic beliefs through communication about cancer plays an important role in cancer control.

In conclusion, it is evident that the awareness and perception about cancer vary by education, sex, age, and SES. This reiterates the need to invest more in information, education, and communication materials for public campaigns that target a variety of people for wider reach and more powerful impact.

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AUTHOR CONTRIBUTIONS
Conception and design: Vidhubala Elangovan, Swaminathan Rajaraman
Collection and assembly of data: All authors
Data analysis and interpretation: Vidhubala Elangovan, Swaminathan Rajaraman, Barsha Basumalik
Manuscript writing: All authors

Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The following represents disclosure information provided by authors of this manuscript. All relationships are considered

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We thank all of the study participants for their time.

Affiliations
All authors: Cancer Institute (Women Indian Association), Chennai, India

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Breast Cancer Knowledge, Behaviors, and Preferences in Malawi: Implications for Early Detection Interventions From a Discrete Choice Experiment

Purpose Breast cancer is the most common female cancer in Africa and leading cause of death resulting from cancer; however, many countries lack early detection services. In Malawi, women are frequently diagnosed with large tumors after long symptomatic periods. Little is known about local cancer knowledge.

Methods We administered a cross-sectional survey with a discrete choice experiment to a random sample in urban and rural areas of Lilongwe district. Bivariable and multivariable analyses determined factors associated with knowledge. Preference utilities for early detection interventions were estimated using a hierarchical Bayesian model in Sawtooth software.

Results Of 213 women recruited, fewer than half were aware of breast cancer. In multivariable analysis, electricity at home and knowing someone with cancer increased the odds of awareness. Women were more knowledgeable about symptoms than treatment or risk factors; more than 60% erroneously believed local misconceptions. Seventeen percent were aware of breast self-examination, and 20% were aware of clinical breast examination (CBE); few reported either behavior. Common barriers included not knowing where to access CBE and transportation difficulties. Discrete choice experiment results indicated the detection strategy (breast health awareness, CBE, or both) was the most important attribute of an intervention, followed by the encounter setting and travel time.

Conclusion Addressing misconceptions in health messages and engaging survivors to promote early detection may help improve breast cancer knowledge in Malawi. Program designs accounting for women’s preferences should provide breast health education and CBEs in convenient settings to address transportation barriers, particularly for women with low socioeconomic position.

INTRODUCTION

Breast cancer is the most common cancer in Africa and is also the leading cause of death resulting from cancer among female patients. High mortality rates are likely a result of low awareness, large proportions of advanced diagnoses, and a scarcity of screening, diagnostic, or treatment services. Knowledge of the disease and available detection strategies is essential to increase early diagnosis and improve outcomes.

Studies from African countries have shown that cultural and religious beliefs, competing health needs, and low socioeconomic position (SEP) are associated with low breast cancer knowledge and poor help-seeking behaviors. However, previous studies investigated mammography knowledge and behaviors or surveyed health workers or medical students; few studies have assessed knowledge in the general population. Country-specific data are needed because of differences in health system resources, cultural nuances, and social contextual factors.

In Malawi, one of the most resource-limited countries in the world, patients with breast cancer are commonly diagnosed at young ages with large tumors after long symptom duration. Although national health guidelines recommend promoting breast health awareness, including breast self-examination (BSE) and clinical breast examination (CBE), these services are not widely available. International recommendations support these resource-appropriate early detection...
and diagnosis strategies because of the current lack of resources required for mammography.\textsuperscript{2,3} To date, no studies have assessed Malawian women’s breast cancer knowledge, which is imperative to develop locally appropriate public health interventions. The objective of this study was to investigate knowledge, behaviors, and preferences about breast cancer and early detection among Malawian women.

**METHODS**

**Study Setting**

This cross-sectional study was conducted in Lilongwe district in central Malawi. The district includes the capital city Lilongwe, one of four major urban areas in the country, many transitioning periurban residential areas, and rural traditional authority areas.\textsuperscript{21}

The public health system provides free basic health care through local health centers, district hospitals, and four tertiary care hospitals. Two tertiary care hospitals offer chemotherapy for patients with breast cancer; no radiotherapy is available in Malawi. There is no functioning mammography equipment in the public system; however, mammography is available in the private sector for approximately US$125.

**Study Design**

We considered Lilongwe city and the rural traditional authority areas separately and sampled them in proportion to the female population. We randomly selected geographic coordinates within residential areas using ZMaps (Zonums software; http://zonums.com). Fieldworkers used handheld Garmin GPS devices (Olathe, KS) to locate the coordinates and conducted three interviews around each coordinate (Data Supplement provides recruitment procedures and eligibility details). The study was approved by University of North Carolina Institutional Review Board and the Malawi National Health Service Research Committee.

**Data Collection**

Data were collected in the local language (Chichewa) via interviewer-administered surveys from July to August 2014. Fieldworkers entered responses into Open Data Kit Collect (Open Data Kit software; https://opendatakit.org) on tablets, and data were uploaded daily.

**Measures**

The survey included questions on knowledge, beliefs, and behaviors regarding breast cancer, BSE, CBE, and demographic characteristics. Questions were conceptually derived from the Health Belief Model, which posits that multiple factors influence the adoption of health behaviors, including perceived threat of a health condition, perceived benefits and barriers, cues to action, and self-efficacy.\textsuperscript{22,23} Traditional instruments measuring Health Belief Model variables, such as Champion’s breast cancer beliefs measures,\textsuperscript{24–26} do not assess CBE beliefs and may not be valid in an African context. Therefore, we adapted scales to match locally available strategies (Data Supplement).\textsuperscript{25,26} Fatalism measures derived from P owe’s scale assessed beliefs about the inevitability of death associated with a cancer diagnosis.\textsuperscript{27} We used “yes,” “no,” or “don’t know” responses because of difficulties in translating meaningful Likert-scale responses. Knowledge scores were calculated by summing correct responses for signs, risk factors, and treatment options.

**Discrete Choice Experiment**

A discrete choice experiment (DCE) is used to elicit preferences for health services.\textsuperscript{28,29} This approach is based on the assumption that a health service can be broken down into separate attributes, and the total utility gained from using that service is a function of the individual utilities of the attributes.\textsuperscript{30} Respondents are given hypothetical scenarios and forced to choose one preferred option.\textsuperscript{31} Respondents should choose the scenario producing the highest utility.\textsuperscript{32} Estimation models calculate utilities for each attribute level and determine the relative importance of attributes.

We previously described the development of the DCE, where we followed the International Society of Pharmacoeconomics and Outcomes Research guidelines to determine optimal design.\textsuperscript{32,33} The DCE attributes included travel time (< 1, 1 to 2, or > 2 hours by foot), intervention encounter or setting (health talk in facility waiting area, community health gathering, cervical cancer screening, family planning [FP] clinic, or well-child visit clinic), health worker (physician or health surveillance assistant), health worker sex, and early detection strategy (breast health awareness, CBE, or both).

We used Sawtooth software (version 8; Sequim, WA) to create an efficient and balanced fractional factorial design. Cognitive testing suggested that 16 choice cards were burdensome, so we presented nine cards with two scenario descriptions and images of the attribute levels on each. A multiple-choice design also complicated comprehension, so we used a binary choice format.\textsuperscript{33}
Statistical Analyses

Sociodemographic characteristics, knowledge, beliefs, and behavior responses were summarized descriptively using STATA software (version 13; STATA, College Station, TX). We used multivariable logistic regression to identify associations with knowledge and assessed covariates one by one. Collinearity was evaluated with Pearson’s correlation coefficient; personal water tap was excluded because of significant correlation with electricity.

The DCE results were analyzed using the hierarchic Bayesian module for choice-based conjoint analysis in Sawtooth software. A multinomial logit model estimated the probabilities of an individual choosing particular alternatives. The Bayesian approach allowed us to compare and update an individual’s estimates on the basis of the distribution of preferences from other respondents. Sawtooth uses a Monte Carlo Markov chain to estimate parameters through an iterative process until the model converges at the right distributions of the parameters. The individual utility estimates of each attribute level were averaged after 10,000 random draws. Results are presented as raw utilities and can be interpreted as the attractiveness of each level within the attribute, with higher numbers indicating more attractive options. We also estimated the mean importance of attributes across all respondents.

RESULTS

Study Characteristics

Of 262 women approached to participate, 22 (8%) were ineligible (age < 18 years), and 27 (10%) refused (generally because of lack of time). We successfully recruited 213 women; the mean age was 38 years; most women were married and Christian; 64% had no formal or some primary education. Most had low SEP; only 28% had electricity at their residence, and 38% had access to a personal water tap in their homes.

Breast Cancer Knowledge

Fewer than half of the sample (44%) were aware of breast cancer, indicating they had never before heard of the disease. Most women who were aware reported learning about it from a health worker, family member, or friend.

In bivariate analyses (Table 1), women who were aware of breast cancer were more likely to have a higher education level \( (P = .002) \) and electricity \( (P < .001) \) and to have had a recent physical examination \( (P = .04) \). Those who knew any type of cancer survivor were more likely to be aware of breast cancer \( (P < .001) \). Most known survivors were a relative \( (41\%) \), friend \( (26\%) \), neighbor \( (19\%) \), or parent, spouse, or child \( (15\%) \). Among peer survivors, cervical cancer and Kaposi’s sarcoma (often described as cancer of the leg or skin) were the most common cancer types \( (n = 23 \text{ each}) \), followed by breast \( (n = 14) \) and stomach \( (n = 4) \); lung, anus, and bladder were each mentioned once. Only one participant reported encountering multiple survivors; only one had a first-degree relative with breast cancer. Breast cancer awareness was positively correlated with BSE awareness \( (P < .001) \) and CBE awareness \( (P < .001) \).

In a multivariable model adjusted for marital status, education, and recent physical examination, knowing any cancer survivor \( (\text{adjusted odds ratio}, 4.37; P < .001) \) and having electricity at home \( (\text{adjusted odds ratio}, 3.84; P < .001) \) significantly increased the odds of awareness (Table 2).

We assessed knowledge in more detail among those who were aware of breast cancer (Fig 1).
Women were more knowledgeable about the signs or symptoms of the disease compared with treatment or risk factors (Table 3). Although 80% correctly identified a lump as a sign or symptom, 11% did not know any signs. Twenty-four percent did not know any correct risk factors, and misconceptions were common (Table 4). For example, many believed storing a cell phone (64%) or money (61%) in a bra could increase risk, and 30% believed breast cancer was contagious. Although most knew surgery to remove the breast was a form of treatment, religious healing practices were also reported.

Beliefs
Women had varying levels of perceived threat of breast cancer (Table 5). Approximately 44% of those who were aware of breast cancer believed they would develop breast cancer at some point in their lifetime; 37% were concerned about their chances of developing breast cancer. Those with a lower education level were more likely to perceive breast cancer as a threat. Half of those aware (n = 47) agreed with all three items on the fear scale. More than half (52%) agreed with at least one of the fatalistic statements about breast cancer diagnosis. Those with a lower education level (P < .001) who were not married had more negative beliefs. Women unaware of BSE and CBE had stronger fatalistic beliefs; there were no differences in perceived threat or fear by awareness of early detection behaviors.

BSE
Seventeen percent (n = 36) of the full sample was aware of BSE. Most women learned about BSE from a physician, a family member, a friend, a health talk, or the radio. Among those who knew, 29 (81%) thought performing regular self-examinations would help find cancer early. Twenty-four women (67%) reported performing a self-examination at least once, and 83% reported a physician had motivated them to perform BSE. Women who had performed BSE highly reported benefits, and few barriers were noted (Data Supplement).

CSE
Twenty percent (n = 43) of the full sample had heard of CBE. A physician was the most common information source, followed by a family member, a friend, the radio, a health talk, a religious gathering, and television. Among those who were aware, most women thought CBEs helped find lumps early (91%), decreased the chance of dying as a result of breast cancer (93%), and might help find a lump before a woman could feel it herself (86%). We explored potential barriers to having a CBE among those who were aware; women reported not knowing where to go (45%) and transportation (30%) as common barriers. Four believed other problems were more important; two women indicated they would be embarrassed about exposing their body.

Few women (n = 14) had ever received a CBE; half of those that were performed had occurred within the past 12 months. Examinations were performed by physicians in private clinics or the central hospital. Four women thought the examination was embarrassing, four said it was uncomfortable, and two thought it was painful. Of the women who had never been examined, additional barriers were identified, including concerns about time, pain, and husbands not approving.

Interest and Acceptability
Nearly all women (n = 206) were interested in learning more about breast cancer. Women wanted

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**Table 2.** Associations With Breast Cancer Awareness

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI) Unadjusted</th>
<th>OR (95% CI) Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Married</td>
<td>2.00 (0.93 to 4.33)</td>
<td>1.98 (0.87 to 4.51)</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No formal school (reference)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Primary</td>
<td>1.13 (0.52 to 2.44)</td>
<td>0.93 (0.42 to 2.08)</td>
</tr>
<tr>
<td>≥ Secondary</td>
<td>2.97 (1.25 to 6.53)</td>
<td>1.61 (0.68 to 3.79)</td>
</tr>
<tr>
<td>Electricity</td>
<td>4.07 (2.15 to 7.72)</td>
<td>3.84 (1.91 to 7.71)</td>
</tr>
<tr>
<td>Physical examination within past 6 months</td>
<td>1.84 (1.03 to 3.31)</td>
<td>1.40 (0.71 to 2.74)</td>
</tr>
<tr>
<td>Aware of peer cancer survivor</td>
<td>4.05 (2.19 to 7.50)</td>
<td>4.37 (2.26 to 8.45)</td>
</tr>
</tbody>
</table>

Abbreviation: OR, odds ratio.
information from a physician (64%), community health worker (40%), radio message (20%), seminar at church or school (15%), or health talk at a health facility (15%).

All women were asked whether they would adopt BSE if a health worker offered to teach them. Those who were not interested cited being too busy or too old (n = 3), being unable to do it (n = 3), and the ability of a clinician to do it more effectively (n = 2) as reasons for declining. We also asked all women if they would accept a CBE from a health worker, and 96% were interested. Four women said they would refuse because they were too old or not sick.

Preferences Regarding Breast Cancer Detection Services

We examined the proportion of times the attribute levels were selected when they were presented. The shortest travel time was selected most often (P < .01), and the community health gathering was the most popular setting (60%; P < .01). Physicians were selected 55% of the time. Although respondents favored female health workers, there were no significant differences for sex. The combined early detection strategy of CBE and breast health awareness was selected most often (58%; P < .01). There were no differences in preference by breast cancer awareness. Residence was the only demographic characteristic affecting preferences. Urban women were more likely to favor breast health awareness (P < .01) and were also more sensitive to travel time (P < .01).

Estimated Utilities

We performed multinomial logistic regression with and without interaction terms, which led to similar results and only a slight improvement in model fit. We investigated differences by residence but did not observe significant differences. Therefore, we report the hierarchic Bayesian model with no interactions or covariates (Table 6).

Women valued having a CBE, particularly if it was combined with breast health awareness. Respondents favored shorter travel times and female physicians. They preferred having the intervention available at a FP clinic; interventions offered at a community health gathering were also favored, although not as strongly. Mean importance scores indicated early detection strategy (27%), setting or encounter (24%), and travel time (21%) were the most important attributes; health worker sex and type were less important to women’s choices.

DISCUSSION

To our knowledge, this is the first study examining breast cancer and early detection knowledge in

Table 3. Knowledge Among Women Aware of Breast Cancer (n = 94)

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sign or symptom</strong></td>
<td></td>
</tr>
<tr>
<td>Lump</td>
<td>75 (80)</td>
</tr>
<tr>
<td>Breast pain</td>
<td>67 (71)</td>
</tr>
<tr>
<td>Nipple discharge</td>
<td>63 (67)</td>
</tr>
<tr>
<td>Nipple discoloration</td>
<td>60 (64)</td>
</tr>
<tr>
<td>Skin retraction</td>
<td>58 (62)</td>
</tr>
<tr>
<td>Breast discoloration</td>
<td>67 (71)</td>
</tr>
<tr>
<td>Change in shape</td>
<td>65 (69)</td>
</tr>
<tr>
<td>Itchy nipple</td>
<td>52 (55)</td>
</tr>
<tr>
<td>Dimpling (peau d’orange)</td>
<td>53 (56)</td>
</tr>
<tr>
<td><strong>Percentage score</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>66.2</td>
</tr>
<tr>
<td>SD</td>
<td>37.0</td>
</tr>
<tr>
<td><strong>Risk factor</strong></td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>45 (48)</td>
</tr>
<tr>
<td>Never having children</td>
<td>26 (28)</td>
</tr>
<tr>
<td>First delivery after age 30 years</td>
<td>31 (33)</td>
</tr>
<tr>
<td>Short breastfeeding duration</td>
<td>27 (29)</td>
</tr>
<tr>
<td>Age</td>
<td>28 (30)</td>
</tr>
<tr>
<td>Overweight</td>
<td>19 (20)</td>
</tr>
<tr>
<td>High fat diet</td>
<td>24 (25)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>49 (52)</td>
</tr>
<tr>
<td><strong>Percentage score</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>33.1</td>
</tr>
<tr>
<td>SD</td>
<td>30.5</td>
</tr>
<tr>
<td><strong>Treatment option</strong></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>76 (81)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>23 (24)</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>25 (27)</td>
</tr>
<tr>
<td><strong>Percentage score</strong></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>44.0</td>
</tr>
<tr>
<td>SD</td>
<td>31.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
</tr>
<tr>
<td>No. correct</td>
<td>9.9</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>4.8</td>
</tr>
<tr>
<td>Percentage score</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>49.6</td>
</tr>
<tr>
<td>SD</td>
<td>24.2</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.

*No. of women who correctly identified each response.
Malawi and the first DCE eliciting preferences for breast cancer early detection in Africa. More than half of Malawian women surveyed were unaware of breast cancer. Even among those who were aware, knowledge was low. Local misconceptions about causes were common, and few women knew about or exhibited behaviors in line with recommended early detection strategies. Fatalistic beliefs and fear were more common among women with lower SEP and education level. The DCE showed that women preferred a combination of educational and clinical services being available at FP clinics that did not require long travel. These findings provide important insight into intervention and message development.

Our results suggest that widespread breast cancer education is needed. Whereas some studies in African countries have indicated relatively good breast cancer awareness and lower knowledge of risk factors, our findings were similar to reports of rural African subpopulations exhibiting low levels more generally.\(^5\)\(^,\)\(^6\)\(^,\)\(^16\) Disseminating information about breast cancer signs and symptoms and encouraging CBE for symptomatic women are essential to avoid overwhelming the already strained health system of Malawi. We emphasize that BSE has never proved effective in reducing mortality,\(^37\)\(^,\)\(^38\) but breast health awareness—encouraging women to be familiar with their breasts and to seek help upon noticing concerns—is important in limited-resource settings.

Knowledge was influenced by social networks. Knowing any type of cancer survivor significantly influenced awareness, and many women had learned about breast cancer from friends or family. Compared with urban Tanzanian women, a greater proportion of our sample knew a survivor, but Malawian women had much lower knowledge.\(^39\) Additionally, because fear and fatalism were common in our sample, engaging local survivors may enhance messages about the benefits of early detection. Dispelling misconceptions about causes will be important to address perceived risk. Results also suggest that women of higher SEP (ie, with electricity access at home) are more aware. Targeted communication strategies are needed and must consider communication inequalities, such as access to health information and health literacy, especially in settings like Malawi, where many women have low SEP and little formal education.\(^40\)\(^,\)\(^41\)

Our findings also suggest that early detection could be incorporated into existing health services. Participants preferred having services offered at FP clinics, which likely serve younger women with relatively low breast cancer risk. However, this may have been a natural choice because physical examinations are common at FP clinics and may be associated with preventive care. Interventions offered at other health encounters were not as popular, potentially because of the relevance of certain services, a woman’s age or stage of life (eg, number and age of children,

### Table 4. Local Misconceptions About Causes and Treatment of Breast Cancer (n = 94)

<table>
<thead>
<tr>
<th>Misconception</th>
<th>No.* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factor misconception</strong></td>
<td></td>
</tr>
<tr>
<td>Clogged milk</td>
<td>39 (41)</td>
</tr>
<tr>
<td>Hybrid chickens</td>
<td>42 (45)</td>
</tr>
<tr>
<td>Storing cell phone in bra</td>
<td>60 (64)</td>
</tr>
<tr>
<td>Keeping money in bra</td>
<td>57 (61)</td>
</tr>
<tr>
<td>Contagious</td>
<td>28 (30)</td>
</tr>
<tr>
<td><strong>Treatment misconception</strong></td>
<td></td>
</tr>
<tr>
<td>Herbal medicine</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Prayers</td>
<td>44 (47)</td>
</tr>
<tr>
<td>Fellowships, healing revivals</td>
<td>28 (30)</td>
</tr>
</tbody>
</table>

*No. indicates the number of women who correctly identified each response.

### Table 5. Breast Cancer Beliefs Among Malawian Women Aware of Breast Cancer (n = 94)

<table>
<thead>
<tr>
<th>Belief</th>
<th>No.* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Threat</strong></td>
<td></td>
</tr>
<tr>
<td>Do you think you will get breast cancer in the future?</td>
<td>41 (43.6)</td>
</tr>
<tr>
<td>Are you worried about your chances of developing breast cancer in your lifetime?</td>
<td>35 (37.2)</td>
</tr>
<tr>
<td><strong>Fear</strong></td>
<td></td>
</tr>
<tr>
<td>When you think about breast cancer, do you feel scared?</td>
<td>57 (60.6)</td>
</tr>
<tr>
<td>When you think about breast cancer, do you feel nervous?</td>
<td>72 (76.6)</td>
</tr>
<tr>
<td>When you think about breast cancer, do you feel upset?</td>
<td>73 (77.7)</td>
</tr>
<tr>
<td><strong>Fatalism</strong></td>
<td></td>
</tr>
<tr>
<td>Do you believe cancer will kill most people who get it?</td>
<td>45 (47.9)</td>
</tr>
<tr>
<td>Do you believe if someone gets cancer, it doesn’t matter when they find out about it; they will still die of it?</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Do you believe if someone has cancer, it is already too late to do anything about it?</td>
<td>36 (38.3)</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.
*No. of women who responded yes.
menopausal status), or awareness of other cancers and screening services. Additional research on the optimal packaging of women’s health services is needed.

The results also indicate that access to and convenience of interventions are important. Travel time influenced preferences, and transportation was identified as a barrier to having a CBE. In prior research among Malawian patients with breast cancer, we also found that structural, health system, and health worker factors delayed diagnosis and treatment.\textsuperscript{19} Transportation, cost of care, and access to providers delayed cancer help-seeking behaviors in other African countries.\textsuperscript{42} Our results confirm that structural barriers affect cancer behaviors and preferences for services.

Distributing services throughout lower-level health centers in urban and rural communities will be critical. System-level interventions must coincide with workforce training to ensure access to accurate cancer information, high-quality CBEs, and timely follow-up.\textsuperscript{19} Studies in Malawi and other African settings have suggested that lay health workers may be a promising option for breast cancer education and conducting CBEs.\textsuperscript{43,44}

Although we expected women to have stronger preferences for health worker sex on the basis of the DCE development,\textsuperscript{33} the results demonstrate that sex is not as important as other intervention attributes. Having a female physician may enhance the experience but not affect a woman’s willingness to participate. Instead, women highly valued CBE and were willing to make tradeoffs, which may be a result of paternalistic norms regarding health workers and patients feeling like they do not have the option of requesting a woman.\textsuperscript{33}

This study has some limitations, including that our sample was drawn from one district in Malawi and may not be generalizable to other settings. However, Lilongwe is diverse in terms of tribal background, religion, and education. Limited breast cancer knowledge may mean that our sample values intervention attributes differently than women who are more aware of breast cancer. Evidence for the effect of experience on preference patterns is mixed; some studies have indicated preference differences for experienced versus naïve respondents.\textsuperscript{45,46} Although we did not observe differences by breast cancer awareness, additional research on the influence of awareness of other common cancers is needed, especially given the burden of AIDS-defining cancers and campaign efforts.

In conclusion, interventions are needed to address low knowledge of breast cancer and early detection strategies, especially among low SEP women. Educational messages must address local fears and misconceptions about risk factors and curability. Programs may be more successful if they are tailored to women’s preferences and overcome access barriers, such as bundling breast health awareness and CBEs with other services in convenient settings that do not require substantial travel. Improving knowledge and increasing access to CBEs through existing health services have potential to make a significant impact on cancer burden.

Table 6. Raw Utility Estimates From Discrete Choice Experiment

<table>
<thead>
<tr>
<th>Attribute or Level</th>
<th>Mean Attribute Importance Score</th>
<th>Mean Level Utility</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early detection strategy</td>
<td>26.6</td>
<td>24.83 to 28.30</td>
<td></td>
</tr>
<tr>
<td>Breast health awareness</td>
<td>-1.08</td>
<td>-1.23 to -0.93</td>
<td></td>
</tr>
<tr>
<td>CBE</td>
<td>0.14</td>
<td>-0.02 to 0.05</td>
<td></td>
</tr>
<tr>
<td>Both breast health awareness and CBE</td>
<td>0.94</td>
<td>0.79 to 1.09</td>
<td></td>
</tr>
<tr>
<td>Intervention setting/ or encounter</td>
<td>24.3</td>
<td>23.18 to 25.47</td>
<td></td>
</tr>
<tr>
<td>Health talk in facility waiting area</td>
<td>-0.11</td>
<td>-0.27 to 0.04</td>
<td></td>
</tr>
<tr>
<td>Community health gathering</td>
<td>0.04</td>
<td>-0.19 to 0.27</td>
<td></td>
</tr>
<tr>
<td>Cervical cancer screening</td>
<td>-0.13</td>
<td>-0.29 to 0.03</td>
<td></td>
</tr>
<tr>
<td>Family planning clinic</td>
<td>0.38</td>
<td>0.21 to 0.56</td>
<td></td>
</tr>
<tr>
<td>Well-child age &lt; 5 years visit</td>
<td>-0.19</td>
<td>-0.37 to 0.003</td>
<td></td>
</tr>
<tr>
<td>Travel time, hours by foot</td>
<td>21.2</td>
<td>19.53 to 22.80</td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>0.84</td>
<td>0.69 to 0.99</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>-0.06</td>
<td>-0.17 to 0.05</td>
<td></td>
</tr>
<tr>
<td>&gt; 2</td>
<td>-0.78</td>
<td>-0.93 to -0.63</td>
<td></td>
</tr>
<tr>
<td>Sex of health worker</td>
<td>14.2</td>
<td>12.78 to 16.69</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.20</td>
<td>0.10 to 0.31</td>
<td></td>
</tr>
<tr>
<td>Type of health worker</td>
<td>13.7</td>
<td>12.26 to 15.15</td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>0.52</td>
<td>0.41 to 0.62</td>
<td></td>
</tr>
<tr>
<td>Health surveillance assistant</td>
<td>—</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. We used effects coding (ie, the last level within each attribute was not included in the model but was estimated as the negative sum of the other attribute levels). Attributes are listed in order of importance. Preferred attribute levels are bolded; higher numbers indicate attractiveness. Abbreviation: CBE, clinical breast examination.

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AUTHOR CONTRIBUTIONS

Conception and design: Racquel E. Kohler, Clara N. Lee, Bryan J. Weiner, Bryce B. Reeve, Stephanie B. Wheeler

Financial support: Bryan J. Weiner

Administrative support: Satish Gopal, Stephanie B. Wheeler

Collection and assembly of data: Racquel E. Kohler, Satish Gopal

Data analysis and interpretation: Racquel E. Kohler, Stephanie B. Wheeler

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Racquel E. Kohler
No relationship to disclose

Satish Gopal
No relationship to disclose

Clara N. Lee
No relationship to disclose

Bryan J. Weiner
No relationship to disclose

Bryce B. Reeve
No relationship to disclose

Stephanie B. Wheeler
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Prior Presentation


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Developing a Breast Cancer Screening Program in Nigeria: Evaluating Current Practices, Perceptions, and Possible Barriers

**Purpose** In low- and middle-income countries like Nigeria, women present with advanced breast cancer at an earlier age. Given the limited resources, development of screening programs that parallel resource capabilities of low- and middle-income countries is imperative. The objective of this study was to evaluate the perceptions, practices, and barriers regarding clinical breast examination (CBE) screening in a low-income community in Nigeria.

**Materials and Methods** A cross-sectional survey of women age 40 years or older in Ife, Nigeria, using multistaged sampling was performed. Information on sociodemographics, knowledge of breast cancer, screening practices, and willingness to participate in CBE screening was obtained using an interviewer-administered questionnaire.

**Results** A total of 1,169 women whose ages ranged from 40 to 86 years (mean age, 47.7 years; standard deviation, 8.79 years) were interviewed. The majority of women (94%) knew about breast cancer, whereas 27.5% knew someone who had had breast cancer, the majority of whom (64.5%) had died of the disease. Of the 36% of women who had breast screening recommended to them, only 19.7% had an actual CBE. Of these, only 6% had it in the last year. The majority of women (65.4%) were willing to have regular CBEs and did not care about the sex of the examiner in most instances. Lack of perceived need was the reason cited by women unwilling to participate.

**Conclusion** The majority of women were aware of breast cancer and knew it as a fatal disease. With the relatively encouraging number of those willing to be examined, a carefully designed CBE program coupled with advocacy to correct uneducated beliefs seems promising.

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INTRODUCTION

Breast cancer is a common cause of cancer-related deaths in most developing countries. With most patients presenting in advanced stages, it is not surprising that it is one of the most common causes of cancer mortality. Studies have shown a steady increase in the incidence of breast cancer in Nigeria from 15.3 per 100,000 in 1976 to 33.6 per 100,000 in 1992 to 52.1 per 100,000 in 2012. In developed countries, however, mortality from breast cancer has been on the decline despite the higher incidence of breast cancer. This is a result of early detection through organized screening programs and effective treatment modalities. In the United States, women with an average risk of breast cancer are recommended to undergo annual screening mammography starting at age 45 years and continuing up to age 54 years, after which they can transit to screening every 2 years or continue screening annually. It is also recommended that women between 40 and 44 years of age should have the opportunity to begin annual screening. However, the applicability of mammography-based screening programs is limited in low- and middle-income countries because of the challenges of poor infrastructure, poverty, and inadequate manpower. Waiting until such capabilities are developed, however, will lead to continued loss of life as a result of late presentation.

Therefore, clinical breast examination (CBE) has been recommended as a screening modality that may find usefulness in resource-poor settings while efforts are underway to attain the status of international best practices. Studies of programs...
in Africa and India provide a strong rationale for this assertion. The successes of these programs demonstrate the acceptability and feasibility for resource-limited countries to develop formal programs at various levels of health care delivery that use CBE for screening either solely (where mammography is unavailable) or to complement mammography (where it is in short supply). However, this should be done cautiously, given previous experiences where most participants failed to comply with the screening recommendations after commencement of the program. As a first step in developing such a program, it is imperative to understand the peculiarities of the target community to conduct a successful, socially acceptable, and sustainable program. This study, conducted in a southwestern Nigerian community, set out to determine the perceptions, practices, and possible barriers of CBE-based screening program in a low-resource setting.

MATERIALS AND METHODS

Study Population

This study was conducted in the Ife Central local government area of Osun State, southwestern Nigeria, between February and April 2016. Ife Central local government is one of the two local governments in Ile-Ife, a city in southwestern Nigeria with a population of 167,254 (2006 census). It has a teaching hospital where specialized care, including breast services, is offered. The local government is made up of 11 wards, each having a variable number of streets. Considerable variations exist in the social characteristics of the various wards; hence, we sampled on all the wards for equal representation. Sampling was done using a multistage stratified sampling technique first into wards and then into streets within each ward. The number sampled from each ward was proportional to the population size of the ward. Women age 40 years and older were eligible for the survey.

Instrument

We used a 35-item, study-specific, interviewer-administered questionnaire first designed in English and later translated to Yoruba, the local language in Ile-Ife. Translation was done by a Yoruba language education expert. Pretesting was done using both English and Yoruba versions in a cohort of 20 women in Ile-Ife, and this was reviewed before the final adoption of the questionnaire. Interviews were conducted by a team of undergraduate and graduate students who were trained before commencement of the study and could effectively communicate in both English and Yoruba languages depending on the preference of the participant. Each interview lasted an average of 10 minutes. The questionnaire gathered information on demographic characteristics, breast cancer knowledge and experience, practice of CBE, willingness to participate in a CBE program, and possible barriers to participating in such a program.

Key Variables

The key variables in this study were receipt of CBE, willingness to participate in a regular CBE-based program, and reasons for refusal to participate. We used two measures of receipt of CBE; these were receipt of CBE ever and receipt of CBE during the past year.

Statistical Analysis

Sociodemographic characteristics, awareness of breast cancer, practice of breast cancer screening, willingness to participate in CBE screening, and other key variables were analyzed using descriptive statistics. Simple and multivariate Poisson regression with robust variance estimation was used to derive prevalence ratios with 95% CIs for the assessment of factors associated with willingness to participate in CBE. Variables were selected for the multivariate Poisson regression by the backward stepwise elimination method, with \( P = .25 \) set as the level for removal from the model. Data analysis was done using STATA version 12 (STATA, College Station, TX).

Ethics

This study was approved by the ethical committee of the Institute of Public Health at Obafemi Awolowo University (Ile-Ife, Nigeria). Approval was also obtained from the Ife Central local government authority before the survey was conducted.

RESULTS

Sociodemographics

A total of 1,169 women were surveyed across the entire local government. Their ages ranged from 40 to 86 years, with a mean age of 47.7 years (standard deviation, 8.79 years). Most of the respondents had some form of education, with only 15.6% having no formal education at all. Most were married and were traders, as listed in Table 1.

Knowledge and Experience of Breast Cancer

Most of the respondents (94%) had heard about breast cancer, whereas 27.5% knew someone who had had the disease. Among these, 82.5%
of respondents claimed the women they knew had received treatment in the hospital and that approximately two thirds of the women died of the disease (Table 2).

General Health Behavior
Assessment of the respondents’ general health behavior showed that approximately two thirds of the respondents received treatment of their health issues in the hospital (63.9%), whereas the other respondents self-medicated (19.2%), visited pharmacies (9.2%), or patronized herbalists (3.7%). Other health behaviors assessed included receipt of a blood sugar test and Papanicolaou test. Only 42.8% of respondents had ever had a blood sugar test, whereas the remaining 57.2% had never had a blood sugar check. Papanicolaou testing for cervical cancer was performed in only 10.8% of the women, whereas the majority (89.2%) had never had a Papanicolaou test.

Breast Cancer Screening Practice
Specifically, with regard to breast cancer screening, the majority of women had never been screened by any method. Only 37.7% of the respondents had ever had breast cancer screening recommended to them (Table 3) by a health worker (43%), mass media (37.8%), friends and relatives (13.6%), or religious and public seminars (5.6%). Regular breast self-examination was practiced by 31.2% of the women, whereas 23.5% claimed to examine their breasts irregularly and 45.3% did not examine their breasts.

Only 230 women (19.7%) had ever had their breasts examined by a health practitioner. Of these women, only 6% had their breasts examined in the past year, 4.4% had their breasts examined in the past 2 years, and 9.2% had not had a breast examination in more than 2 years. Mammography screening had only been done in 33 women (2.8%).

Attitude Toward CBE Screening Program
Seven hundred sixty-five respondents (65.4%) were willing to participate in a regular breast examination screening program, whereas 404 respondents (34.6%) were not. Lack of perceived need was the reason given for nonwillingness by those who declined. We examined preferences for the sex of the examiner and found that 249 women (32%) would prefer a female examiner and 15 women (2%) would prefer a male examiner; however, the majority of women (65.5%) did not care about the sex of the examiner. This was the case regardless of religion and level of education (P = .63 and P = .3, respectively). Prevalence ratios derived from Poisson regression with a robust estimate of variance showed that willingness to participate in CBE was significantly higher among women who were civil servants (adjusted prevalence ratio [APR], 1.21; P < .001), who knew someone who had breast cancer (APR, 1.15; P < .001), who practiced regular breast self-examination (APR, 1.22; P < .001), and who had a Papanicolaou test (APR, 1.20; P < .001).

DISCUSSION
The current reality regarding the pattern of breast cancer presentation in most low- and middle-income

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Women, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group, years</strong></td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>687 (58.8)</td>
</tr>
<tr>
<td>50–59</td>
<td>266 (22.8)</td>
</tr>
<tr>
<td>60–69</td>
<td>140 (12.0)</td>
</tr>
<tr>
<td>&gt; 69</td>
<td>76 (6.5)</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>980 (83.8)</td>
</tr>
<tr>
<td>Widowed</td>
<td>150 (12.8)</td>
</tr>
<tr>
<td>Single</td>
<td>15 (1.3)</td>
</tr>
<tr>
<td>Separated</td>
<td>10 (.9)</td>
</tr>
<tr>
<td>Undisclosed</td>
<td>14 (1.2)</td>
</tr>
<tr>
<td><strong>Highest education level</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>182 (15.6)</td>
</tr>
<tr>
<td>Primary</td>
<td>230 (19.7)</td>
</tr>
<tr>
<td>Secondary</td>
<td>486 (41.6)</td>
</tr>
<tr>
<td>College graduate</td>
<td>256 (21.9)</td>
</tr>
<tr>
<td>Undisclosed</td>
<td>15 (1.3)</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
</tr>
<tr>
<td>Artisan</td>
<td>74 (6.3)</td>
</tr>
<tr>
<td>Trader</td>
<td>832 (71.2)</td>
</tr>
<tr>
<td>Farmer</td>
<td>45 (3.8)</td>
</tr>
<tr>
<td>School teacher</td>
<td>52 (4.4)</td>
</tr>
<tr>
<td>University lecturer</td>
<td>14 (1.2)</td>
</tr>
<tr>
<td>Professional</td>
<td>6 (.5)</td>
</tr>
<tr>
<td>Civil servant</td>
<td>76 (6.50)</td>
</tr>
<tr>
<td>Other</td>
<td>83 (7.1)</td>
</tr>
<tr>
<td><strong>Religion</strong></td>
<td></td>
</tr>
<tr>
<td>Christianity</td>
<td>876 (74.9)</td>
</tr>
<tr>
<td>Islam</td>
<td>281 (24.0)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (1.0)</td>
</tr>
</tbody>
</table>
The use of CBE has been considered a surrogate for the standard screening modality in economically deprived countries and has been shown to produce good results. As a means of translating this into practice, we embarked on this study to obtain necessary information that may assist in developing a viable, culturally acceptable screening program. Our findings show that CBE uptake, although poor, is acceptable to the majority of the women without many social concerns.

Most of the respondents, who are women in their 40s, represent the population most affected by breast cancer in Nigeria and, indeed, most black populations. Although mammography is generally recommended in most instances for women older than age 40 years, survival benefit for women younger than age 50 years is controversial. Therefore, it may not be out of place to adopt CBE until capabilities are developed for routine mammography.

The fact that 94% of the respondents had heard about breast cancer is indeed a testimony to the relatively frequent occurrence of breast cancer in our society. However, one wonders what kind of knowledge is entrenched in the community given the high number of respondents who knew someone who died of breast cancer despite having received treatment in the hospital. The fact that less than half of the respondents believed breast cancer can be cured medically further solidifies the notion that breast cancer is mostly perceived as an invariably fatal disease. Although most deaths are a result of late presentation, they are usually attributed to failed treatment, thus perpetuating the idea that death is the inevitable consequence of breast cancer regardless of time of presentation or treatment. This is an aspect of community education that must be strongly addressed during awareness campaigns. However, improvements in the outcome of breast cancer treatment will be the most convincing evidence to correct this misconception.

With barely a third of women having ever had any form of breast cancer screening recommended to them, it is not surprising that less than one fifth have ever had a CBE, with the majority of these women not having received CBE in the past year. Health workers certainly play a major role in creating breast cancer awareness and making screening recommendations to their patients. As shown in this study, the majority of the recommendations were made by health workers. Contacts made with health personnel during visits to the hospital for various health challenges can be used as a means of creating awareness and for opportunistic CBE. A link can also be created between breast health programs and other primary health programs such as maternal and child health services, thereby using such platforms for screening. This leverages already existing infrastructure without creating a separate program that requires mobilization of resources specifically for breast cancer. This is a cost-effective design in resource-constrained settings where the incidence of breast cancer is not high enough for a cancer detection rate that justifies the investment of huge resources on a vertical program. Such an approach has also been favored by other breast cancer experts. Combining breast and cervical cancer screening is another approach that can be used as a cost-effective and more comprehensive screening program for women. This has also been successfully practiced with some good results.

### Table 2. Knowledge of Breast Cancer

<table>
<thead>
<tr>
<th>Question</th>
<th>Women, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever heard of breast cancer?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1,099 (94.0)</td>
</tr>
<tr>
<td>No</td>
<td>70 (6.0)</td>
</tr>
<tr>
<td>Do you know anyone who has had breast cancer?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>321 (27.5)</td>
</tr>
<tr>
<td>No</td>
<td>848 (72.5)</td>
</tr>
<tr>
<td>Did the person receive medical treatment?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>265 (82.5)</td>
</tr>
<tr>
<td>No</td>
<td>15 (4.7)</td>
</tr>
<tr>
<td>Do not know</td>
<td>41 (12.8)</td>
</tr>
<tr>
<td>Total</td>
<td>321 (100)</td>
</tr>
<tr>
<td>What was the outcome in that person?</td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>207 (64.5)</td>
</tr>
<tr>
<td>Alive and well</td>
<td>60 (18.7)</td>
</tr>
<tr>
<td>Alive but sick</td>
<td>32 (10)</td>
</tr>
<tr>
<td>Do not know</td>
<td>22 (6.8)</td>
</tr>
<tr>
<td>Total</td>
<td>321 (100)</td>
</tr>
<tr>
<td>Do you think breast cancer can be cured medically?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>482 (41.2)</td>
</tr>
<tr>
<td>No</td>
<td>209 (17.9)</td>
</tr>
<tr>
<td>Do not know</td>
<td>478 (40.9)</td>
</tr>
</tbody>
</table>
Training personnel to effectively carry out breast examinations is key to the success of such a program, and this has been successfully demonstrated by interventional programs that have used such a model.\textsuperscript{11,17} Nurses and midwives involved in maternal and child health, who make regular contacts with women, have been suggested as ideal personnel to carry out such examinations.\textsuperscript{16}

Although known to be relatively inexpensive without any requirement for technology, a CBE screening program will require funding for training and other running costs. However, the relatively lower cost of CBE compared with other screening modalities may serve as a basis for lobbying policymakers to incorporate it into the health insurance scheme in countries where such programs exist.\textsuperscript{18,19} A similar concept may also be of benefit in low- and middle-income countries where access to health care constitutes a challenge.

Because the breast is a private area of the body and because of the various social and religious factors that may hinder the acceptance of CBE, seeking the opinion of the target population about such intervention becomes imperative. This is particularly important because approximately 99\% of women respondents in our study ascribed to some religious affiliation. It is encouraging that more than two thirds of the respondents were willing to have regular CBEs. Responses from women who declined such examination suggest that with proper education and awareness, many more women are likely to be won over, given that the reasons for nonwillingness were related to lack of perceived need. Such perceptions are probably based on the misconception of the essence of screening as a test meant only for those who know they have the disease. Understanding the essence of screening should thus feature prominently during public education campaigns. Regarding women’s preferences for the sex of the examiner, it is quite interesting to note that the majority of women did not care about the sex of the examiner. This was the case regardless of age, level of education, or religion. This finding was also observed in a study from southern Nigeria that evaluated, among other factors, the impact of the examiner’s sex on breast screening practices.\textsuperscript{20} However, this finding may not be generalizable, bearing in mind the concept of hidden sociocultural and religious barriers. As such, it is recommended that early detection programs be implemented alongside educational programs coupled with modifications culturally appropriate to the target community.\textsuperscript{21}

As previously mentioned, there is a great opportunity for trained health personnel to provide breast cancer advocacy and screening to women who visit hospitals for various health challenges. A hospital-based CBE screening program can be designed to target such women. Even if the detection rate is low, minimal resources would be

### Table 3. Breast Cancer Screening Practices

<table>
<thead>
<tr>
<th>Question</th>
<th>Women, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has anyone recommended any method of early detection to you?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>441 (37.7)</td>
</tr>
<tr>
<td>No</td>
<td>728 (62.3)</td>
</tr>
<tr>
<td>How regularly do you examine your breasts?</td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td>365 (31.2)</td>
</tr>
<tr>
<td>Irregularly</td>
<td>275 (23.5)</td>
</tr>
<tr>
<td>Never</td>
<td>529 (45.3)</td>
</tr>
<tr>
<td>Have you ever had your breasts examined by a health practitioner (CBE)?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>230 (19.7)</td>
</tr>
<tr>
<td>No</td>
<td>939 (80.3)</td>
</tr>
<tr>
<td>When was the last time you had a CBE?</td>
<td></td>
</tr>
<tr>
<td>Within the past year</td>
<td>70 (6)</td>
</tr>
<tr>
<td>&gt; 1 year ago</td>
<td>160 (13.7)</td>
</tr>
<tr>
<td>Never had a CBE</td>
<td>939 (80.3)</td>
</tr>
<tr>
<td>Have you ever had a mammogram?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (2.8)</td>
</tr>
<tr>
<td>No</td>
<td>1,136 (97.2)</td>
</tr>
</tbody>
</table>

Abbreviation: CBE, clinical breast examination.
expended and awareness would increase. Women who do not visit hospitals regularly may be reached through community outreach programs. The willingness of women to have a breast examination, the few social concerns, and the negligible cost of CBE make a carefully designed program seem promising. In addition to creating an opportunity for early detection, CBE also serves as a means of improving the general health-seeking behavior of the populace, which certainly creates the necessary ground work for optimal use of standard screening facilities when they become widely available.

A limitation of this study is the lack of information on the perceptions of women and possible decisions that may be made in the event of a positive finding. Incorporating such information into prescreening awareness campaigns may promote compliance among those who screen positive. Another limitation is the homogeneity of the sampled population in terms of culture. Perhaps a more culturally diverse population reflecting the multiethnicity of Nigeria would make findings from this study more generalizable.

In conclusion, our findings show that CBE practice, although poor, is acceptable to the majority of women in the studied population with few social concerns. Creating awareness with educational programs is needed to correct erroneous perceptions about breast cancer and the need for screening.

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AUTHOR CONTRIBUTIONS

Conception and design: Olalekan Olasehinde, Carla Boutin-Foster, Olusegun I. Alatise, Adewale O. Adisa, Oladejo O. Lawal, Thomas P. Kingham

Collection and assembly of data: Olalekan Olasehinde

Data analysis and interpretation: Olalekan Olasehinde, Olusegun I. Alatise, Akinbolaji A. Akinkuolie, Abdul-Rasheed K. Adesunkanmi, Olujide O. Arije, Thomas P. Kingham

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Olalekan Olasehinde
No relationship to disclose

Carla Boutin-Foster
No relationship to disclose

Olusegun I. Alatise
No relationship to disclose

Adewale O. Adisa
No relationship to disclose

Oladejo O. Lawal
No relationship to disclose

Akinbolaji A. Akinkuolie
No relationship to disclose

Abdul-Rasheed K. Adesunkanmi
No relationship to disclose

Olujide O. Arije
No relationship to disclose

Thomas P. Kingham
No relationship to disclose

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Affiliations

Olalekan Olasehinde, Olusegun I. Alatise, Adewale O. Adisa, Oladejo O. Lawal, Akinbolaji A. Akinkuolie, Abdul-Rasheed K. Adesunkanmi, and Olujide O. Arije, Obafemi Awolowo University, Ile-Ife, Nigeria; Carla Boutin-Foster, State University of New York, Downstate Medical Center, Brooklyn; and Thomas P. Kingham, Memorial Sloan Kettering Cancer Center, New York, NY.

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REFERENCES


Factors Relating to Late Presentation of Patients With Breast Cancer in Area 2 KwaZulu-Natal, South Africa

abstract

Purpose Patients with breast cancer (BC) in Area 2 KwaZulu-Natal, South Africa, often present with advanced disease. We performed a review of the patients’ sociodemographic characteristics and their reasons for late presentation to identify what changes could be made to improve time to presentation.

Patients and Methods Fifty women with T1, T2, T3, or T4 BC were assessed for sociodemographic data. Patients in T3 and T4 groups were asked to provide reasons for late presentation.

Results Of 172 patients, 50 had T2, T3, or T4 BC, and 22 had T1. Age ranged from 23 to 100 years (average, 56 years). There was no significant difference in age for different tumor sizes. The average size of a T1 tumor was 1.8 cm; T2, 3.6 cm; T3, 11.4 cm; and T4, 14.8 cm. Regarding education, 19% of patients had never attended school (T1, 5%; T2, 12%; T3, 22%; T4, 32%), and 19% had completed their education (finished 12th grade). The average education level was 6th grade. Patients with larger tumors had less education ($P < .05$). Of the patients who lived in rural areas, 41% had T1, 52% had T2, 66% had T3, and 78% had T4 tumors ($P < .01$). Patients with larger tumors were associated with having less electricity in their homes than patients with smaller tumors ($P < .05$). Patients presented with a variety of symptoms. A breast lump was the presenting complaint in 96% of T1 and T2, 68% of T3 and 32% of T4; with a nipple or skin change, 2% of T3 and 8% of T4; because their families insisted, 6% of T3 and 8% of T4; because of pain, 24% of T3; and because of pain with malodorous smell, 50% of T4. Patients’ reasons for late presentation were fear (40%), not aware of disease severity (40%), fear of losing a breast (40%), referral problems (34%), financial problems (8%), and transportation problems (6%). Approximately 33% sought medical help from traditional healers, and 65% regularly attended clinics.

Conclusion Patients who presented late often lived in rural areas with fewer amenities (such as having no electricity in their homes), less education, and poor understanding of BC. Pictorial information about BC needs to be introduced to people who live in rural communities, and opportunistic screening needs to be provided at local clinics.

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INTRODUCTION

Area 2 in KwaZulu-Natal, South Africa, has a population of around 3.5 million people; 75% are younger than age 35 years. The population is largely rural and the majority are low income.1 Approximately 300 new cases of breast cancer (BC) are diagnosed in the public sector each year. From previous local studies, 48% of newly diagnosed patients with BC (54% of black women) required neoadjuvant or palliative oncologic treatment of inoperable or metastatic disease because of late presentation.2 These were women with American Joint Committee on Cancer (AJCC) classification of T4 or N3 or M1 BC.3 This could be attributed in part to sociodemographic factors. This study was undertaken to review the validity of this assumption and to identify where changes could be made to promote earlier presentation of women with BC.

PATIENTS AND METHODS

The AJCC staging system provides a strategy for grouping patients with respect to prognosis.3 TNM staging assesses the tumor (T), regional nodes (N), and distant metastases (M). Using the T component of this classification for BC, this prospective study (undertaken at Grey’s Hospital, KwaZulu-Natal, Pietermaritzburg, South Africa, during 2014) aimed to recruit 50 patients in each of the four T stages of BC. This was an arbitrary number that was considered obtainable within 1 year in our hospital. Sociodemographic data, presenting complaint of the patient, health-seeking
behaviors (clinic visits), and information on tumor size were collected. Those with T3 or T4 BC were asked why they delayed presenting and why they presented now. The information was entered into a local BC database approved by an ethics committee (Biomedical Research Ethics Committee Reference Number: BCA434/14). Fisher’s exact test was used to compare categorical variables. All tests were two-tailed and significance was set at \( P \leq .05 \). The duration of symptoms was not evaluated because we found that patients’ responses to this question were often unreliable and were not concordant with the clinical picture. Women with T3 or T4 BC often gave the duration of symptoms as a few weeks, which did not fit the clinical signs.

**RESULTS**

During 2014, data were collected prospectively on 50 women with BC in each T2, T3, and T4 group, but only 22 women with T1 BC were diagnosed and reviewed. Overall, 172 patients with BC were evaluated. The mean age was 56 years (range, 23 to 100 years). There was no significant difference in the average ages among the tumor size groups (T1, 55 years; T2, 59 years; T3, 52 years; T4, 57 years.) Ethnicity was self-reported: black, 82%; Indian, 9%; white, 5%; and colored, 4%. The average size of the tumors was 1.4 cm in the T1 group and 3.6 cm in the T2 group. A T3 tumor is > 5 cm; in this study, the mean T3 size was 11.4 cm (Fig 1). T4 lesions (invading the chest wall, ulcerated, having peau d’orange or inflammatory BC) had associated masses with a mean size of 14.8 cm (Fig 2).

Regarding education, 19% of patients had never attended school, and only 19% had completed high school (grade 12). The average level of education was 6th grade. Approximately one third, 32%, of patients with T4, 22% with T3, 12% with T2, and 5% with T1 lesions had never been to school. Patients with larger tumors had less education (\( P < .05 \)). This was significant for all ethnicities and for black patients alone (Fig 3). Only 27% of patients were employed, and there was no difference with respect to tumor size and employment. Women with more advanced tumor sizes were more likely to reside in rural areas (\( P < .01 \)) and to have no electricity in their homes (\( P < .05 \); Table 1).

Patients with T3 or T4 BC were asked why they had delayed presenting to a clinic or doctor; then they were given a list of possible reasons and asked to indicate which of the reasons applied to them. Forty percent of patients were not aware that the lump could be cancer, 40% did not understand the severity of their disease, 40% stayed away out of fear, 40% were afraid of losing a breast, and 34% had difficulty with the referral system and rural clinics. Only a few patients had financial (8%) or transportation (6%) issues. Approximately 33% of women with T3 or T4 cancers had seen a traditional healer before presenting, and one patient was a Sangoma (traditional healer) herself.

The main presenting complaint for women with T1 or T2 tumors was a lump (96%). Nipple discharge and breast pain were the other main concerns. The majority of women with T3 lesions (68%) presented because of a breast lump, and another 24% presented because of breast pain. The main concern for patients with T4 tumors was the malodorous smell with pain (Fig 4). Local clinics were attended monthly by 65% of all the study patients, 55% attended for antihypertensive medications, and 17% attended for antiretroviral medication (of whom 7% received treatment for hypertension as well). Overall, 17% were HIV positive.

**DISCUSSION**

BC is the most common cancer in women, accounting for 25.1% of all cancers. Incidence of BC in developed countries is higher, whereas relative...
mortality is highest in less developed countries. Educating women is suggested in all countries to help achieve early detection and treatment. In this study, we found that patients presenting with advanced cancers (T3 or T4 tumors) had lower levels of education. This may reflect their lack of understanding of the disease severity (40%) and that a breast lump might be malignant (40%). In Mongolia, employment and education were found to be associated with greater awareness of both cervical and breast cancers.

This study showed that the majority of patients lived in rural areas, which was significant with respect to tumor size. Other studies showed that women in rural areas had lower levels of knowledge of BC than those in urban areas. In a review of 1,590 participants from Bangladesh, 81.9% had never heard of BC, and awareness of BC was inversely associated with rural dwelling, primary education, and having no education.

The lack of electricity in women’s homes for the 30% of patients with T3 or T4 tumors may mean less exposure to media (radio and television) and less awareness of BC. Studies have shown that books, magazines, brochures, and television were among the most common sources of information regarding BC.

Forty percent of the women in our study with T3 or T4 BC were fearful of the hospital, 40% were concerned about loss of a breast, and approximately 33% had seen a traditional healer. Some of the same themes were identified as causes of late presentation in a study from Ghana, namely a lack of knowledge about BC, fear of cancer treatment and its outcomes, poverty, and traditional and spiritual beliefs. A strong influence of complementary and alternative medicine was cited as a reason for delay in presentation in Malaysia. A systematic review of 18 studies (a total of 6,183 participants) of black women with BC found that delay was multifactorial, individual, and complex. Factors that contributed to delay included poor knowledge of symptoms and risk factors, fear of detecting a breast abnormality, fear of cancer treatments, fear of partner abandonment, embarrassment at disclosing symptoms to health care professionals, taboos, and the stigma of having cancer. The review stated that one of its limitations was the paucity of studies conducted outside the United States. In Africa, ignorance, the use of alternative medicine, and a fear of surgery were common reasons given for late presentation.

A way to overcome these issues and improve time to presentation is through better education and awareness of BC. This should be done with visual aids such as videos that could be shown at local clinics. Discussion about BC with pictures of what to look for and who to see and how to proceed once a problem is identified would need to be included. Review could be undertaken by the community caregivers or nursing staff at the local clinics who could then give direct referrals to breast clinics in regional hospitals. It must be emphasized that early BC presentation may help preserve the breast and improve survival. Written pamphlets would be less useful in promoting BC awareness because many patients in our study could not read; 27% of patients with T3 or T4 BC

**Table 1. Percentage of Patients by Type and Location of Residence**

<table>
<thead>
<tr>
<th>Residence Type and Location</th>
<th>T Stage</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All T</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>78</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Live in rural areas, %</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Live in home without electricity, %</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>&lt; .05</td>
</tr>
</tbody>
</table>

Fig 3. Level of education for patients in each tumor stage group.
had never attended school, and the average grade completed (6th grade) was less than half that required for a high school education (12th grade). Nursing staff in the local clinics should be taught to do breast examinations and to opportunistically screen women. Screening could take place when patients present for their monthly supply of prescription medication: 65% of our study patients were receiving regular medications from local clinics. These measures to improve BC education along with providing supportive community personnel and easy referral systems are means for decreasing patient and system delays.

In conclusion, patients with BC who present late are often from rural areas with few amenities. They tend to have lower levels of schooling, poor understanding of BC, and are often fearful of hospitals and surgery. Pictorial means of conveying information about BC needs to be introduced to the rural community, along with opportunistically screening at local clinics. Methods of improving BC awareness and implementing easy referral systems to breast clinics should improve time to presentation and improve survival for patients with BC.

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AUTHOR CONTRIBUTIONS
Conception and design: Sharon R. Čačala
Collection and assembly of data: All authors
Data analysis and interpretation: Sharon R. Čačala
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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Sharon R. Čačala
No relationship to disclose

José Gilart
No relationship to disclose

Affiliations
All authors: Grey’s Hospital, University of KwaZulu-Natal, Pietermaritzburg, South Africa

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Pilot Educational Intervention and Feasibility Assessment of Breast Ultrasound in Rural South Africa

**Purpose** Breast cancer is the leading cause of cancer death in women worldwide, with high mortality in low- and middle-income countries because of a lack of detection, diagnosis, and treatment. With mammography unavailable, ultrasound offers an alternative for downstaging. The literature reports successful training in various domains, but a focus on the breast is novel. We assessed the feasibility (knowledge acquisition, perceived usefulness, and self-efficacy) of breast ultrasound training for nonphysician providers.

**Methods** Training was implemented for 12 providers at Hlokomela Clinic in Hoedspruit, South Africa, over 3 weeks. Didactic presentations and example cases were followed by a presurvey and test (n = 12). All providers received hands-on training with nurses as models; five providers trained with patients. A post-test (n = 12) assessed knowledge acquisition and a postsurvey (n = 10) assessed perceived program usefulness and provider self-efficacy.

**Results** The pre- to post-test averages improved by 68% in total and in four competencies (foundational knowledge, descriptive categories, benign vs malignant, and lesion identification). On the postsurvey, providers expressed that ultrasound could significantly influence breast cancer detection (9.1 out of 10), treatment (7.9 out of 10), and survival (8.7 out of 10) in their community and endorsed moderate confidence in their scanning (6.3 out of 10) and interpreting abilities (5.6 out of 10).

**Conclusion** Our research supports the feasibility of breast ultrasound training as part of a breast education program in low- and middle-income countries. Pre- and post-test results and observed proficiency indicate that training nonphysician providers is achievable; postsurvey responses indicate program acceptance, community-based ownership, and provider self-efficacy with ultrasound. Future work may show that breast ultrasound is viable for early detection where mammography is unavailable.

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**INTRODUCTION**

Breast cancer, the leading cause of cancer death among women,

1 is becoming an increasingly urgent problem in low- and middle-income countries (LMICs). By 2020, more than 1 million cases per year are projected to occur in LMICs alone,2 representing 70% of all cases worldwide.3 Although mortality rates in developed countries have decreased,4 they remain disproportionately high in LMICs because of late-stage presentation, indicating barriers in early detection and scarcity of resources for optimal treatment.5,6 For example, in a South African report, 78% of black women who had cancer presented with advanced-stage disease,7 which is consistent with a disparate 5-year survival rate of 53% in South Africa compared with 89% in the United States between 2005 and 2009.1 In addition, lack of awareness about breast cancer and screening poses barriers to downstaging.8,9 Strong evidence supports that early-stage diagnosis allows for initiation of effective treatment, which is vital to improving outcomes in LMICs.8,10,11

Although mammography is the gold standard for screening in developed countries, it is currently infeasible in limited-resource settings.10,11 Resources, infrastructure, and access to skilled breast care teams determine which screening tool is best for each location, from clinical breast examination (CBE) to mammography and molecular breast imaging.8,12 Ultrasound, used in developed countries to augment mammography and to examine localized findings, offers a viable alternative for screening in LMICs given the technology’s economy, portability, and versatility.11,13 Breast ultrasound has been shown to be particularly useful for imaging palpable lesions, differentiating cystic and solid masses, and describing
lesion features, thus aiding in the assessment of the likelihood of malignancy. Moreover, it has been argued that the breast cancer detection rate with ultrasound is comparable to the detection rate with mammography, and potentially greater than mammography in women with dense breasts. However, high false-positive rates have been put forth as a potential drawback of ultrasound screening. Although the literature reports successful training and use of portable ultrasound devices in limited-resource settings across many domains, a multiweek curriculum focused on breast ultrasound training for nonphysician providers is novel.

Our study assessed the feasibility, primarily defined by knowledge acquisition, perceived usefulness, and provider self-efficacy, of a breast ultrasound training program for nonphysician providers. Incorporated into an integrated early detection and education program in limited-resource settings, breast ultrasound has the potential to improve breast lesion characterization and thus enhance detection at stages when treatment is more effective, with the ultimate goal of reducing breast cancer mortality.

METHODS

Study Design and Setting

Our pilot study assessed the feasibility of training nonphysician providers (n = 12) in a limited-resource setting to use ultrasound for breast lesion detection. The curriculum-based training program included learning objectives, experiential hands-on training, and both pre- and posteducational assessments and was implemented at Hlokomela Clinic in Hoedspruit, South Africa. The clinic serves farm workers in the Maruleng and Bushbuckridge municipalities in the Limpopo and Mpumalanga provinces, respectively. The site was chosen for its nonprofit status, prominent standing in the community, and the staff’s willingness to incorporate breast cancer care into services offered. Training was focused on nonphysician providers because of their paramount role in patient care at Hlokomela and because of our belief that this would be the most sustainable approach.

Ultrasound Educational Intervention

The 3-week training program began with introductory didactic presentations that included breast cancer facts, indications for ultrasound, breast anatomy, ultrasound technical factors, lesion characterization, and example cases. The presentations were modified versions of presentations developed by a team with experience in implementing similar education programs in low-resource areas, and were based on the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) Atlas. The introductory session was followed by a presurvey (n = 12) to assess providers’ initial attitudes toward early detection and breast cancer knowledge. A pretest (n = 12; Data Supplement) was administered to elucidate areas in which to focus training and to serve as a baseline score for post-training comparison. Additional didactic resources were provided throughout the training, including handouts summarizing critical teaching points and step-by-step instructions for using the ultrasound equipment (Data Supplement), the ACR BI-RADS Atlas, and case discussions.

Most of the program consisted of experiential training. All providers received hands-on ultrasound training with nurses acting as models. Among the 12 providers, training was increased systematically so that five providers had additional training with 21 patients in total. Each patient visit involved gathering personal and family histories of breast cancer; screening for common symptoms including lump or thickening, discharge, skin changes, pain, and nipple abnormalities; performing a CBE; counseling on breast self-examination technique; and conducting whole breast ultrasound with the Chison Portable Eco 3, Version 1.0. Providers first observed patient visits, but by the program’s end were conducting visits under the supervision of the on-site trainer. This trainer performed a repeat CBE to ensure accuracy and reviewed scanning in real time. Images of any concerning ultrasound findings were sent to breast imaging radiologists (S.L., S.C.H.) for prompt consultation.

On-site ultrasound training, including the introductory presentations, was conducted by a medical student who had undergone an intensive 5-month breast ultrasound training program at Johns Hopkins Radiology in Baltimore, MD (L.K.D.). Breast imaging radiologists (S.L., S.C.H.) were involved extensively in all aspects of the training, including ensuring that the medical student was proficient in breast ultrasound, vetting the program curriculum and all training materials, communicating regularly during program implementation, and being readily available to provide remote consultation for ultrasound images. In addition, a radiologist (S.L.) visited Hlokomela before training, to ensure everything was in place for training to begin and to teach CBE to Hlokomela’s staff, and after training completion (S.C.H.), to assess the program’s success and to collaborate with Hlokomela on follow-up and future plans.
Assessment

Two methods of assessment were used to evaluate the training. First, a post-test (n = 12; Data Supplement) assessed knowledge retention and acquisition. The pre- and post-test content, which was based on the didactic presentations, ACR BI-RADS Atlas, and learning objectives, evaluated four competencies: foundational knowledge, descriptive categories for masses, benign and malignant characteristics, and lesion identification. Second, a postsurvey (n = 10) assessed program acceptance, perceived ultrasound usefulness, perceived successes and limitations of training, and provider self-efficacy and investment. Furthermore, provider proficiency with ultrasound and in conducting visits was observed by the on-site trainer.

Analysis

Pre- and post-test averages with 95% CIs and the percentage increase in test averages (n = 12) were calculated for the four competencies and the total scores. Paired t tests were used to determine if the difference between the pre- and post-test scores was significant (α = 0.05). Pre- and post-test averages and percentage increases were also calculated for the five providers who had undergone additional training. Average ratings on a 1 to 10 scale for postsurvey responses were calculated (n = 10 and n = 5). Provider responses regarding areas in which they felt most and least confident after training were summarized in pie charts (providers could list as many areas as desired).

RESULTS

A total of 12 nonphysician providers, including nurses (n = 4), nursing assistants (n = 3), and lay counselors (n = 5), completed the program. On the presurvey, all 12 providers responded that early detection is very important for survival (mean = 5, out of 5 possible), that breast ultrasound can detect cancer earlier, and that patients would be willing to receive breast ultrasound. Answers were more varied with respect to knowledge about the lifetime chance of developing breast cancer and 5-year survival in South Africa: 75% of providers correctly identified the answer to the former, whereas 33% correctly identified the latter. The pre- to post-test total averages (n = 12) improved by 68%, from 12.3 out of 28 points on the pretest to 20.8 out of 28 points on the post-test, with slightly greater increases for the five providers with additional patient training (71% improvement). Averages improved in all four competencies—foundational knowledge (focal zone placement, normal breast anatomy, and breast cancer symptoms); descriptive categories for mass characterization on the basis of the ACR BI-RADS lexicon (shape, orientation, margin, echo pattern, posterior features); benign and malignant characteristics; and lesion identification of common breast and axillary findings—by 59%, 72%, 28%, and 125%, respectively (P value for test of difference < .01, except for the “benign v malignant” competency P = .14; Table 1).

After the educational intervention, providers recognized that ultrasound could have a significant impact on breast cancer detection, treatment, and survival in their community, with an average rating on a 1 to 10 scale of 9.1, 7.9, and 8.7, respectively. There was a trend for higher ratings among the five with more training (9.6, 9.2, and 9.6, respectively). Providers also viewed the training program as useful (7.9 out of 10 [n = 10] and 9 out of 10 [n = 5]) and enjoyable (8.8 out of 10 [n = 10] and 10 out of 10 [n = 5]). Moreover, they indicated considerable investment in continuing breast ultrasound (7.5 out of 10 [n = 10] and 8.2 out of 10 [n = 5]) and spreading breast cancer awareness (9.3 out of 10 [n = 10] and 9.4 out of 10 [n = 5]; Table 2).

Providers expressed moderate confidence in scanning (6.3 out of 10) and image interpretation (5.6 out of 10), with the five with more training indicating slightly greater assurance (6.4 and 6.2,

### Table 1. Comparison of Pre- and Post-Test Averages by Competency and in Total

<table>
<thead>
<tr>
<th>Competency</th>
<th>Pretest Average, % (95% CI)</th>
<th>Post-Test Average, % (95% CI)</th>
<th>P*</th>
<th>Increase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foundational knowledge (5 points)</td>
<td>57 (40 to 74)</td>
<td>90 (83 to 97)</td>
<td>&lt;.01</td>
<td>59</td>
</tr>
<tr>
<td>Descriptive categories (12 points)</td>
<td>35 (25 to 45)</td>
<td>60 (49 to 70)</td>
<td>&lt;.01</td>
<td>72</td>
</tr>
<tr>
<td>Benign v malignant (5 points)</td>
<td>60 (40 to 80)</td>
<td>77 (56 to 98)</td>
<td>.14</td>
<td>28</td>
</tr>
<tr>
<td>Lesion identification (6 points)</td>
<td>39 (26 to 52)</td>
<td>88 (71 to 104)</td>
<td>&lt;.01</td>
<td>125</td>
</tr>
<tr>
<td>Total (28 points)</td>
<td>44 (33 to 55)</td>
<td>74 (64 to 84)</td>
<td>&lt;.01</td>
<td>68</td>
</tr>
</tbody>
</table>

*Two-sided paired t test of difference between the pre- and post-test means.
respectively). When asked to comment, providers listed scanning (“moving the [ultrasound] probe”), performing a CBE (“palpation”), and breast self-examination counseling as the skills in which they felt most confident (Fig 1A). However, they endorsed the need for additional practice to gain more self-assurance in image interpretation, image export (especially the process of sending images for remote consultation), and technical aspects such as measuring lesions and freezing and labeling images (Fig 1B).

**DISCUSSION**

In this pilot study, we implemented a short-term educational intervention involving didactic and experiential components that trained and assessed nonphysician providers in the use of breast ultrasound. We found that training for only 3 weeks resulted in acquisition of knowledge and skills, as well as provider self-efficacy. Furthermore, the intervention was well received, rated highly for usefulness, and successful in promoting community-based ownership of breast cancer awareness. Our research supports the feasibility of a training program for use of breast ultrasound in limited-resource settings as part of a larger breast cancer detection and education campaign.

Significant improvement from pre- to post-test scores in all four competencies indicates that trainees can learn practical information about breast ultrasound, thus demonstrating proficient knowledge after a short training course. This is consistent with the findings of a recent review of the use of portable ultrasound in LMICs by Becker et al,23 which suggested that short training programs, even for trainees with limited prior experience, can lead to substantial knowledge retention and skill acquisition. We consider the pre- to post-test objective assessment of knowledge acquisition to be a strength of our study.

We recognize that successful and sustainable education programs necessitate an affirmation of the local relevance of the project. To this end, Morgan and Deutschmann24 maintain that effective training programs in LMICs must maximize learner input and stake. Postsurvey responses indicate that providers felt strongly about breast ultrasound’s usefulness, with one commenting that its role is “early detection leading to early [treatment] and expanding life to the community.” In addition to viewing breast ultrasound as a valuable local service, providers demonstrated a commitment both to incorporating ultrasound into clinic practice and to promoting breast cancer awareness.

### Table 2. Average Ratings in Postsurvey Responses on a 1 to 10 Scale

<table>
<thead>
<tr>
<th>No. of Providers</th>
<th>Early Detection Impact</th>
<th>Treatment Impact</th>
<th>Survival Impact</th>
<th>Usefulness of Training</th>
<th>Enjoyment of Learning</th>
<th>US Investment</th>
<th>Awareness of Investment</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>9.1 (6, 10)</td>
<td>7.9 (4, 10)</td>
<td>8.7 (7, 10)</td>
<td>7.9 (5, 10)</td>
<td>8.8 (5, 10)</td>
<td>7.5 (5, 9)</td>
<td>9.3 (8, 10)</td>
</tr>
<tr>
<td>5</td>
<td>9.6 (8, 10)</td>
<td>9.2 (8, 10)</td>
<td>9.6 (9, 10)</td>
<td>9.0 (5, 10)</td>
<td>10.0 (10, 10)</td>
<td>8.2 (7, 9)</td>
<td>9.4 (9, 10)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are presented as average (minimum, maximum).

**Abbreviation:** US, ultrasound.
Providers expressed self-efficacy in skills fundamental to a breast ultrasound visit such as conducting scans and CBE. Although providers’ average confidence ratings were moderate, the on-site trainer observed a level of proficiency that would allow providers to perform independently with continued support. We view the providers’ desire for additional practice as a commitment to learning and skill mastery. Moreover, we systematically increased training among the 12 providers to try to understand how the magnitude of training might influence post-test scores, confidence, and opinions about breast ultrasound usefulness. We noted that the five providers who received additional training had slightly greater improvements in pre- to post-test scores and gave higher average ratings across all postsurvey questions. Although we can generally interpret this to mean that increased training correlates with greater knowledge and skills acquisition, statistically significant comparisons are limited because of the small sample size.

As noted across numerous studies, ultrasound has many advantages as a diagnostic imaging modality because it is safe, portable, inexpensive, and versatile; requires minimal maintenance; and is relatively easy to learn. Ultrasound continues to gain widespread use in limited-resource settings with applications in domains such as emergency medicine, obstetrics, cardiology, and infectious diseases. Furthermore, a number of studies have demonstrated success in ultrasound training exclusively for nonphysician providers. With breast cancer incidence and mortality rising steeply, we agree with Yip et al that research in LMICs should focus on strategies to downstage breast cancer at presentation. In addition, with mammography currently infeasible and a general shortage of doctors in limited-resource and rural settings, we believe breast ultrasound could fill a technology and physician gap in early breast cancer detection. In a recent breast ultrasound pilot project in the Kamuli District of Uganda, an experienced local sonographer was trained over 8 days in breast ultrasound, and all images were sent to an American board-certified radiologist for review. The authors concluded that breast ultrasound is a resource-appropriate strategy for breast cancer downstaging in LMICs. Our work offers a fresh perspective because it involved a multweek training program in both breast ultrasound use and image interpretation, was designed for local providers with no prior imaging experience, and relied on remote radiologists for occasional image consultation only.

A limitation of our study was that, although most providers spoke English well, there was a minor language barrier with less common words or more complicated medical terminology. This may have contributed to difficulty in communicating certain nuances of the pre- and post-test and survey questions. However, our data confirm that most of the training materials and assessments were well understood. Furthermore, because of the narrow timeframe, we could not systematically assess the trainees’ ability to properly and consistently detect lesions. We agree with the point made by Adler et al after the introduction of a portable ultrasound into a Tanzanian refugee camp that objectively assessing trainee skills is critical to Knowing that ultrasound is being used “effectively in medical decision making.” We also agree with the conclusion made by Lagrone et al in their review of ultrasound training opportunities that maintaining connections with local implementers is invaluable for long-term training success.

To this end, a radiologist (S.L.) has begun monthly visits to Hlokomela to continue ultrasound training and ensure quality control. This also addresses another potential limitation of our study—that time and travel constraints did not allow for board-certified radiologists to be on site during the 3-week training program. Because this was a feasibility assessment, our intention was to ascertain whether implementing a breast ultrasound training program for providers in limited-resource settings is achievable and thus has the potential to be beneficial with the direct involvement of breast imaging experts and longitudinal follow-up. Building on the success of this pilot study, future research will assess the efficacy of breast ultrasound screening by nonphysician providers in a longitudinal clinical study overseen by qualified medical professionals and with appropriate quality control measures.

The use of ultrasound in LMICs is well established, as is the efficacy of short-term training programs when post-training quality assessment and continued support are provided. Our pilot study is unique in that it involves breast ultrasound as a way to address the escalating urgency of breast cancer care by primarily nonphysician providers in limited-resource settings. Our findings support...
the feasibility of breast ultrasound training in rural South Africa, with the larger implication being that breast ultrasound could become a viable downstaging tool and point of care in other limited-resource settings where mammography is unavailable. Future directions should focus on obtaining additional high-quality data on the effectiveness and cost of ultrasound as a breast cancer screening tool in LMICs, including consideration of its potential limitations. Furthermore, we acknowledge that any early-detection technique must be paired with accessible diagnosis and treatment, work that we are exploring through additional projects. The vision is one of available, accessible, and centralized breast cancer care for women globally, empowering women to seek breast care early when lives can be saved by effective treatment. Next steps include needs and readiness assessment for larger populations and ultimately, implementation on a greater scale.

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AUTHOR CONTRIBUTIONS
Conception and design: Lindsay K. Dickerson, Susan Lucas, Susan C. Harvey
Collection and assembly of data: Lindsay K. Dickerson, Susan Lucas
Data analysis and interpretation: Lindsay K. Dickerson, Anne F. Rositch, Susan C. Harvey
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Lindsay K. Dickerson
No relationship to disclose
Anne F. Rositch
No relationship to disclose
Susan Lucas
No relationship to disclose
Susan C. Harvey
Travel, Accommodations, Expenses: Hologic

Affiliations
Lindsay K. Dickerson, Johns Hopkins University School of Medicine; Anne F. Rositch, Johns Hopkins Bloomberg School of Public Health; Susan C. Harvey, Johns Hopkins Medical Institutions, Baltimore, MD; and Susan Lucas, Chris Hani Baragwanath Academic Hospital, University of Witwatersrand School of Medicine, Johannesburg, South Africa.

REFERENCES
Knowledge and Attitudes About Breast Cancer in Limpopo, South Africa

Purpose Breast cancer survival is unacceptably low in many low-resource settings, including rural South Africa, where access to screening and treatment services is limited. To describe the context for implementing an early detection program, we assessed knowledge and attitudes toward breast cancer risk, early detection, and treatment.

Methods We conducted a cross-sectional survey among 243 women presenting to Hlokomela Clinic in Hoedspruit, South Africa, during April and May 2016. We used quantitative and qualitative analyses to determine levels of knowledge of risk factors, symptoms, and treatment of breast cancer, as well as experience with and attitudes toward detection and treatment methods.

Results Thirty-one percent of women correctly identified at least six of 12 risk factors for breast cancer, and 53.1% identified breast lumps as an important symptom. Although >97% of women stated that self–breast examination and early detection were highly important and that they would seek care for changes in their breasts, only 33.3% of women reported performing self–breast examination, and only 24.3% reported receiving a clinical breast examination. Age and education were not associated with knowledge, and level of knowledge did not predict care-seeking behaviors or attitudes.

Conclusion Although women demonstrated moderate levels of knowledge of breast cancer symptoms and risk factors and the importance of early detection, few women reported seeking services. These data demonstrate sufficient levels of knowledge and positive attitudes toward care seeking and suggest both a need and readiness for increased access to cost-effective services to facilitate early diagnosis and improved outcomes.

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INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women in both high- and low-resource settings.¹ Although widely recognized as a significant public health concern in developed nations, breast cancer is also becoming an increasingly urgent issue in low- and middle-income countries (LMICs). Both incidence and mortality rates in LMICs have dramatically increased over the past few decades, and a majority of deaths resulting from breast cancer now occur in developing nations.² In South Africa, breast cancer incidence has doubled in the past 20 years and now accounts for >20% of all female cancers.³,⁴ Despite rapidly increasing incidence rates, early detection and treatment remain extremely limited in LMICs, and these countries face significantly higher mortality rates than high-income countries. The average 5-year survival in Africa is half of that in the United States (50% vs 98.6%), and the age-standardized mortality rate for breast cancer in South Africa is 16.5 in 100,000, as compared with 14.1 in 100,000 in the United States.⁵,⁶,⁷

A primary cause of poor breast cancer survival in LMICs, including South Africa, is poor access to and uptake of early detection and cancer care. There is a paucity of research on breast cancer awareness and care-seeking behaviors in the rural provinces of Limpopo and Mpumalanga, South Africa. Therefore, we aimed to describe knowledge of and attitudes toward breast health in rural South Africa to determine the need and readiness for an early detection program in this population.

METHODS

Study Population and Design

We conducted a cross-sectional study at the Hlokomela Clinic in Hoedspruit, South Africa, from April to May 2016. The clinic serves both the Maruleng municipality in the Limpopo province and the Bushbuckridge municipality in the Mpumalanga province. The site was chosen because of its nonprofit status and long-standing positive presence in the community; the clinic population is demographically representative of our target
population (ie, African women living in rural areas). Participants were sampled consecutively; each woman age \( \geq 18 \) years was approached for inclusion.

Data collectors were members of the local community with experience in lay counseling and basic data collection, trained in both research methods and human research ethics and fluent in English, Xitsonga, and Northern Sotho (Sepedi). Data collectors collected written informed consent using a participant information sheet in the participant’s language of choice (English, Xitsonga, or Northern Sotho). Data collectors then verbally administered a five-page questionnaire in a quiet, private room. The five-part survey took approximately 10 minutes to administer and contained questions on demographic information, including age and level of education; personal and family histories of breast cancer; experience with breast cancer screening; knowledge of breast cancer risk and protective factors and symptoms; and knowledge of and attitudes toward breast cancer treatment. To assess knowledge of breast cancer risk and protective factors, participants were asked to state whether each of 12 factors increased the risk of breast cancer, decreased the risk of breast cancer, or had no impact (Table 1). We assigned a binary score of correct or incorrect to each response and totaled the percentage of risk factors or protective factors that participants correctly identified. Knowledge of and attitudes toward breast cancer treatment were assessed qualitatively, with participants asked to answer a series of open-ended questions. Ethical approval for this study was granted by the University of Witwatersrand Human Research Ethics Committee.

Data Analysis

Descriptive statistics are reported to describe the demographics of the study population. Percentages are reported for categorical variables including personal and family histories of breast cancer, screening and treatment histories, and knowledge of risk factors. We determined mean knowledge scores and categorized participants as having high or low knowledge on the basis of whether they were able to correctly identify \( > 50 \% \) of the 12 risk or protective factors.

Knowledge of symptoms and treatment and attitudes toward care seeking were assessed using qualitative methods. Qualitative analysis was conducted by coding and categorizing responses to open-ended questions. There were a total of three open-ended questions: “list any symptoms of breast cancer that you know of”; “if you think there is treatment available for breast cancer in South Africa, please explain what you understand that treatment to be”; and “please state any reason you can think of why you might not contact a doctor if you noticed changes in your breasts.” We categorized similar responses and reported totals for each symptom, treatment method, and reason for deferral that we identified.

One-way analysis of variance was used to compare mean knowledge scores between demographic groups. \( \chi^2 \) tests were used to determine associations between level of knowledge and self-reported action. All data analyses were conducted using STATA software (version 13.1; STATA, College Station, TX), and tests of significance were two tailed at \( \alpha = 0.05 \).

RESULTS

We interviewed a total of 243 black African women between the ages of 18 and 68 years, with a mean age of 38 years (standard deviation, 9.7 years). A majority (59.0\%) of respondents had an education level lower than grade 11, and 4\% had a university or postgraduate degree (Table 2). The self-reported prevalence of breast cancer in the population was 1.2\%; all of these women reported having received treatment. More than one third of women (33.8\%) reported knowing either a family member or community member who had been diagnosed with breast cancer, including 7.0\% who reported having a family member with breast cancer. Of women who reported knowing someone with breast cancer, 42.0\% knew at least one person who had died as a result of breast cancer.
Knowledge of Breast Cancer Risk Factors, Symptoms, and Treatment

Respondents demonstrated moderate levels of knowledge with regard to breast cancer risk factors, symptoms, and treatment. Nearly one third of women (31.3%) were able to correctly classify six of 12 risk factors (Table 1). Thirty-two percent of women demonstrated low understanding of risk factors, correctly identifying fewer than four risk or protective factors. On average, women were able to correctly classify 41.3% (standard deviation, 22.8%) of risk factors. Just over half of women (53.1%) were aware that a lump in the breast was a symptom of breast cancer. The second most frequently cited symptom was pain in the breast (23.9%), and the third was inflammation of the breast, with 23.9% of women listing this symptom.

In comparison with symptoms and risk factors, respondents had lower knowledge of breast cancer treatment, with 38.7% stating that they were unaware of the methods of treatment, and 2.9% stating that breast cancer is not treatable. Less than one third (31.3%) of respondents stated that medicine or pills are used for treatment, although only 1.7% specified chemotherapy. Mastectomy (25.9%) and lumpectomy (9.1%) were the second and third most commonly identified treatment methods (Table 3).

Attitudes Toward Care Seeking

Women in our population demonstrated strong positive attitudes toward care seeking, with > 97% of respondents stating that it was important to check their breasts regularly for breast cancer, that it was important to go to a physician or other care provider if they felt something abnormal in their breasts, and that they would be likely to go to a physician or other care provider should they notice changes in their breasts. A majority of women (67.1%) stated that they believed they would survive breast cancer if detection occurred early, whereas only 6.2% of women thought that they would be very likely to survive breast cancer if it was detected late. Women significantly overestimated their personal risk of breast cancer, with 47.7% responding that they were either very likely or somewhat likely to develop breast cancer in their lifetimes. The most commonly reported potential reason for not seeking care was fear of death or of having the breast cut off, although this was expressed by only 3.3% of respondents. Other potential reasons for not seeking care included lack of money, perceived poor quality of care at health facilities, long queues (particularly at public hospitals), and a belief that breast pain was not an important symptom. These reasons were only reported by a small minority of respondents (Table 3).

Access to Care and Care-Seeking History

In contrast to high levels of care-seeking intention, only 24.8% of women reported having ever received a clinical breast examination (CBE), and only 33.3% of women reported having ever conducted a self-breast examination (SBE; Table 3). Increased levels of knowledge did not predict care-seeking behaviors. There were no correlations between risk factor knowledge and reported history of conducting SBE (P = .43) or age (P = .10). Those with greater than grade 11 education did have a higher mean score for risk or protective factor identification (43.5% v 39.7% for those with ≤ grade 11 education), but this did not meet statistical significance (P = .20).

DISCUSSION

This study is the first to our knowledge to report data on knowledge, attitudes, and practices related to breast cancer in rural South Africa. Our findings generally echo those of similar studies conducted in urban and periurban settings in South Africa as well as other LMIC settings. Our results support findings from the Western Cape province that South African women perceive breast cancer to be both common and curable if detected early.8 Despite reported positive attitudes toward care seeking and higher levels of knowledge in comparison with those in other LMIC settings, our study identified an intention–action gap with respect to breast cancer care seeking in this population, indicating the need for increased access to early detection and treatment services. Knowledge of breast cancer risk factors was significantly higher than knowledge levels reported in similar studies across Africa.9 Conversely, women in our study population demonstrated lower levels of knowledge of breast cancer symptoms than those surveyed in the Western Cape, as well as lower levels of SBE (33.3% v 65.0%) and CBE.

Table 2. Study Population Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
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<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Grade 11</td>
<td>143</td>
<td>59.3</td>
</tr>
<tr>
<td>Grade 11</td>
<td>42</td>
<td>17.4</td>
</tr>
<tr>
<td>Matric</td>
<td>46</td>
<td>19.1</td>
</tr>
<tr>
<td>University</td>
<td>9</td>
<td>3.7</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Table 3. Knowledge of Breast Cancer Risk Factors, Symptoms, and Treatment

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td>Family history of breast cancer</td>
<td>47.7</td>
<td></td>
</tr>
<tr>
<td>Personal history of breast cancer</td>
<td>31.3</td>
<td></td>
</tr>
<tr>
<td>Menopause status</td>
<td>26.0</td>
<td></td>
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<tr>
<td>Obesity status</td>
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<td></td>
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<tr>
<td>Smoking status</td>
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<td></td>
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<tr>
<td>Drinking status</td>
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<td></td>
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<td>Physical activity</td>
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<td></td>
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<tr>
<td>Education level</td>
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<td></td>
</tr>
<tr>
<td>Age at menarche</td>
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<tr>
<td>Prior breastfeeding</td>
<td>26.0</td>
<td></td>
</tr>
<tr>
<td>Prior pregnancy</td>
<td>26.0</td>
<td></td>
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</tbody>
</table>

Table 4. Breast Cancer Treatment Methods

<table>
<thead>
<tr>
<th>Treatment Method</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy</td>
<td>25.9</td>
<td></td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>23.9</td>
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<tr>
<td>Hormone therapy</td>
<td>23.9</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>25.9</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9.1</td>
<td></td>
</tr>
</tbody>
</table>
Although reported family and personal histories in our population were lower than those in previous South African studies, the relatively high proportion of women reporting knowledge of a family or community member with breast cancer (33.8%) suggests breast cancer prevalence rates similar to those seen in high-income countries.3

In previous reports on LMICs, delays in the decision to seek care have been reported to be the result of cultural influences on the decision to act, including fatalism, fear of stigma, and preference for traditional healers.10 Although women in both rural and urban or periurban settings in South Africa demonstrate an intention–action gap with regard to breast cancer care seeking, women in our study did not report the same justifications for delay in care seeking as their urban counterparts. Krombein and De Villiers8 found that the most commonly cited reasons for choosing not to seek care among women in the Western Cape included a fear of being diagnosed with breast cancer, insufficient knowledge, pain of the procedure, and cost. Although a small proportion of women in our population identified these same barriers, a vast majority of women did not report any reason for delay in seeking care. The comparatively high levels of knowledge and positive attitudes toward care seeking identified in our study suggest that structural barriers, including poor access to care, are responsible for limited breast care use in this population.

In low-resource and economically transitioning countries, breast cancer control can be conceptualized as a spectrum of stages or implementation phases from CBE to advanced imaging, which may include mammography and breast magnetic resonance imaging. Although SBE and CBE may be the only feasible options in low-resource settings, when combined with education about the early signs and symptoms of breast cancer, these may be important tools to facilitate early detection.11 However, it is clear that, for a screening program to improve outcomes, an accessible treatment program must also be in place. There are several ways this could be achieved, again ranging from promising nonsurgical options such as ablative techniques to traditional treatments with surgery, chemotherapy, and/or radiation therapy.12 A similar paradigm, where alternative screening and treatment options are acceptable in a given context on the basis of available resources and capacities, has been put forth by the WHO for cervical cancer prevention.13 Thus, research is needed to provide an evidence base for alternative strategies to detect and treat breast cancer.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge</td>
<td></td>
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<tr>
<td>Low</td>
<td>78</td>
<td>32.4</td>
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<tr>
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<td>21.6</td>
</tr>
<tr>
<td>Known symptoms identified</td>
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<tr>
<td>Lumps</td>
<td>129</td>
<td>53.1</td>
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<tr>
<td>Pain in breast</td>
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<td>23.9</td>
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<td>Breast inflammation</td>
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<tr>
<td>Breast discharge</td>
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<td>Sores on breast</td>
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<tr>
<td>Infection</td>
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<td>1.2</td>
</tr>
<tr>
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<td>Medicine/pills</td>
<td>76</td>
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<td>Chemotherapy (specified)</td>
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<td>63</td>
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<tr>
<td>Lumpectomy (“remove lumps”)</td>
<td>22</td>
<td>9.1</td>
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<td>Traditional medicine</td>
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<tr>
<td>“There is treatment available for breast cancer in South Africa&quot;</td>
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<td>173</td>
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<td>1.3</td>
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<tr>
<td>Moderate</td>
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<td>4.6</td>
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<td>Somewhat unlikely</td>
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<td>9.1</td>
</tr>
<tr>
<td>Very unlikely</td>
<td>37</td>
<td>15.4</td>
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<tr>
<td>“How likely would you be to visit a doctor if you noticed changes in your breasts?”</td>
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<td></td>
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<tr>
<td>Very likely</td>
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<td>1.3</td>
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<td>0.4</td>
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<tr>
<td>Moderate</td>
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<td>0.4</td>
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<td>Somewhat unlikely</td>
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<td>Very unlikely</td>
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<tr>
<td>History of CBE</td>
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<td>75.0</td>
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<tr>
<td>Yes</td>
<td>60</td>
<td>25.0</td>
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</table>

Abbreviations: CBE, clinical breast examination; SBE, self-breach examination.
cancer that may be better suited to low-resource settings. The present research will be used to inform further work by the authors on alternative screening options, including breast ultrasound, as well as nonsurgical treatment options for low-resource settings.

There are limitations to this study that must be considered when interpreting the results. First, the sample size was relatively small and may not be representative of all women in the rural setting, because women were enrolled while seeking care at a primary health care clinic. Our study site, Hlokomela Clinic, also uses a peer health education model, in which trained community members (called nompilos) disseminate health information throughout the community. Thus, the women in this population may be both more educated about breast health and more comfortable with seeking health care than the general population in rural South Africa. The relative homogeneity of our population (with > 95% of participants having ≤ high school education) meant that we were unable to identify variations by education level. Future research should aim to determine whether differences in primary versus high school education predict levels of knowledge in low-resource settings, as well as what roles socioeconomic status and access to health services play in determining knowledge, attitudes, and practices. As is the case in all cross-sectional surveys, our study is subject to both misclassification and social desirability bias. Data on family and personal histories as well as history of early detection practices were dependent on self-report and thus may have been under- or over-reported, which is the standard in this region and generally in LMICs where no formal medical data collection exists. Social desirability bias may have led to over-reporting of care-seeking intentions. The adaptation of our survey from English for a low-literacy, Tsonga- and Sepedi-speaking population may have also led to misclassification. Women were asked in the survey how likely they were to visit a physician. After completion of the survey, it became clear that women in the study population typically distinguish between physicians and other care providers (eg, the general care practitioners and nurses who practice at local clinics). We were unable to assess familiarity with and history of screening ultrasound or mammogram, because of a translation error in the survey. Future research should seek to identify current practices with regard to these technologies in South Africa.

Women in our study population demonstrated moderate levels of knowledge about breast cancer risk factors and symptoms, recognized the importance of early detection for breast cancer treatment, and demonstrated positive attitudes toward care seeking for breast cancer despite low access to care in the region. Our data suggest that implementation of an early detection and treatment program has a high likelihood of acceptability. Further research is needed on the feasibility and impact of such a program.

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AUTHOR CONTRIBUTIONS

Conception and design: Lydia A. Trupe, Su Lucas, Susan C. Harvey
Collection and assembly of data: Lydia A. Trupe
Data analysis and interpretation: Lydia A. Trupe, Anne Rositch, Lindsay Dickerson, Susan C. Harvey
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Lydia A. Trupe
No relationship to disclose

Anne Rositch
No relationship to disclose

Lindsay Dickerson
No relationship to disclose

Su Lucas
No relationship to disclose

Susan C. Harvey

Travel, Accommodations, Expenses: Hologic

AFFILIATIONS

Lydia A. Trupe, University of Cape Town School of Public Health and Family Medicine, Cape Town; Su Lucas, University of Witwatersrand School of Medicine and Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa; Anne Rositch, Johns Hopkins Bloomberg School of Public Health; Lindsay Dickerson and Susan C. Harvey, Johns Hopkins University School of Medicine; and Susan C. Harvey, Johns Hopkins Hospital, Baltimore, MD.
REFERENCES

Abstract

Purpose The primary objective of this study was to evaluate 1- and 2-year survival rates and durable remissions in pretreated patients with advanced (unresectable or metastatic) malignant melanoma treated with ipilimumab in a South African expanded-access program (SA-EAP).

Patients and Methods This multicenter, retrospective study obtained data from pretreated patients with advanced malignant melanoma who were eligible for the ipilimumab SA-EAP. Ipilimumab was administered at a dose of 3 mg/kg intravenously every 3 weeks for four cycles to adults with advanced melanoma for whom at least one line of treatment for metastatic disease had failed. Data from the medical records of 108 patients treated within the SA-EAP were collected and statistically analyzed to determine overall (OS) and progression-free survival (PFS) at 1 and 2 years.

Results In the population of 108 patients, a median OS of 8.98 months (95% CI, 7.47 to 10.79 months) was observed. One-year OS was 36% (95% CI, 26% to 45%), and 2-year survival was observed as 20% (95% CI, 12% to 27%). The median survival without progression (ie, PFS) was 3.44 months (95% CI, 2.98 to 4.16 months), and 1- and 2-year PFS were 22% (95% CI, 14% to 29%) and 14% (95% CI, 8% to 21%), respectively. The longest recorded survival was 3.4 years. No independent prognostic variables were identified to predict for OS by multivariate Cox proportional hazards model.

Conclusion In this multicenter South African setting, ipilimumab at a dose of 3 mg/kg was an effective treatment with long-term OS in a subset of patients with pretreated advanced malignant melanoma.

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Introduction

In South Africa, melanoma is the eighth most common documented cancer in men, with a lifetime risk of one in every 186 men; in women, melanoma is the sixth most common cancer, with a lifetime risk of one in every 297 women. According to the South African National Cancer Registry (2005), whites are at higher risk; melanoma is the fifth most common cancer among white men and remains the sixth most common cancer in white women. Although evidence indicates that mortality rates are declining or stabilizing for certain populations or countries, partially because of heightened awareness and detection of disease at an earlier stage, mortality for advanced (unresectable or metastatic) melanoma remains high. Survival for stage IV disease, in particular, remains poor, with median survival times across studies ranging from 6 to approximately 12 months. Treatment of metastatic melanoma continues to represent a considerable unmet medical need on the basis of the rising worldwide incidence of the disease and the unsatisfactory efficacy and significant toxicities of currently available drugs.

Ipilimumab (YERVOY; Bristol-Myers Squibb, New York, NY) is a fully humanized monoclonal antibody directed against cytotoxic T-cell lymphocyte antigen-4 and the first treatment to demonstrate a survival benefit in advanced malignant melanoma. Efficacy data are largely based on results from two phase III clinical trials. The MDX010-20 study compared ipilimumab 3 mg/kg with an interventional vaccine, with increased median overall survival (OS) in the ipilimumab arm of 3.7 months (hazard ratio, 0.66; $P = .003$). The other study compared ipilimumab 10 mg/kg plus dacarbazine with dacarbazine alone, with higher 1-year OS in...
the ipilimumab arm (47.3% vs 36.3%). A meta-analysis of 15 trials reported a median OS of 18.8 months with ipilimumab monotherapy (at 3 mg/kg) compared with 12.3 months with single-agent chemotherapy. Because of the limited data reported on the use of ipilimumab in metastatic malignant melanoma in developing countries, our retrospective study was undertaken to evaluate the long-term outcomes of ipilimumab, administered within a South African expanded access program (SA-EAP) in pretreated patients with this disease.

**PATIENTS AND METHODS**

**Patient Population**

Patients were enrolled in the SA-EAP according to the following criteria: histologically confirmed stage III (unresectable) or stage IV (metastatic) cutaneous, ocular or mucosal melanoma, or asymptomatic brain metastases resulting from melanoma; failure of or intolerance to at least one prior systemic treatment; age ≥ 18 years; and Eastern Cooperative Oncology Group performance status of 2 or less. Patients were excluded from the study on the basis of contraindication to ipilimumab therapy (eg, known autoimmune disease, HIV, hepatitis B or C); presence of symptomatic brain metastases; receipt of other concurrent systemic anticancer treatments for melanoma; or presence of another active concurrent malignant disease, with the exception of adequately treated basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix.

**Study Design**

In this multicenter retrospective study, data were extracted from patients’ medical records to evaluate the outcomes of ipilimumab treatment. Institutional ethics approval was obtained from the Human Sciences Research Council of South Africa.

**Data Collection and Statistical Analysis**

The participating practices and academic institutions collected and recorded the required data on patient case report forms, which were returned to the study facilitator. The collected data were electronically captured on an Excel-based capturing tool (Microsoft, Redmond, WA) for analysis and analyzed using RStudio software (version 3.2.3; RStudio, Boston, MA).

Data from different points in time throughout a patient’s medical history were reviewed. These data included four aspects of treatment history: demographic features, disease characteristics, initial treatment at the time of enrollment in the SA-EAP, and courses of treatment. The data reported on patient- and disease-related factors, including demographic information, melanoma

### Table 1. Baseline Patient Demographic and Clinical Characteristics (N = 108)

<table>
<thead>
<tr>
<th>Characteristic</th>
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<td>Male</td>
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<td>(reported for n = 100 patients)</td>
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Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal.

*Time from advanced melanoma diagnosis to first ipilimumab dose.
Fig 1. Kaplan-Meier plot of overall survival (OS)
subtype and stage, presence of brain or liver metastases, lactate dehydrogenase values, BRAF mutational status, ECOG performance status, and previous treatments.

Treatment-related information included history of concomitant drug use, details of ipilimumab treatment (date of first ipilimumab dose, number of infusions, date of reinduction, and reason for discontinuation or omission), date of first measured disease progression (PD), and overall tumor response rate after completion of induction therapy. Distribution of overall tumor response (proportion of patients with complete response [CR], partial response [PR], stable disease [SD], or PD) was defined according to the sum of the numbers of patients with PR, CR, and SD. Objective response rate was defined as the sum of the numbers of patients with CR and PR. Relevant biologic values and incidence and grading of adverse events (AEs) were also collected. A total of 247 patients from 35 participating centers were registered in the ipilimumab SA-EAP. Ten patients underwent treatment reinduction, and one patient was reinduced twice. CRFs were received for 108 patients from 21 centers.

The collected data were statistically analyzed using descriptive statistics, with medians and ranges of continuous variables and frequencies and percentages for categorical variables. OS and progression-free survival (PFS) were estimated using the Kaplan-Meier method, with 95% CIs reported. A Cox proportional hazards model was used to identify covariates independently associated with survival.

OS was analyzed using time from ipilimumab initiation date and date of most recent visit or death, whichever occurred first. PFS was analyzed using time from ipilimumab initiation date to end of follow-up or date of first measured PD or death resulting from any cause, whichever occurred first. Patients with neither PD nor death were right censored at the last date of tumor assessment. Time to progression was defined as the sum of the numbers of patients with PD, CR, or SD. Objective response rate was defined as the sum of the numbers of patients with CR and PR. Relevant biologic values and incidence and grading of adverse events (AEs) were also collected. A total of 247 patients from 35 participating centers were registered in the ipilimumab SA-EAP. Ten patients underwent treatment reinduction, and one patient was reinduced twice. CRFs were received for 108 patients from 21 centers.

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Efficacy

The median OS (n = 108) was 8.98 months (95% CI, 7.47 to 10.79 months), and the 1-year survival rate was 36% (95% CI, 26% to 45%). The 2-year survival rate was 20% (95% CI, 12% to 27%). The median PFS (n = 108) was 3.44 months (95% CI, 2.98 to 4.16 months). The 1-year PFS rate was 22% (95% CI, 14% to 29%). The 2-year PFS rate was 14% (95% CI, 8% to 21%). At a median follow-up of 24 months, the median survival of patients who attained a CR, PR, or SD was not reached (Figs 1A to 1C).

Cox multivariate analysis for OS and PFS of various patient characteristics, using stepwise backward elimination, failed to demonstrate any significant variable. The relationships between absolute lymphocyte count and absolute eosinophil count and both OS and PFS were also examined. Although there was a trend toward increased OS and PFS with high absolute lymphocyte and eosinophil counts, significance was not demonstrated (P > .05).

The median time to progression (n = 108) was 3.44 months (95% CI, 2.98 to 4.16 months). Seventy-three percent of patients had experienced PD by 10 months (95% CI, 65% to 82%), and 90% (95% CI, 84% to 96%) had experienced PD by 40 months. Analysis of best overall response rates (n = 62) showed that the DCR was 53% (95% CI, 41% to 66%). Best overall response rates are listed in Table 2. According to the timeframes and retrospectively captured data, the median time to best response for patients whose best response was PR was 12 weeks; for patients achieving a CR, it was 24 weeks. Individual best overall response rates for patients with mucosal melanoma, uveal melanoma, or metastatic melanoma of unknown primary site are listed in Table 3.

AEs

Eleven severe AEs (grades 3 and 4) were reported; a majority of these were GI events. There were no reported deaths resulting from treatment-induced toxicities. Because these data were collected retrospectively, it is possible that toxicities were under-reported, particularly for grades 1 and 2. Additionally, and in view of the nature of the study, information on date of resolution and potential sequelae was not captured. AEs are summarized in Table 4.

DISCUSSION

This retrospective analysis of the SA-EAP in a population of 108 patients with advanced malignant melanoma showed that patients treated with ipilimumab obtained a median OS of 8.98 months (95% CI, 7.47 to 10.79 months) and 1-year OS of 36% (95% CI, 26% to 45%). These results are comparable to the outcomes reported in the prospective phase III pivotal trial of ipilimumab at a dose of 3 mg/kg in pretreated patients with melanoma.8 It must be emphasized that before registration of ipilimumab, there was no evidence-based second-line treatment approved

Table 4. AEs Reported During the Study

<table>
<thead>
<tr>
<th>AE</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td>8 (7)</td>
<td>3 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>6 (5)</td>
<td>10 (8)</td>
<td>7 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>2 (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood related</td>
<td>2 (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>5 (4)</td>
<td>3 (3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: AE, adverse event.

Table 5. Results of Published Ipilimumab EAPs

<table>
<thead>
<tr>
<th>Author and Country</th>
<th>Dose (mg/kg)</th>
<th>No. of Patients</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>1-Year OS (%)</th>
<th>2-Year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexander15 (Australia)</td>
<td>3</td>
<td>104</td>
<td>3</td>
<td>9.6</td>
<td>42.00</td>
<td>18.00</td>
</tr>
<tr>
<td>Ascierto16 (Italy)</td>
<td>3</td>
<td>833</td>
<td>3.7</td>
<td>7.2</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Delyon17 (France)</td>
<td>3</td>
<td>73</td>
<td>NR</td>
<td>9.1</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Wilgenhof18 (Belgium)</td>
<td>3</td>
<td>50</td>
<td>NR</td>
<td>7</td>
<td>45.20</td>
<td>28.80</td>
</tr>
<tr>
<td>Ahmad19 (UK)</td>
<td>3</td>
<td>193</td>
<td>2.8</td>
<td>6.1</td>
<td>31.00</td>
<td>14.80</td>
</tr>
<tr>
<td>Berrocal20 (Spain)</td>
<td>3</td>
<td>144</td>
<td>NR</td>
<td>6.5</td>
<td>32.90</td>
<td>NR</td>
</tr>
<tr>
<td>Ku14 (USA)</td>
<td>10</td>
<td>53</td>
<td>2.6</td>
<td>7.2</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Altomonte21 (Italy)</td>
<td>10</td>
<td>74</td>
<td>7</td>
<td>NR</td>
<td>17.00</td>
<td>NR</td>
</tr>
<tr>
<td>SA-EAP (South Africa)</td>
<td>3</td>
<td>108</td>
<td>3.4</td>
<td>8.9</td>
<td>36.00</td>
<td>20.00</td>
</tr>
</tbody>
</table>

Abbreviations: EAP, expanded-access program; NR, not reported; OS, overall survival; PFS, progression-free survival; SA-EAP, South African expanded-access program.
or recommended by South African guidelines for these patients.

These outcomes exceed suggested benchmark survival targets (proposed from a meta-analysis of second-line melanoma treatments) of 6.5 months for median OS and 25% for 1-year OS. The real-world survival data from our study are similar to those reported in an ipilimumab access scheme using a 10-mg/kg dosing regimen (median OS, 7.2 to 9 months). The median PFS of 3.44 months (95% CI, 2.98 to 4.16 months) was also similar to those reported in an Australian study of a similar nature (3.0 months; 95% CI, 2.7 to 3.4 months) and in another published access scheme study (95% CI, 2.6 to 4.3 months).

One of the main weaknesses of our study relates to the retrospective nature of the investigation, the difficulties in controlling for selection bias, and the lack of a control group. A proportion of our patients did not complete ipilimumab treatment because of PD. Some of these patients may have had a short, predictable life expectancy with advanced disease. These patients are typically heavily overtreated and have limited therapeutic options and a lack of alternative options; they had an opportunity to receive ipilimumab within the framework of this EAP. As a result of the retrospective nature of the study, investigations of patients did not occur at predefined times; therefore, this may have resulted in over-reporting of DCR.

Of the 108 patients, 43% discontinued ipilimumab permanently before having completed four doses. PD was cited as the most common reason for discontinuation of treatment. These results are comparable to those of other studies using a 3-mg/kg dose of ipilimumab (33% v 40.3%). Only 2% of patients discontinued treatment with ipilimumab because of severe immune-related AEs. This incidence is somewhat lower than percentages reported in the other studies (9.9% and 11.1%) however, the retrospective nature of our study might account for this observation.

Overall, our results are in line with those previously reported for EAPs with ipilimumab at doses of 3 and 10 mg/kg. Those results are summarized in Table 5.

One of the main weaknesses of our study relates to the retrospective nature of the investigation, the difficulties in controlling for selection bias, and the lack of a control group. A proportion of our patients did not complete ipilimumab treatment because of PD. Some of these patients may have had a short, predictable life expectancy with advanced disease. These patients are typically heavily overtreated and have limited therapeutic options and a lack of alternative options; they had an opportunity to receive ipilimumab within the framework of this EAP. As a result of the retrospective nature of the study, investigations of patients did not occur at predefined times; therefore, this may have resulted in over-reporting of DCR.

Some patients with melanoma treated with ipilimumab exhibit an initially increased size of tumor lesions, proved by biopsy as inflammatory cell infiltrates or necrosis, followed by a decreased tumor burden. These immune-related response patterns have been recognized in clinical trials of ipilimumab, including the documentation of new tumors associated with edema and infiltrates of immune cells and transient increases in baseline tumor lesions. Clinicians should be aware of the possible presence of pseudotumor progression, which could be regarded as PD. However, this effect occurs in less than 10% of patients and could not account for the early PD documented among the pretreated patients with metastatic melanoma accrued into our EAP.

Of the 108 patients, 43% discontinued ipilimumab permanently before having completed four doses. PD was cited as the most common reason for discontinuation of treatment. These results are comparable to those of other studies using a 3-mg/kg dose of ipilimumab (33% v 40.3%). Only 2% of patients discontinued treatment with ipilimumab because of severe immune-related AEs. This incidence is somewhat lower than percentages reported in the other studies (9.9% and 11.1%) however, the retrospective nature of our study might account for this observation.

Treatment with ipilimumab is associated with immune-related AEs. These immune-related AEs are related to the drug mechanism of action. In comparison with other published studies of ipilimumab, the overall incidence of grade 3 and 4 immune-related AEs (9.2%) in the SA-EAP was similar to that reported in the multicenter phase III
randomized controlled trial conducted by Hodi et al. These data suggest that the toxicity profile in the real-world setting is not different from that observed in clinical trial settings. Additionally, the use of ipilimumab at a dose of 3 mg/kg has a better safety profile than at 10 mg/kg, with similar outcomes. Some patients discontinued treatment early, decreasing the chance of developing immune-related AEs, which may account for the lower incidence of immune-related AEs.

Prior reports have indicated that an increase in absolute lymphocyte count and absolute eosinophil count occurring 3 weeks after treatment initiation may be associated with improved survival. Our data failed to show that. However, this once again may be a result of the retrospective nature of our study. Future studies should address this issue to further characterize this observation. Prospective studies examining lymphocyte subpopulations are required.

One of the most important aspects of treatment with checkpoint inhibitors is the improvement in survival and documentation of long-term durable remissions in some patients (Figs 2A and 2B). Future research should focus on improving the number of patients who will experience durable remissions and should include combination with other checkpoint inhibitors, gene therapy, vaccine therapy, and other immunostimulatory approaches.

In conclusion, our study of ipilimumab in the South African setting found that the efficacy and tolerability of ipilimumab at 3 mg/kg for the treatment of unresectable metastatic melanoma in pretreated patients align with data reported in several published studies with similar treatment doses and patient populations.

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AUTHOR CONTRIBUTIONS
Conception and design: Bernardo L. Rapoport, Daniel A. Vorobiof, Lydia M. Dreosti, Adam Nosworthy, Georgina McAdam, Helen Miller-Jansön, Margreet de Necker, Hennie Duvenhage
Provision of study materials or patients: Daniel A. Vorobiof, Adam Nosworthy
Collection and assembly of data: Bernardo L. Rapoport, Daniel A. Vorobiof, Lydia M. Dreosti, Adam Nosworthy, Georgina McAdam, Johan P. Jordaan, Helen Miller-Jansön, Margreet de Necker
Data analysis and interpretation: Bernardo L. Rapoport, Daniel A. Vorobiof, Lydia M. Dreosti, Georgina McAdam, Johan P. Jordaan, Helen Miller-Jansön, Margreet de Necker, Janetta C. de Beer
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/twc or ascopubs.org/jco/site/ifc.

Bernardo L. Rapoport
Honoraria: Tesaro, Merck, Bristol-Myers Squibb
Consulting or Advisory Role: Tesaro, Merck, Bristol-Myers Squibb
Speakers’ Bureau: Tesaro, Merck, Bristol-Myers Squibb
Research Funding: Tesaro, Merck, Bristol-Myers Squibb
Travel, Accommodations, Expenses: Tesaro, Merck, Bristol-Myers Squibb

Daniel A. Vorobiof
Consulting or Advisory Role: Amgen, Roche, Bristol-Myers Squibb

Lydia M. Dreosti
Honoraria: Roche, Janssen Pharmaceuticals
Consulting or Advisory Role: Roche, Janssen Pharmaceuticals, Novartis
Speakers’ Bureau: Janssen Pharmaceuticals
Travel, Accommodations, Expenses: Roche, Janssen Pharmaceuticals, Merck Serono

Adam Nosworthy
Speakers’ Bureau: Key Oncologics
Travel, Accommodations, Expenses: Bristol-Myers Squibb, Janssen Oncology

Georgina McAdam
No relationship to disclose

Johan P. Jordaan
Speakers’ Bureau: Merck Serono
Research Funding: Roche, PAREXEL International, Ipsen, Quintiles, Novartis
Travel, Accommodations, Expenses: Roche

Helen Miller-Jansön
Consulting or Advisory Role: HEXOR (Inst)
Research Funding: HEXOR (Inst)

Margreet de Necker
Consulting or Advisory Role: HEXOR (Inst)
Research Funding: HEXOR (Inst)

Janetta C. de Beer
Consulting or Advisory Role: HEXOR (Inst)
Research Funding: HEXOR (Inst)

Hennie Duvenhage
Employment: Bristol-Myers Squibb
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Affiliations
Bernardo L. Rapoport, Medical Oncology Centre of Rosebank; Daniel A. Vorobiof, Sandton Oncology Center; Adam Nosworthy, Wits Oncology Donald Gordon Medical Center; Hennie Duvenhage, Bristol-Myers Squibb South Africa, Johannesburg; Lydia M. Dreosti, University of Pretoria, Pretoria; Georgina McAdam, Rondebosch Oncology Medical Center, Cape Town; Johan P. Jordaan, Westridge Oncology Center, Durban; and Helen Miller-Jansén, Margreet de Necker, and Janetta C. de Beer, HEXOR, Midrand, South Africa.

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REFERENCES


Systematic Review and Meta-Analysis of Individual Patient Data to Assess the Sensitivity of Cervical Cytology for Diagnosis of Cervical Cancer in Low- and Middle-Income Countries

Purpose To assess the sensitivity of cervical cytology to cancer by pooling individual patient cytology results from cancers diagnosed in studies that assessed cervical screening in low- and middle-income countries.

Methods Two authors reviewed studies identified through PubMed and Embase databases. We included studies that reported cervical cytology in which at least one woman was diagnosed with cervical cancer and in which abnormal cytology results were investigated at colposcopy and through a histologic sample (if appropriate). When cytology results were not reported in the manuscript, authors were contacted. Stratified analyses and meta-regression were performed to assess sources of heterogeneity between studies.

Results We included 717 cancers from 23 studies. The pooled sensitivity of cytology to cancer at a cutoff of a high-grade squamous intraepithelial lesion (HSIL) or worse was 79.4% (95% CI, 67.7% to 86.0%). Results from stratified analyses did not differ significantly, except among studies that recruited symptomatic women or women referred because of abnormal cytology, when the sensitivity of cytology was much higher (95.9%; 95% CI, 86.5% to 99.9%). The cutoff of an HSIL or worse detected 85% of the cancers that would have been detected at a cutoff of atypical squamous cells of undetermined significance or worse (relative sensitivity, 85.2%; 95% CI, 80.7% to 89.7%).

Conclusion Cytology at a high cutoff could be an excellent tool for targeted screening of populations at high risk of cervical cancer with a view to diagnose cancer at an earlier stage.

INTRODUCTION

Cervical cancer is the fourth most common cancer in women. Approximately 85% of the global burden occurs in less-developed regions. To reduce the incidence of cervical cancer, screening has been offered to women in an attempt to identify precursors that can be treated to avoid progression to cancer. Cervical cytology relies on the ability of sample takers to sample the affected region adequately and on the ability of observers to identify precursor disease. In less-developed countries, the lack of both infrastructure and quality management has led to wide variations in the sensitivity and specificity of cytology testing. In a recent meta-analysis that compared screening methods in low-income countries, the sensitivity of cervical cytology to cervical intraepithelial neoplasia (CIN) grade 2 or worse (CIN2+) in studies that assessed visual inspection with acetic acid and cytology ranged from 33% to 100%. This wide variation in cytology performance has meant that recent research has focused on new screening technologies (eg, human papillomavirus [HPV] testing), which are less user dependent.

In resource-poor settings with limited facilities to treat advanced cancers, the ability to use cytology in targeted high-risk populations as a tool to detect cancer at an early stage could have a big impact on cervical cancer mortality. However, little has been published on the sensitivity of cytology to cancer, and strategies to detect cervical cancer at an early stage have been overlooked.
Here, we aim to assess the sensitivity of cytology to cancer by pooling cytology results from cancers diagnosed among participants in studies that assessed cytology screening in low- and middle-income countries (LMICs).

METHODS

Inclusion Criteria and Outcomes

The protocol outlined the research question, populations, exposures, outcome of interest, search strategies, study selection, inclusion and exclusion criteria, and methods for data extraction and statistical analysis (including subgroup analyses but not the meta-regression).

We searched the PubMed and Embase databases with standard terms to cover the concepts of cervical intraepithelial neoplasia, sensitivity, Pap test and developing countries (see Data Supplement for the full search description). We searched for published articles that resulted from identified conference abstracts. In addition, bibliographies of published papers were searched to locate additional papers. A few manuscripts were identified after authors were contacted about related studies. We identified studies in English published through December 2014 that included cytology, were conducted in LMICs (as determined by the World Bank list of economies, July 2014), and in which at least one woman was diagnosed with invasive cervical cancer.

All studies were reviewed by two investigators independently (divided among A.C., R.L., D.M., H.L., and R.B.) for eligibility criteria according to a standardized inclusion form. Any differences of opinion were reconciled by a consensus between A.C. and R.L.

Inclusion criteria were studies that reported cervical cytology and confirmed abnormal results at colposcopy and through a histologic sample (if appropriate). Studies were eligible even if the cytology results were not reported in the manuscript. We excluded studies restricted to HIV-positive women, studies of women who had all previously undergone cervical treatment, and studies that were restricted to women who had a single cytology result (eg, only atypical squamous cells of undetermined significance [ASCUS] cytology). Most cytology results were reported with the Bethesda system terminology; however, a few studies used CIN terminology. We classified results in risk order as follows: normal; inadequate; ASCUS; mild dysplasia/CIN grade 2, severe dysplasia/CIN grade 3, carcinoma in situ, and adenocarcinoma in situ grouped with HSIL; and squamous and adenocarcinoma grouped as invasive cancers.

Two studies reported both conventional and liquid-based cytology (LBC). However, the LBC was reported by experts, so conventional cytology results were considered in the main analysis. As a subanalysis, we show LBC results from these two studies and from those in Zhao et al.

Data Collection Process

When data were not reported in the required format in the published manuscript, we attempted to contact the corresponding author from each study via e-mail. Two reminders were sent during a period of 8 months and/or alternative authors were contacted.

We collected information on the cytology results and number of cancers by asking the authors to complete a simple table of aggregated data (Data Supplement). Results reported in the manuscript were extracted directly.

Information was extracted from each included study on the following: study population data, including country, age, and inclusion and exclusion criteria; study design, including type of screening tests offered, population enrolled, and criteria for assessment of disease; number of women tested with cytology overall and with a cancer diagnosis; type of cytology laboratory used; and cytology results from the last test before cancer diagnosis regardless of how long before diagnosis.

Two authors assessed the quality of included studies through the QUADAS-2 tool for quality assessment of diagnostic accuracy studies. Disagreements were resolved through discussion.

Summary Measures and Data Analysis

Sensitivity was calculated as the proportion of women with cancer who had a positive test when ASCUS or worse, LSIL or worse, and HSIL or worse were considered. Exact binomial 95% CIs were calculated (and, when the sensitivity was 100% or 0%, we estimated 97.5% one-sided intervals). We performed a variance-stabilizing transformation by taking the arcsine of the square root of the sensitivity estimate and 1 divided by (4 x the number of cancers) as the variance. These were analyzed in STATA 12 with the METAAN command (StataCorp, College Station, TX). The pooled estimates (and 95% CIs) were back-transformed to give the sensitivity.
We assessed statistical heterogeneity with the Cochran $Q$ and Higgins $I^2$ tests, and we defined heterogeneity as $I^2 > 25\%$ or $P < .05$. In addition, meta-regressions were run as separate univariate analyses to estimate how much of the heterogeneity was explained by covariates.\textsuperscript{9,10}

Subanalyses and meta-regressions were conducted by pooling results from studies on the basis of the following: criteria for assessment of disease—all enrolled women were referred for colposcopy assessment, or women who tested positive to any screening test were referred to colposcopy; type of population studied—symptomatic women and those referred after an abnormal cytology test, or a screening population; quality of cytopathology—local laboratory without mention of special training for the study (lower quality), or a cancer referral center cytopathology laboratory or training and quality assurance carried out as part of the study (higher quality); number of cancers in each study—one to nine cancers (small), 10 to 24 cancers (medium), or 25 or more cancers (large); World Bank developmental indicator—LMIC (no studies in low-income countries), or upper-middle income country; and type of screening test offered—HPV testing, no HPV testing, or LBC.

To explore how the quality of cytology affects the sensitivity of the test, we included as a continuous variable in the meta-regression the sensitivity of cytology to CIN2+ at a cutoff of an ASCUS or worse, when available.\textsuperscript{4,11-23}

Details of Ethics Approval
The study used a combination of previously published data and aggregated data from individual studies. All data were anonymous. No ethical approval was required.

RESULTS
A total of 570 unique studies were identified through PubMed and Embase. An additional 27 studies were identified through searches of reference lists. Of the 597 abstracts reviewed, 426 (71\%) were excluded. Full texts were reviewed for 166 papers; we were unable to locate five papers. We excluded 26 manuscripts with no original data, 41 that were not relevant or did not contain any cervical cancers, and 33 because of duplication of data across more than one manuscript. Three manuscripts were published before 1994, and, although we attempted unsuccessfully to contact the authors, we considered it unlikely that research data would have been kept for longer than...
Table 1. Summary of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country/World Bank Development Indicator 2014</th>
<th>Type of Study/Type of Population/Women Tested/Age of Women (years)</th>
<th>Screening Tests Offered</th>
<th>Criteria for Referral to Colposcopy</th>
<th>Risk of Bias (QUADAS-2)*</th>
<th>Quality Assurance of Cytology</th>
<th>Cancer With HSIL or Worse Cytology/Total No. of Cancers in Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatla et al13 (2012)</td>
<td>India/lower middle</td>
<td>Cross-sectional/symptomatic; 512 women age &gt;30</td>
<td>Conventional, VIA, HPV (self and clinician administered)</td>
<td>All women offered colposcopy</td>
<td>Low risk of bias</td>
<td>Cytology read and reported at the local laboratory</td>
<td>7/8</td>
</tr>
<tr>
<td>Boonlikit25 (2008)</td>
<td>Thailand/upper middle</td>
<td>Retrospective review/women who attended colposcopy after abnormal (LSIL or worse); 421 women ages 16-66</td>
<td>Conventional</td>
<td>All women had colposcopy</td>
<td>At risk for bias</td>
<td>Cytology was read at the local laboratory</td>
<td>19/19</td>
</tr>
<tr>
<td>Christie et al14 (2008)</td>
<td>India/lower middle</td>
<td>Cross-sectional/symptomatic; 100 women ages 20-75</td>
<td>Conventional, VIA, VILI, vaginal pH, Whiff test</td>
<td>All women had colposcopy</td>
<td>Low risk of bias</td>
<td>Cytology slides read at the cancer referral hospital</td>
<td>3/3</td>
</tr>
<tr>
<td>Cremer et al30 (2010)</td>
<td>El Salvador/lower middle</td>
<td>Cross-sectional/women who attended colposcopy after abnormal (ASCUS or worse); 207 women age 18-70</td>
<td>DART (digital camera) v colposcopy</td>
<td>All women had colposcopy</td>
<td>At risk for bias</td>
<td>Cytology read and reported at community laboratories</td>
<td>4/5</td>
</tr>
</tbody>
</table>

(Continued on following page)
Table 1. Summary of Included Studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country/World Bank Development Indicator 2014</th>
<th>Type of Study/Type of Population/Women Tested/Age of Women (years)</th>
<th>Screening Tests Offered</th>
<th>Criteria for Referral to Colposcopy</th>
<th>Risk of Bias (QUADAS-2)*</th>
<th>Quality Assurance of Cytology</th>
<th>Cancer With HSIL or Worse Cytology/Total No. of Cancers in Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Vuyst et al (2005)</td>
<td>Kenya/lower middle</td>
<td>Cross-sectional/Women who attended family planning clinic (includes both screening and referred because of abnormal ASCUS or worse); 629 women ages 25-55</td>
<td>Conventional, VIA, HPV and cervicography</td>
<td>All women were offered colposcopy</td>
<td>Low risk of bias</td>
<td>Cytology read and reported at the local laboratory</td>
<td>6/6</td>
</tr>
<tr>
<td>Denny et al (2000)</td>
<td>South Africa/upper middle</td>
<td>Cross-sectional/unscreened women; 2,944 women ages 35-65</td>
<td>Conventional, HPV, VIA, direct visual inspection, and cervigram</td>
<td>Positive on any test</td>
<td>Low risk of bias</td>
<td>Cytology slides interpreted locally at a highly quality assured laboratory</td>
<td>9/12</td>
</tr>
<tr>
<td>Deodhar et al (2012)</td>
<td>India/lower middle</td>
<td>Cross-sectional/unscreened; 5,440 women ages 30-49</td>
<td>Conventional, VIA, VILI</td>
<td>All women offered colposcopy</td>
<td>Low risk of bias</td>
<td>Cytology and sample takers retrained every 6 months; final results are consensus of two or three cytopathologists</td>
<td>14/22</td>
</tr>
<tr>
<td>Ferreccio et al (2003)</td>
<td>Costa Rica/upper middle</td>
<td>Cohort/screening population; 8,481 women with conventional cytology and 8,082 with LBC age ≥ 18</td>
<td>Conventional, LBC, cervicography, HPV</td>
<td>Positive on any test and a sample of those testing negative</td>
<td>At risk for bias</td>
<td>Highly trained sample takers; conventional cytology read locally by cyto technicians and a pathologist; LBC read in the United States</td>
<td>12/24</td>
</tr>
<tr>
<td>Goel et al (2005)</td>
<td>India/lower middle</td>
<td>Cross-sectional/ symptomatic women; 400 women; mean age, 32.6</td>
<td>Conventional, VIA</td>
<td>All women had colposcopy</td>
<td>Low risk of bias</td>
<td>Cytology slides read at a cancer referral hospital</td>
<td>1/1</td>
</tr>
</tbody>
</table>

(Continued on following page)
<table>
<thead>
<tr>
<th>Study</th>
<th>Country/World Bank Development Indicator</th>
<th>Type of Study/Type of Population/Women Tested/Age of Women (years)</th>
<th>Screening Tests Offered</th>
<th>Criteria for Referral to Colposcopy</th>
<th>Risk of Bias (QUADAS-2)*</th>
<th>Quality Assurance of Cytology</th>
<th>Cancer With HSIL or Worse Cytology/Total No. of Cancers in Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hegde et al27 (2011)</td>
<td>India/lower middle</td>
<td>Cross-sectional/unscreened women; 225 women ages 20-50</td>
<td>Conventional, VIA</td>
<td>Positive on any test and a sample of those testing negative</td>
<td>Low risk of bias</td>
<td>Cytology read and reported at the local laboratory</td>
<td>3/3</td>
</tr>
<tr>
<td>Jeronimo et al17 (2014)</td>
<td>India, Nicaragua, and Uganda/lower middle</td>
<td>Cross-sectional/unscreened women; 16,951 women ages 25-60</td>
<td>Conventional, VIA, careHPV, HPV (self and clinician administrated)</td>
<td>Positive on any test</td>
<td>At risk for bias</td>
<td>Cytology slides read by local pathologists</td>
<td>17/29</td>
</tr>
<tr>
<td>Kumar et al18 (2007)</td>
<td>India/lower middle</td>
<td>Cross-sectional/symptomatic; 133 women, age not reported</td>
<td>Conventional, HPV</td>
<td>All women had colposcopy</td>
<td>Low risk of bias</td>
<td>Cytology slides read by two independent observers locally</td>
<td>3/4</td>
</tr>
<tr>
<td>Londhe et al19 (1997)</td>
<td>India/lower middle</td>
<td>Cross-sectional/who attended gynecology outpatient department; 500 women, age not reported</td>
<td>Conventional, VIA</td>
<td>All women offered colposcopy</td>
<td>At risk for bias</td>
<td>Cytology read and reported at the local laboratory</td>
<td>0/1</td>
</tr>
<tr>
<td>Nessa et al1 (2013)</td>
<td>Bangladesh/lower middle</td>
<td>Cross-sectional/unscreened women; 650 women ages 30-45</td>
<td>Conventional, VIA</td>
<td>All women had colposcopy</td>
<td>Low risk of bias</td>
<td>Cytology slides read at a large referral hospital where the study was carried out</td>
<td>0/4</td>
</tr>
<tr>
<td>Patel et al21 (2004)</td>
<td>India/lower middle</td>
<td>Retrospective review/screened women; 19,215 Pap smears in women ages 25-85</td>
<td>Conventional</td>
<td>Positive on any test</td>
<td>At risk for bias</td>
<td>Cytology slides read at a cancer referral hospital, by two technicians; if disagreements, a third provided consensus</td>
<td>159/189</td>
</tr>
</tbody>
</table>

(Continued on following page)
<table>
<thead>
<tr>
<th>Study</th>
<th>Country/World Bank Development Indicator 2014</th>
<th>Type of Study/Type of Population/Women Tested/Age of Women (years)</th>
<th>Screening Tests Offered</th>
<th>Criteria for Referral to Colposcopy</th>
<th>Risk of Bias (QUADAS-2)*</th>
<th>Quality Assurance of Cytology</th>
<th>Cancer With HSIL or Worse Cytology/Total No. of Cancers in Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanad et al (2014)</td>
<td>Egypt/lower middle</td>
<td>Cross-sectional/Women who underwent colposcopy after abnormal (ASCUS or worse); 486 women ages 21-59</td>
<td>Conventional, VIA after positive cytology</td>
<td>All women underwent colposcopy</td>
<td>At risk for bias</td>
<td>Cytology read and reported at the local laboratory</td>
<td>2/2</td>
</tr>
<tr>
<td>Sankaranarayanan et al (2005 and 2009)</td>
<td>India/lower middle</td>
<td>RCT/unscreened; 25,549 women ages 30-59</td>
<td>Conventional, HPV, VIA Positive on any test</td>
<td>Low risk of bias</td>
<td>Cytology slides read at a cancer referral hospital and cytopathologists were specially trained</td>
<td>143/201</td>
<td></td>
</tr>
<tr>
<td>Sankaranarayanan et al (2004)</td>
<td>India/lower middle</td>
<td>Cross-sectional/ unscreened; 24915 women ages 25-65</td>
<td>Conventional</td>
<td>All women had colposcopy</td>
<td>Low risk of bias</td>
<td>Cytology slides interpreted at local laboratories but technicians were trained and quality assured.</td>
<td>55/74</td>
</tr>
<tr>
<td>Sarian et al (2005)</td>
<td>Brazil and Argentina/upper middle</td>
<td>Cross-sectional/ unscreened; 10,138 women ages 18-60</td>
<td>Conventional, VIA, VILI, HPV In two sites, all women referred; in two sites, all positives referred and 5% of negatives</td>
<td>Low risk of bias</td>
<td>Cytology slides read at a cancer referral hospitals</td>
<td>22/29</td>
<td></td>
</tr>
<tr>
<td>Singla et al (2012)</td>
<td>India/lower middle</td>
<td>Cross-sectional/V symptomatic; 450 women ages 20-70</td>
<td>Conventional, VIA, VILI Positive on any test</td>
<td>Low risk of bias</td>
<td>Cytology slides read at a cancer referral hospital</td>
<td>3/3</td>
<td></td>
</tr>
</tbody>
</table>
Table 1. Summary of Included Studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country/World Bank Development Indicator 2014</th>
<th>Type of Study/Type of Population/Women Tested/Age of Women (years)</th>
<th>Screening Tests Offered</th>
<th>Criteria for Referral to Colposcopy</th>
<th>Risk of Bias (QUADAS-2)*</th>
<th>Quality Assurance of Cytology</th>
<th>Cancer With HSIL or Worse Cytology/Total No. of Cancers in Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhao et al6 (2010)</td>
<td>China/upper middle</td>
<td>Cross-sectional pooled analysis/unscreened women; 8,663 women ages 15-59</td>
<td>LBC, HPV, VIA</td>
<td>Three of 17 studies gave colposcopy to all women. The rest to those positives</td>
<td>Not applicable</td>
<td>Cytology slides read at a cancer referral hospital and in six studies reviewed by international experts</td>
<td>48/50</td>
</tr>
</tbody>
</table>

NOTE. For studies by Almonte et al,5,12 Cremer et al,30 and Zhao et al,6 not all cancers in the manuscript had a cytology result. For studies by Ferreccio et al,4 Deodhar et al,15 and Sankaranarayanan et al20,31 (2005 and 2009), ongoing follow-up as part of these studies makes comparison with the number of cancers reported in the published manuscript not possible.

Abbreviations: ASCUS+, atypical squamous cells of undetermined significance or worse; DART, digital assessment of the reproductive tract; HSIL, high-grade squamous intraepithelial lesion; HPV, human papillomavirus; LSIL+, low-grade squamous intraepithelial lesion or worse; LBC, liquid-based cytology; PH, potential of hydrogen; RCT, randomized controlled trial; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol iodine.

*QUADAS-2 is a tool for quality assessment of diagnostic accuracy studies (Data Supplement). This tool is not applicable to the manuscript by Zhao et al, because the study design of the 17 studies included is not the same.
20 years; therefore, we excluded these manuscripts. A total of 63 manuscripts were deemed eligible (Fig 1).

Data were reported in the format required in 11 studies, which included a total of 247 cervical cancers.11,14,16,18,19,21,23-27 We attempted to

Table 2. Sensitivity of Cervical Cytology to Cancer: Crude Pooled Results From 23 Studies

<table>
<thead>
<tr>
<th>Cytology Test Result or Summary</th>
<th>No. of Cancers</th>
<th>% of Cancers (95% CI)</th>
<th>% of Cancers Diagnosed With Test Result or Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>87</td>
<td>—</td>
<td>100</td>
</tr>
<tr>
<td>Inadequate</td>
<td>2</td>
<td>—</td>
<td>87.9</td>
</tr>
<tr>
<td>ASCUS</td>
<td>48</td>
<td>—</td>
<td>87.6</td>
</tr>
<tr>
<td>LSIL</td>
<td>14</td>
<td>—</td>
<td>80.9</td>
</tr>
<tr>
<td>ASC-H</td>
<td>20</td>
<td>—</td>
<td>78.9</td>
</tr>
<tr>
<td>HSIL</td>
<td>243</td>
<td>—</td>
<td>76.2</td>
</tr>
<tr>
<td>Cancer</td>
<td>303</td>
<td>—</td>
<td>42.3</td>
</tr>
<tr>
<td>Total</td>
<td>717</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary

| Sensitivity ASCUS or worse     | 87.6 (85.2 to 90.0) |
| Sensitivity LSIL or worse      | 80.9 (78.0 to 83.8) |
| Sensitivity HSIL or worse      | 76.2 (73.0 to 79.3) |

Abbreviations: ASC-H, atypical squamous cells unable to exclude high-grade squamous intraepithelial lesion; ASCUS, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.
contact the investigators from the remaining 52 studies. Authors responded with data for 12 separate studies. For 10 studies, contact details were out of date or not provided. No data were available for two of the requested manuscripts, and no response was obtained from 28 authors. Approximately 309 cancers were included among the 40 studies for which no response was obtained (the number of cancers were not reported in seven studies).

For analysis, we include 23 studies with 717 cancers (Table 1). We estimate that we included 70% of all cancers from the identified literature. Sensitivity results for individual studies at a cutoff of HSIL or worse are shown in Figure 2. As summary of cytology results and crude sensitivities for included studies is listed in Table 2. The crude pooled analysis of all studies showed a sensitivity of 76.2% (95% CI, 73.0% to 79.3%) of cervical cytology to cancer at a cutoff of HSIL or worse. The random effects model estimated the sensitivity to be 79.4% (95% CI, 67.7% to 86.0%), and substantial heterogeneity between studies was observed ($I^2$, 88.8%; $P < .001$). The respective results for a cutoff of LSIL or worse were 80.9% (95% CI, 78.0% to 83.8%) and 86.3% (95% CI, 75.2% to 94.5%); for a cutoff of ASCUS or worse, they were 87.6% (95% CI, 85.2% to 90.0%) and 91.1% (95% CI, 81.2% to 97.5%).

Quality assessment of included studies is listed in Table 1 (Data Supplement). The majority of studies (n = 15) were deemed at low risk of bias. Bias was assessed through several subanalyses, which are presented at a cutoff of HSIL or worse (Table 3; Fig 3).

Sensitivity was 81.1% (95% CI, 57.1% to 96.6%) among studies that assessed disease status on all enrolled women compared with 76.4% (95% CI, 64.9% to 86.1%) among studies that only assessed it in women who tested positive to any of the

<table>
<thead>
<tr>
<th>Subanalyses</th>
<th>No. of Cancers</th>
<th>No. of Studies</th>
<th>Sensitivity</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria for assessment of disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All women received colposcopy</td>
<td>149</td>
<td>12</td>
<td>81.1</td>
<td>57.1 to 96.6</td>
</tr>
<tr>
<td>Women received colposcopy if positive on any screening test</td>
<td>568</td>
<td>11</td>
<td>76.4</td>
<td>64.9 to 86.1</td>
</tr>
<tr>
<td>Screening tests offered</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Include HPV testing</td>
<td>391</td>
<td>11</td>
<td>75.4</td>
<td>63.4 to 85.7</td>
</tr>
<tr>
<td>Do not include HPV testing</td>
<td>326</td>
<td>12</td>
<td>83.3</td>
<td>59.5 to 97.7</td>
</tr>
<tr>
<td>Studies reporting liquid-based cytology</td>
<td>95</td>
<td>3</td>
<td>78.5</td>
<td>55.6 to 94.6</td>
</tr>
<tr>
<td>Type of population enrolled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic or abnormal cytology</td>
<td>52</td>
<td>10</td>
<td>95.9</td>
<td>86.5 to 99.9</td>
</tr>
<tr>
<td>General screening</td>
<td>665</td>
<td>13</td>
<td>70.1</td>
<td>57.5 to 81.2</td>
</tr>
<tr>
<td>Quality assurance of cytology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower quality</td>
<td>89</td>
<td>9</td>
<td>84.6</td>
<td>63.1 to 97.7</td>
</tr>
<tr>
<td>Higher quality</td>
<td>35</td>
<td>6</td>
<td>80.1</td>
<td>38.8 to 99.9</td>
</tr>
<tr>
<td>No. of cancers in each study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small (1-9)</td>
<td>49</td>
<td>12</td>
<td>84.9</td>
<td>60.4 to 98.6</td>
</tr>
<tr>
<td>Medium (10-24)</td>
<td>96</td>
<td>5</td>
<td>72.2</td>
<td>46.8 to 91.6</td>
</tr>
<tr>
<td>Large (&gt; 25)</td>
<td>572</td>
<td>6</td>
<td>78.4</td>
<td>68.2 to 87.1</td>
</tr>
<tr>
<td>World Bank development indicator</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower middle income</td>
<td>555</td>
<td>16</td>
<td>79.7</td>
<td>63.6 to 91.9</td>
</tr>
<tr>
<td>Upper middle income</td>
<td>162</td>
<td>7</td>
<td>79.3</td>
<td>60.7 to 93.2</td>
</tr>
<tr>
<td>Pooled (overall)</td>
<td>717</td>
<td>23</td>
<td>79.4</td>
<td>67.7 to 86.0</td>
</tr>
</tbody>
</table>

Abbreviations: HSIL, high-grade squamous intraepithelial lesion; HPV, human papillomavirus.
screening tests offered. Note that, in some studies, cytology was the only screening test, but in all studies, women with any abnormality on cytology were referred to colposcopy. There was evidence of statistical heterogeneity among studies in both analyses (all enrolled women: $I^2$, 85.7%; $P = .001$; only women who tested positive: $I^2$, 84.0%; $P = .001$).

The effect of verification bias on the sensitivity of the test was studied by splitting the studies into those that included HPV testing and those that did not, because a large proportion of women who are negative on cytology are referred to colposcopy when HPV testing also is carried out. As predicted, we observe lower sensitivities when HPV testing was used to ascertain disease status—75.4% (95% CI, 63.4% to 85.7%)—compared with 83.3% (95% CI, 59.5% to 97.7%) among studies that did not include it.

When the LBC results, instead of the conventional cytology results, for Almonte et al$^{5,12}$ and Ferreccio et al$^4$ were included, the overall sensitivity of the test was higher (Data Supplement), because the LBC results had better sensitivity. However, when results from Zhao et al$^6$ (the only other study to report LBC) were added, the sensitivity of LBC was similar to the overall pooled estimate (78.5%; 95% CI, 55.6% to 94.6%).

Among studies that provided cytology testing to the general screening population, the sensitivity was 70.1% (95% CI, 57.5% to 81.2%) compared with 95.9% (95% CI, 86.5% to 99.9%) among studies that recruited symptomatic women or women referred because of a previous abnormal cytology. Little evidence of heterogeneity among studies that included symptomatic women or those referred because of abnormal cytology was observed ($I^2$, 25.6%; $P = .06$). These results are supported by the meta-regression: 76% of the variance was between studies ($I^2$ residual, 82.1%); 57% remained unexplained (adjusted $R^2$, 43.0%). Meta-regression analyses did not show a significant effect of any of the other covariates (Fig 3).

When the quality of the cytology was considered, we found higher sensitivities, although CI overlap,
among studies that had lower-quality cytology (84.6%; 95% CI, 63.1% to 97.7%) than higher-quality cytology (75.8%; 95% CI, 62.1% to 87.2%). Similar results were observed when the number of cancers in each study was considered. It is worth noting that studies with lower-quality cytology only were also more likely to offer colposcopy to women with abnormal cytology. The World Bank development indicator made little difference to the sensitivities (Table 3).

We estimated the relative sensitivity of HSIL or worse compared with ASCUS or worse to account for the exclusion of women with negative cytology from some studies. For this analysis, the study by Boonlikit\(^\text{25}\) was excluded, because no one with a result of ASCUS was enrolled. The relative sensitivity was 85.2% (95% CI, 80.7% to 89.7%). There was no evidence of statistical heterogeneity between studies in this analysis ($I^2$ res, 6.2%; $P = .730$).

The sensitivity of cytology to cancer was strongly correlated to the sensitivity of cytology to CIN2++; 46% of the variance was between studies ($I^2$ res, 45.9%; $P = .005$). Sensitivity to CIN2+ was able to explain 85% of the variance between studies, and only 15% remained unexplained (adjusted $R^2$, 85.0%).

**DISCUSSION**

Overall, we found that cytology at a cutoff of HSIL or worse had a sensitivity to cancer of 79%. Considerably higher sensitivity (96%) was observed among studies that included symptomatic women or women who had abnormal cytology than among studies that enrolled women from the general screening population (70%). We consider a cutoff of HSIL or worse to be appropriate when cytology was used to diagnose cancer, because it detected 85% of cancers with abnormal cytology. Results suggest that the use of cytology to identify cancer would be well suited for use in high-risk or targeted groups.

This study takes data from studies that use cervical cytology as a screening tool and assessed its use as a test for early detection of cancer. It is the first study, to our knowledge, to evaluate the use of cytology to diagnose cervical cancer in LMICs, and it includes approximately 70% of cancers identified as eligible for this study from a wide range of settings.

Verification bias could potentially affect sensitivity of cytology in all included studies, because colposcopy can easily miss endocervical cancers, particularly when it is not guided by prior cytology. Here, we take a pragmatic approach and consider verification bias to be minimal if all HPV-positive women have colposcopy. The risk of bias, then, will be related to the proportion of those referred to colposcopy who receive colposcopy. It is seen that the absolute sensitivity of cytology at HSIL or worse is indeed dependent on the study population and referral criteria, whereas the relative sensitivity (compared with ASCUS or worse) is homogeneous.

Authors from research organizations that mainly aim to carry out this type of research were more likely to respond to our requests for data, and cytology samples taken as part of these studies may be better than cytology taken in routine settings.

Judgement of the quality of cytology through the details reported in each study was not straightforward and is subjective. Bias toward a higher sensitivity than that observed in routine practice may remain.

We used the country income level from the World Bank in 2014, though most of the studies were conducted before then. It is possible that countries have moved from lower-middle to upper-middle income levels, or vice versa, in the intervening period; this would lead to misclassification bias in that subanalysis.

Most cross-sectional studies took the cytology within 3 months of the diagnosis of cancer. However, for some studies, in particular the cohort studies, we do not know how long before diagnosis of cancer the cytology was taken. One would expect the sensitivity of the test for cancer to be lower, the longer it was before diagnosis.

Despite these limitations, the overall high sensitivity of HSIL or worse cytology to invasive cancer is clear.

The sensitivity of cytology to cancer at a cutoff of HSIL or worse (79%) was similar to the sensitivity of cytology at a cutoff of ASCUS or worse to CIN2+ reported in a meta-analysis by Mustafa et al.\(^\text{2}\) They found that, among studies (all of which were from LMICs) that compared visual inspection with acetic acid to cytology, the sensitivity of cytology to CIN2+ at a cutoff of ASCUS or worse was 84% (95% CI, 76% to 90%). This suggests that the sensitivity of cytology to cancer is similar to its sensitivity to CIN2+ in a population screening context.

The main benefit of using cytology at a high cutoff to diagnose cervical cancer would be earlier stage at diagnosis, with the ability to offer lifesaving treatment options, reduce mortality, and improve quality of life. In developing countries, which lack screening programs, the incidence of cervical cancer may be up to six times higher than in developed countries, and up to 80% of patients present with advanced disease.\(^\text{32}\) In addition, facilities to treat advanced cancers are limited in many developing countries; for example, many countries have more
than 2 million people per radiotherapy unit, and some countries do not have any radiotherapy units.\textsuperscript{33}

The use of cytology to downstage cancers has not been given appropriate consideration as a viable alternative, even though the low-cost alternative (visual inspection of the cervix with a speculum) is proven not to be a suitable primary screening modality for cervical cancer.\textsuperscript{34} In England, Landy et al\textsuperscript{35} found that the majority of cancers (72.6\%) in women diagnosed at age 66 years or older who did not have a cytology test within 12 months of diagnosis were diagnosed with FIGO stage 2 or worse. However, among women of the same age who had cytology in the 12 months before diagnosis (presumably because of symptoms, because screening is not offered in this age group), the proportion with FIGO stage 2 or worse disease decreased to 56.2\%, and these women had better survival than women without cytology. Several other authors also have found that, among symptomatic women, diagnosis of cervical cancer through cytology resulted in better survival.\textsuperscript{36,37}

Although one may expect the sensitivity of cytology to cancer to be high even when the sensitivity to CIN2+ is low, we found that the sensitivity of cytology to cancer was highly related to the sensitivity to CIN2+ (at a lower cutoff). Therefore, quality control of cytology will remain necessary when cytology is used to diagnose cancer.

Restriction of cytology to symptomatic women and HSIL or worse referral for further investigation at colposcopy of those who have a result of HSIL or worse would free up resources that could be used to improve the quality of cytology to ensure sensitivities of HSIL or worse to cancer greater than 75\% in all settings.

In conclusion, cytology testing at a threshold of HSIL or worse is an excellent tool for targeted screening of populations at high risk of cervical cancer, with a goal of cancer diagnosis at an earlier stage. Evidence suggests that a sensitivity of greater than 75\% would be observed in all settings.

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Affiliations
Alejandra Castanon, Rebecca Landy, Dimitrios Michalopoulos, Roshni Bhudia, Hannah Leaver, and Peter Sasieni, Wolfson Institute of Preventive Medicine, London, United Kingdom; and You Lin Qiao and Fanghui Zhao, National Cancer Center and Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China.

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Prior Presentation

REFERENCES
Use of Palliative Cisplatinum for Advanced Cervical Cancer in a Resource-Poor Setting: A Case Series From Kenya

Purpose To evaluate the effectiveness and feasibility of cisplatinum for palliative treatment of advanced cervical cancer in a resource-poor setting.

Methods An observational case series is reported from a university teaching hospital in Kenya. All women presenting with advanced cervical cancer and planned for palliative cisplatinum therapy from 2010 to 2014 were included. Women were treated with cisplatinum 50 mg/m² every 4 weeks in an outpatient setting. Data on tumor stage and symptoms control were prospectively collected in an electronic database. The main outcome measure was control of symptoms such as bleeding, discharge, and pain.

Results Of the women who originally presented with bleeding, 62% reported improvement in this symptom, 31.3% reported the bleeding completely stopped, 58% had improvement of their vaginal discharge, and 20.5% reported complete resolution. Of the women who presented with pain, 54% reported improvement; 30.9% reported pain had completely resolved. After each treatment cycle, approximately 30% of patients did not return for their next treatment.

Conclusion Cisplatinum as palliative treatment of advanced cervical cancer is feasible in a resource-poor setting and leads to effective symptom control. However, unknown barriers may inhibit women from returning for regular treatment.

INTRODUCTION

In Kenya and other parts of sub-Saharan Africa, most women with cervical cancer present with an advanced stage of the disease. In 2012, the WHO stated that there were 528,000 new cervical cancer cases annually worldwide, of which 84% occurred in the less-developed world. Cervical cancer is the most common gynecologic cancer in Kenya and other Eastern African countries. Mortality in high-resource countries is 4.1 women per 100,000, whereas it is five times greater in Kenya (21.8 per 100,000 [age-standardized rates]). It is possible that the mortality is even higher than reported because the quality of the data for cancer in Kenya and surrounding countries is limited and likely misses a proportion of the cervical cancer cases. In Kenya, cervical cancer is the leading cause of cancer mortality.

Many factors contribute to the difference in cervical cancer burden (ie, prevalence and mortality) between high- and low-resource countries, including lack of comprehensive screening, lack of adequate treatment, and barriers to access to health care. In most regions of the world, women with advanced cervical cancer would be treated with a combination of chemotherapy and radiotherapy. Chance of cure would range from 30% to 40%, but the likelihood of benefiting and getting relief of symptoms would be extremely high, greater than 95%. In Kenya, there is limited access to both chemotheraphy and radiotherapy. For a woman to receive radiotherapy treatment in Kenya, she would need to travel to Nairobi. This is a 6-hour drive from our hospital in Eldoret. She would also have to arrange and pay for her lodging and, even in that situation, she would have to wait between 6 and 12 months before starting treatment. Only external beam therapy is available in Nairobi; the cost is KES 80,000 (US $785). An alternative option would be to travel to Kampala, Uganda, also a 6-hour drive, where both external beam and intracavitary treatment are available at a cost of KES 160,000 (US $1,570).

In Kenya, 79% of the population live in a rural setting, and 33.6% live below the poverty line, defined as living on less than $1.90/day. Kenya is also one of the African countries hardest hit by HIV/AIDS. Fifteen percent of women diagnosed with...
cervical cancer are HIV positive. Most women live in rural settings and below the economic poverty line. For the majority of those women diagnosed with cervical cancer, radiotherapy is simply not accessible.

In the neoadjuvant setting, cisplatinum in doublet or triplet combination with other chemotherapeutics in intervals of 10-20 days for three cycles has been shown to lead to complete or partial tumor response in more than half of women. Basile et al suggested the use of platinum-based chemotherapy for palliative treatment of advanced or recurrent cervical cancer when radiotherapy facilities are far away, as it is in many African countries. In Brazil, a retrospective study of 153 women treated with carboplatin and paclitaxel for advanced and recurrent cervical cancer showed that 34.6% had an objective response and a median survival of 10.6 months. In Canada, 40% of women (n = 25), most of whom were pretreated with radiation, had a complete or partial response after palliative treatment with carboplatin and paclitaxel; the median overall survival was 21 months. In Nigeria, administration of cisplatin 70 mg/m² every 3 weeks resulted in cessation of vaginal bleeding for 81 of 116 patients.

Our hypothesis was that for women who could not access radiotherapy, single-agent cisplatinum would alleviate symptoms in those presenting with advanced cervical cancer. Our objectives were to assess the feasibility and acceptability of single-agent cisplatinum for palliative symptom control of advanced cervical cancer in a low-resource setting.

METHODS

We conducted this study at Moi Teaching and Referral Hospital, in Eldoret in western Kenya. This is a level 6 referral hospital that serves a population of 5 million people. It recently developed an oncology program in collaboration with AMPATH (Academic Model Providing Access to Healthcare), a consortium of North American universities led by Indiana University. The hospital recently built a new outpatient facility to see and treat oncology patients. It does not yet have the capacity to provide radiation therapy.

All women who presented with cervical cancer between January 2010 and December 2014 were evaluated in a gynecologic oncology clinic setting. For every woman, demographics and disease-related data were captured in a prospective electronic database. For this study, we included all women who planned to undergo chemotherapy treatment with palliative intent and who received at least one cycle of cisplatinum.

Chemotherapy consisted of cisplatinum 50 mg/m² every 4 weeks. This is a lower dose and frequency than is used in the neoadjuvant setting, where the aim is to reduce tumor size to make patients amenable for surgery. In an early Gynecologic Oncology Group study evaluating different cisplatinum doses, patients receiving 100 mg/m² every 21 days had better response rates but no improvement in complete remission rate, response duration, progression-free interval, and survival as compared with those receiving 50 mg/m² every 21 days. However, this higher dose was also associated with greater myelosuppression and nephrotoxicity. In our situation, cisplatinum was used with palliative intent and aimed at symptom control. By reducing the dose and frequency, we wanted to make the treatment as tolerable for these women as possible. The treatment regimen included hydration with 1 L of intravenous normal saline before and after chemotherapy. Premedication also included intravenous ondansetron 8 mg and dexamethasone 12 mg administered 30 minutes before administration of cisplatinum. Postchemotherapy, the patients were observed for at least 1 hour. On discharge, ondansetron 4 mg was continued twice daily for a week and women were advised to increase oral fluid intake to at least 2 L/day. If, during a subsequent cycle, a patient reported excessive nausea and vomiting during the previous chemotherapy session, she was advised to stay overnight in the hospital for parenteral rehydration and antiemetics (eg, ondansetron, dexamethasone, and even, sometimes, parenteral chlorpromazine). When women presented with pain, morphine syrup was used to support pain control. However, morphine was not expected to control bleeding or discharge. No hemostatic agents were given and only if women had a low hemoglobin level and presented with complaints was a blood transfusion offered. Chemotherapy was prepared in the dedicated pharmacy and delivered by nurses in an outpatient day-care setting. Chemotherapy was continued until a maximum of six doses or control of symptoms had been achieved.

Before the first and each subsequent cycle of chemotherapy, patients had complete blood cell count and serum creatinine measurements. Cisplatinum was postponed as long as the hemoglobin level was < 8 mg/dL, the creatinine level was > 80 mmol/L, and the absolute neutrophil count was < 0.001/µL.

The cost for treatment was KES 3,930 (US $40), which included consultation, administrative cost, and chemotherapy. Initially, when the program
was subsidized by AMPATH, the patient cost was only KES 400 (US $4). Currently, a financial support program is available to assist those who can only afford a partial payment.

At every follow-up visit, patients reported their symptoms and whether the symptoms were the same, better, or worse. To establish the rate at which symptoms improved, we also included those women in the denominator who only came once and for whom we could not evaluate the effect of chemotherapy. Rates reported are for the entire cohort. If women had not returned for follow-up, their relatives were contacted by telephone in May 2015. In this way, disease status and, if applicable, date of death was ascertained. Adverse effects of treatment were not recorded systematically.

Data are summarized using descriptive statistics. The Moi University/Moi Teaching and Referral Hospital Institutional Research and Ethics Committee approved this study. All women gave informed consent.

RESULTS

Between January 2010 and December 2014, 519 women were diagnosed with cervical cancer in our hospital. Of these, 106 (20%) were planned to receive neoadjuvant chemotherapy followed by surgery, 90 were planned to undergo radical hysterectomy, 67 (13%) were referred for radiotherapy, and 44 (9%) were referred for palliative hospice care. After evaluation, and discussion with the patient and relatives about possible options, 124 women (24%) were planned to receive palliative chemotherapy. These were women who were not able to afford the cost or had other reasons to refuse radiotherapy. Not all of these women went on to have chemotherapy, because some had renal impairment that prevented the use of cisplatinum and others did not return for their planned chemotherapy. Of the 124 women, 98 went on to have at least one cycle of chemotherapy and were included for this study. The mean age of this cohort was 53 years (range, 29-81 years). Eighty-five percent of the patients were International Federation of Gynecology and Obstetrics stage 3 or 4. Of the 77 patients tested, 25 (32.4%) were HIV positive and a CD4 cell count was known for 13 of these (mean, 472 CD4 cells; range, 34-732 CD4 cells). All women were already receiving antiretroviral treatment or started this treatment as soon as the diagnosis of cervical cancer had been made. Forty-five percent of the patients undergoing treatment received three or more cycles of chemotherapy (Table 1).

Most women came to the hospital because of their symptoms. We identified less than 20% through our cervical cancer screening program. Of the women in our study, 83 (84.6%) presented with bleeding, 68 (69.3%) with discharge, and 68 (69.3%) with low abdominal pain.

At each subsequent visit after the first cycle of cisplatinum, the response of the symptoms to treatment was evaluated. These data are presented in Figure 1. Data on symptom control after one treatment were available for 70% of the patients. The other 30% did not return after their first cycle and response could not be evaluated. Of the women who originally presented with bleeding, 62% reported improvement; for 31.3%, the bleeding completely stopped. Improvement in vaginal discharge was reported by 58% of women; 20.5% reported complete resolution. Of the women who presented with pain, 54% reported improvement; for 30.9%, the pain completely resolved. Symptoms improved after a median of two cycles.

The most common observed chemotherapy adverse effects included nausea and vomiting, nephrotoxicity, abnormal blood parameters (ie, low hemoglobin levels and low absolute neutrophil counts), and peripheral neuropathy. The majority of the women (64.3%) had more than one chemotherapy treatment and we evaluated renal symptoms.

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics and Cisplatinum Use</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
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</tr>
<tr>
<td>Age, years, mean (range)</td>
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</tr>
<tr>
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<tr>
<td>2B</td>
</tr>
<tr>
<td>3A</td>
</tr>
<tr>
<td>3B</td>
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<tr>
<td>4A</td>
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<td>HIV status (n = 77)</td>
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<td>3</td>
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<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

*Data given as no. (%) unless otherwise indicated.
toxicity based on consecutive serum creatinine values after chemotherapy. At the start of their chemotherapy, 85 of 98 women (86.7%) had a normal creatinine level. Of those who had at least two chemotherapy treatments, the creatinine level rose in four of 57 (7%) who initially presented with a normal value. Treatment was never withheld because of adverse effects other than those discussed in the Methods.

DISCUSSION

Our results show that palliative chemotherapy with single-agent cisplatinum is feasible in a low-resource setting. For the more than half of the women in this study, this treatment improved the most distressing and limiting symptoms, including bleeding, pain, and the foul discharge.

The main limitation to our study is the lack of follow-up, which leads to uncertainty about the length of time symptom control is maintained. One of the possible reasons that women did not return may have been a worsening of symptoms or the adverse effects the women experienced. However, there are many other barriers that prevent these women from attending our clinic and receiving treatment. One-fifth of women never even started the proposed treatment, which not only affected our study population but was also true for all women with cervical cancer seen in this period. Lack of funds to cover both the direct and indirect costs of those seeking treatment in the hospital probably played a significant role in limiting their ability to access treatment. Some women choose to use indigenous medicine, some do not have independent decision-making power in their home, some have transportation difficulties, and some lack of understanding of their cancer, all of which may play a role. These barriers, in combination with barriers in the health-care system, are probably also the reason so many women present so late with their disease.

The generalizability of our study is limited to a specific setting. We have shown that delivery of chemotherapy is safe and can be done in a low-resource setting, but it does require specific infrastructure. Our hospital includes a pharmacist, trained nursing staff, and trained physicians, and a supply chain that ensures that drugs and materials needed to administer these are routinely available. This means chemotherapy will likely have to be administered in a regional hospital and, when not possible, will at least have to be supported by a regional hospital.

We do think that our approach can benefit many women in sub-Saharan Africa. Before initiating this program, women with advanced cervical cancer typically would present to the emergency room because of bleeding, pain, and with or without discharge. They did not know their diagnosis and most often they would have very low hemoglobin levels. They would then be admitted, receive a transfusion of red blood cells, and then be discharged to their homes where they would die. It is highly unlikely that they would have any relief of their symptoms. We found several reports describing cohorts of women such as ours. Some describe women being referred for radiotherapy but do not state whether these women actually got the treatment. Strategies to develop palliation for advanced cervical cancer are necessary for settings where there is limited access to health care, limited expertise about cancer, and no radiation oncology treatment options. This situation defines much of sub-Saharan Africa outside of South Africa.

It is clear that the use of cisplatinum as palliative treatment is not ideal. Treatment with a combination of chemotherapy and radiation would be more effective; however, even a recent Cochrane review did not find any randomized studies to support this. Also, carboplatinum is an option that is associated with less toxicity, but this is more expensive, which would put it out of reach for most women. Many women with advanced cervical cancer come from regions where there is limited access to medical care and no access to radiotherapy. This study showed that cisplatinum used in this setting did alleviate some of the severe symptoms affecting women with advanced stage cervical cancer.

Improving symptoms also provides an opportunity for these women to have some symptom-free time, to be at home, and to plan for their deaths.
Many of these women will have young children and the additional time they have and, in particular, symptom-free time, can be very beneficial to them.

Better even than treating the disease would be preventing it either through vaccination or screening. This palliative program was established in parallel with a cervical cancer screening program that, in turn, is identifying preinvasive disease and early-stage cancers that are amenable to a curative treatment strategy.

Improving care for women with advanced cervical cancer in sub-Saharan Africa is possible despite the multitude of barriers. A potential benefit of this program may be the stimulation of greater interest by governments or regions in starting screening programs once they better understand the impact of advanced cervical cancer on affected women. The alternative of no treatment, no attempt at palliation, is not an acceptable option.

For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Elkanah Orang’o
No relationship to disclose

Peter Itsura
No relationship to disclose

Philip Tonui
No relationship to disclose

Hellen Muliro
No relationship to disclose

Barry Rosen
Travel, Accommodations, Expenses: Intuitive Surgical, da Vinci Surgery

Luc van Lonkhuijzen
No relationship to disclose

Affiliations
Elkanah Orang’o, Peter Itsura, Philip Tonui, and Hellen Muliro, Moi University School of Medicine, Eldoret, Kenya; Barry Rosen, Oakland University, Rochester, MI; Luc van Lonkhuijzen, Academic Medical Center, Amsterdam, the Netherlands.

REFERENCES


Pediatric Hodgkin Lymphoma Treated at Cancer Institute, Chennai, India: Long-Term Outcome

Abstract

Purpose Pediatric Hodgkin lymphoma (HL) is a highly curable malignancy. Outcomes for pediatric HL may vary between developed and developing countries for multiple reasons. This study was conducted to ascertain the outcomes of children with HL at our center and to identify risk factors for recurrent disease.

Methods We analyzed the outcomes of 172 consecutive, previously untreated patients with pediatric HL presenting at our center from 2001 to 2010. Patients were treated with either adriamycin, bleomycin, vinblastine, and dacarbazine or adriamycin, bleomycin, vinblastine, cyclophosphamide, vincristine, prednisone, and procarbazine chemotherapy initially, and radiation to bulky sites or a single site of residual disease when appropriate.

Results The median duration of follow-up was 77 months. The median age of the patients was 10 years; 127 (74%) of the 172 patients were male. The extent of disease was stage I and II in 59% of the patients. B symptoms were present in 32% of the patients, and 27% had bulky disease. The most common histologic subtype was mixed cellularity (45%). The 5-year overall survival (OS) and progression-free survival (PFS) of the entire cohort were 92.9% and 83.1%, respectively. The 5-year OS rates for patients with stage I, II, III, and IV were 96%, 94.7%, 84%, and 69.8%, respectively. On univariate analysis, advanced stage, response on interim radiologic assessment, and presence of B symptoms significantly predicted inferior PFS and OS. On multivariate analysis, only interim radiologic response significantly predicted PFS ($P < .001$) and OS ($P < .001$).

Conclusion Overall, the outcomes of patients treated at our center are comparable to those observed in other centers in India and globally.

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Introduction

The evolution of treatment over the past 4 decades has altered the outcome of pediatric Hodgkin lymphoma (HL) such that the majority of patients are cured. The changes in the management of pediatric HL include better assessment of the extent of disease through improvements in imaging and better understanding of the long-term complications of treatment. Currently, the goal is to minimize exposure and choose appropriate chemotherapy regimens so that long-term effects are minimal. Although developing countries, like India, have kept pace with changes in management of HL globally, there are significant variables that might affect outcome. The biologic and demographic differences that have been noticed in pediatric HL between the West and India include a higher male preponderance, poor nutritional status, younger age at presentation, and increased incidence of a mixed cellularity pathologic subtype in India. Although variations of mechlorethamine, vincristine, procarbazine, and prednisone were used in India initially, adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD), which is used to treat adult HL, is used more commonly now. This is in contrast to Europe and North America where the use of the ABVD regimen is less common because of the increase in long-term cardiac issues and the potential for lung toxicity. We, like other centers in India, use ABVD or its hybrid variations because it can be administered in the outpatient clinic, it is economical, and it does not require frequent monitoring of blood counts, all of which are important in a resource-challenged setting. This study was conducted to ascertain the outcomes of children with HL treated with ABVD or adriamycin, bleomycin, vinblastine, cyclophosphamide, vincristine, prednisone, and procarbazine (ABV/COPP) chemotherapy at our center and to identify risk factors for recurrence of disease.
STAGE THE PATIENTS. The patients underwent modification of Ann Arbor staging was used to stage the patients. The patients underwent contrast-enhanced computed tomography scan of the neck, chest, abdomen, and pelvis for staging and assessment for response. All patients underwent unilateral iliac crest bone marrow aspiration and bone marrow biopsy for diagnosis of bone marrow involvement. Bulky disease was defined as size of lymph nodal mass > 6 cm or mediastinal mass size more than one third of maximal thoracic diameter on chest x-ray. The WHO weight-for-age chart was used for nutritional assessment. Patients with a weight for age less than the third centile were considered malnourished.

The chemotherapy regimens used to treat the patients during the study period were ABVD or ABV/COPP. In treatment of patients with ABVD or ABV/COPP, the number of cycles of chemotherapy, the addition of involved field radiotherapy (IFRT), and the IFRT dose was individualized on the basis of the decision of the hospital multidisciplinary tumor board. Patients with early-stage disease (stages I and II) and advanced-stage disease (stages III and IV) were scheduled for a minimum of four and six cycles of chemotherapy, respectively. Response was assessed clinically after each cycle and radiologically after completion of four cycles of chemotherapy. A few patients had radiologic assessment of response after completing six cycles. It was the practice during the period of study in our center to give two additional cycles of chemotherapy after documentation of radiologic complete response (CR) for a maximum of eight cycles. In patients who initially had bulky disease, IFRT was given, with a total dose of between 20 and 30 Gy, and in patients with residual disease, IFRT was administered to the site at a dose that was between 30 and 36 Gy. IFRT was administered in a daily fraction of 1.8 to 2 Gy and was given 5 days of the week. Toxicities caused by chemotherapy were captured according to the case records. Patients usually underwent follow-up clinical examinations at 3-month intervals for the first 3 years, then at 6-month intervals for 5 years, and then yearly. Investigations on follow-up were performed only if there were clinical signs or symptoms.

CR was defined as complete disappearance of all clinical and radiologic evidence of disease. Partial response (PR) was a reduction of > 50% of the tumor area (the product of the two greatest diameters), but less than a CR. Appearance of a new lesion or a > 25% increase in an existing lesion was considered progressive disease (PD). All other responses were considered as stable disease (SD).

Progression-free survival (PFS) was calculated from the initiation of treatment to the date of recurrence or documented progression. Overall survival (OS) was calculated from the date of initiation of treatment to the date of death or date of last follow-up. All patients were censored at the date of last follow-up, or the date of telephonic contact if lost to follow-up, or March 6, 2015, whichever was earliest. PFS and OS were estimated using the Kaplan-Meier method, and variables were compared using the log-rank test. P values < .05 were considered significant. Cox regression analysis was used for multivariate analysis of variables significant on univariate analysis, and results are reported as hazard ratio (HR) with 95% CI. Statistical analysis was performed using SPSS software (IBM SPSS Statistics Version 17; SPSS, Chicago, IL).
The most common histologic subtype was mixed cellularity (45%), followed by nodular sclerosis (35%). All patients received chemotherapy at presentation. ABVD was administered to 120 of 172 patients (70%) and ABV/COPP to 52 of 172 patients (30%). IFRT was given to 32 of 172 patients (19%). Radiologic assessment at four to six cycles of planned treatment showed that 148 of 172 (86%) were in CR, 13 of 172 (8%) were in PR, two of 172 (1%) had SD, and two of 172 (1%) had PD. Both the patients with SD had stage 3 disease, whereas the two patients with PD had stage 2 and stage 4 disease, respectively. Response was not assessed in seven patients because of treatment abandonment (n = 5), death (n = 1), and no available record (n = 1). Eleven patients discontinued treatment (6.3%) and eight of them later presented to the hospital with recurrence.

Early-Stage Disease

At presentation, 102 of 172 patients (60%) had stage I and II disease. A median of six cycles of chemotherapy was administered (range, three to eight cycles). Six cycles of chemotherapy were given to 71 of 102 patients (70%), whereas 17 of 102 (17%) received fewer (three to five), and 14 of 102 (14%) received eight. Among the 17 patients who received fewer than six cycles of chemotherapy, one did not attend hospital after three cycles (and later relapsed), six received four cycles with IFRT, nine received four cycles without IFRT (one patient later relapsed), and one received five cycles without IFRT. IFRT was given to 25 of 102 patients with early-stage disease; the indication for IFRT was bulky disease (n = 16; two patients in PR) or PR (n = 1), and it was also administered as part of consolidation after four cycles of chemotherapy (n = 4). In addition, four patients received IFRT despite receiving six cycles of chemotherapy and being in CR. IFRT was not given to 11 of 27 patients with bulky disease and six of nine patients (66%) in PR.

Advanced-Stage Disease

At presentation, 70 of 172 patients (40%) had stage III and IV disease. A median of eight cycles of chemotherapy were administered (range, two to eight cycles). Of the 11 patients who received fewer than six cycles of chemotherapy, 10 did not attend for treatment regularly, and the remaining patient died as a result of bleomycin toxicity. Among the 10 patients who did not receive proper treatment, seven had a recurrence or progression of disease and one died in an accident; only two

---

Table 1. Baseline Characteristics and Treatment Details

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>25 (15)</td>
</tr>
<tr>
<td>II</td>
<td>77 (44)</td>
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<tr>
<td>III</td>
<td>56 (33)</td>
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<tr>
<td>IV</td>
<td>14 (8)</td>
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<tr>
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<tr>
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<td>&lt; 5</td>
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<td>65 (38)</td>
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<td>&gt; 10</td>
<td>82 (47)</td>
</tr>
<tr>
<td>B symptoms</td>
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<td>B+</td>
<td>55 (32)</td>
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<tr>
<td>B-</td>
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<td>Stage I and II</td>
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<td>Nodular sclerosis</td>
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are alive and in CR, and these two patients had received four and five cycles of chemotherapy, respectively. Six and eight cycles of chemotherapy were administered to 21 of 70 patients (30%) and 37 of 70 patients (53%), respectively. IFRT was given to seven of 102 patients (7%). The indication for IFRT was bulky disease (n = 5; two with PR). In addition, two patients received IFRT despite having received eight cycles of chemotherapy and being in CR. IFRT was not given to 14 of 19 patients (74%) with bulky disease and four of six patients (66%) with PR or SD.

### Table 1. Baseline Characteristics and Treatment Details (Continued)

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<td>ABV/COPP hybrid</td>
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<td>Stage I and II</td>
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<td>Radiologic response</td>
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<td>CR</td>
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<td>SD</td>
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<tr>
<td>PD</td>
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Abbreviations: ABV/COPP, adriamycin, bleomycin, vinblastine, cyclophosphamide, vincristine, prednisone, and procarbazine; ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; CR, complete response; LDH, lactate dehydrogenase; PD, progressive disease; PR, partial response; SD, stable disease.

* N = 172.
† Fever, weight loss more than 10% of body weight in preceding 6 months, and night sweats.

![Fig 1](image-url) (A) Progression-free survival and (B) overall survival according to stage.

### Survival

The median duration of follow-up of all patients was 77 months. The actuarial 5-year OS and PFS rates of the entire cohort were 92.9% and 83.1%, respectively. The 5-year PFS rates for stages I, II, III, and IV were 91.7%, 86.6%, 78.3%, and 57.1%, respectively (P = .004) (Fig 1A). The 5-year OS rates for stage I, II, III, and IV were 96%, 94.7%, 84%, and 69.8%, respectively (P = .01; Fig 1B). On univariate analysis, advanced stage, presence of B symptoms, and interim radiologic response significantly predicted inferior PFS and OS (Table 2; Figs 2 and 3). On multivariate analysis, only interim radiologic response significantly predicted PFS (HR, 1.74; 95% CI, 1.35 to 2.24; P < .001) and OS (HR, 2.02; 95% CI, 1.46 to 2.8; P < .001). Sex, serum albumin, elevated lactate dehydrogenase > 400 IU, erythrocyte sedimentation rate > 40 mm/h, hemoglobin < 10.5 g/dL, histology, bulky disease, nutritional status, addition of radiotherapy, delay in presentation of > 1 month, and splenomegaly were not significant factors. The omission of radiotherapy in early-stage patients who had received fewer than six cycles of chemotherapy, in patients in PR in interim radiologic assessment, and in patients with bulky disease was not significant.

### Relapse and Mortality

Overall, recurrence of disease was observed in 27 of 172 patients (16%) and two of 172 (1.7%) had primary progression. There were 17 documented deaths, among which 14 were a result of relapse or progression, two were a result of bleomycin toxicity, and one was a result of an accident. Among
the 14 deaths caused by relapse of disease or progression, 10 occurred because patients refused further treatment.

Second-Line Treatment

The median duration to relapse of disease from presentation was 15.17 months (range, 1.97 to 79.03 months). Among the 29 patients who had a recurrence or were refractory, 41% had early-stage and 59% had advanced-stage disease at initial diagnosis. Chemotherapy at recurrence of disease was given to 17 of 29 patients (59%; Table 3), and radiotherapy alone was given to two of 29 (7%). On completion of second-line chemotherapy, the CR, PR, and PD rates of response were 11 of 17 (65%), three of 17 (17%), and two of 17 (12%), respectively, and the remaining patients (6%) failed to attend to evaluate response. All 11 patients who achieved CR are alive and well on follow-up, and three of six patients with less than CR have died. Regarding the two patients who received IFRT alone, one is alive and well and the other has died as a result of progression of disease. Ten patients who did not receive further treatment at relapse of disease because of non-attendance at the hospital were found on telephonic/postal inquiry to have died. Consolidation with high-dose chemotherapy supported by peripheral blood stem cell rescue was performed in four of 29 patients (14%) with recurrent disease after second-line treatment and achievement of CR, all of whom remained in CR at last follow-up.

Toxicity

The most common acute toxicity was febrile neutropenia (grade 4), which was observed in 11 patients. Two patients had bleomycin lung toxicity while on treatment, which was fatal, and both deaths occurred during the fourth cycle of ABVD. We documented three long-term toxicities in our study: infertility in one patient and cardiomyopathy in two patients. There were no cases of second malignancy.

DISCUSSION

Our study provides insight into the long-term outcomes of patients with pediatric HL treated at a tertiary cancer center. We previously published data from our center on outcomes in 134 pediatric patients with HL treated with ABV/COPP chemotherapy during the period 1989 to 1998. The 5-year PFS and OS in our previous study were 86.7% and 92.5%, respectively. Unlike this study, the staging was performed using ultrasound and chest x-ray, none of the patients received ABVD, there

<table>
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<tr>
<th>Parameter (No.)</th>
<th>5-Year PFS (SE)</th>
<th>P*</th>
<th>5-Year OS (SE)</th>
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<td><strong>B symptoms</strong></td>
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<td>.4</td>
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<td>96.6 (3.4)</td>
<td>.1</td>
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<td>Yes (32)</td>
<td>87.2 (6)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No (140)</td>
<td>82.2 (3.3)</td>
<td></td>
<td>89.5 (2.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Interim radiologic response</strong></td>
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<td>.0001</td>
<td>97.3 (1.4)</td>
<td>.0001</td>
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<tr>
<td>CR (148)</td>
<td>90.2 (2.5)</td>
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<td></td>
<td></td>
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<tr>
<td>PR (13)</td>
<td>53.8 (13.8)</td>
<td></td>
<td>69.2 (12.8)</td>
<td></td>
</tr>
<tr>
<td>SD (2)</td>
<td>50 (35.4)</td>
<td></td>
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</tr>
<tr>
<td>PD (2)</td>
<td>0</td>
<td></td>
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</table>

(Continued on following page)
were more advanced-stage patients (64%), and only 5% received IFRT. The recommendation for diagnosing bone marrow involvement in HL is to perform bilateral iliac crest bone marrow aspiration and biopsy. At our center, unilateral bone marrow testing is preferred because it is associated with less pain when performed under local anesthesia. Bone marrow involvement in HL is rare, and it probably does not have a major impact on the treatment and outcome of patients. Mixed cellularity was the most common histologic subtype (45%) in this cohort and this has not changed substantially compared with the previous study and as observed in other studies from India. Nodular sclerosis is a more common histologic subtype in developed countries. The increased mixed cellularity pathology in pediatric HL from developing countries has been attributed to a higher prevalence of Epstein-Barr virus infection. Children younger than 5 years of age constituted 15% of the current cohort of patients, which is similar to the proportion at other Indian centers. This is in contrast to Western data, which show that less than 5% of patients are under 5 years of age. Two thirds of our patients were male, and a similar trend has been reported from other centers in India. However, accounting for the trends in other pediatric malignancies, such a major difference cannot be explained. Malnutrition is a significant problem in developing countries, and it has been associated with poor outcomes in pediatric malignancies, but it was not a significant prognostic factor in this study.

The treatment offered to our patients was heterogeneous over the duration of the report because of the evolution of treatment and imaging. It is therefore difficult to draw any conclusions regarding the preference for a chemotherapy regimen, schedule, and addition of IFRT. However, our study indicates that, with the use of appropriate chemotherapy regimens, children with HL from resource-challenged settings can have similar outcomes to Nodular sclerosis is a more common histologic subtype in developed countries. The increased mixed cellularity pathology in pediatric HL from developing countries has been attributed to a higher prevalence of Epstein-Barr virus infection. Children younger than 5 years of age constituted 15% of the current cohort of patients, which is similar to the proportion at other Indian centers. This is in contrast to Western data, which show that less than 5% of patients are under 5 years of age. Two thirds of our patients were male, and a similar trend has been reported from other centers in India. However, accounting for the trends in other pediatric malignancies, such a major difference cannot be explained. Malnutrition is a significant problem in developing countries, and it has been associated with poor outcomes in pediatric malignancies, but it was not a significant prognostic factor in this study.

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those of the Western population. At centers where access to radiation is not available, it can be replaced by six cycles of ABVD or ABV/COPP. Our results show that patients with advanced-stage disease who receive fewer than six cycles of ABVD or ABV/COPP have poor outcomes. The most common reason for patients receiving less than optimal chemotherapy is noncompliance, rather than toxicity. Approximately 10% of early-stage patients who were in CR after six cycles received a further two cycles of chemotherapy, which, in hindsight, is excessive and is not recommended. The reason for this was that these patients were documented to be in CR only after six cycles and it was our policy to give a further two cycles of chemotherapy after CR. Because of improvements in imaging over the duration of this study, we are not treating patients beyond six cycles. Only 19% of our patients received radiation. This was tempered by the fact that it was necessary to avoid radiation unless absolutely necessary because of its impact on growth. The omission of IFRT did not affect outcomes in patients with bulky disease, with PR on interim scans, or with early-stage disease who had received fewer than six cycles of chemotherapy (Table 2). However, this result is not based on randomized data, because the majority of patients had received six cycles of chemotherapy.

Table 3. Second-Line Chemotherapy

<table>
<thead>
<tr>
<th>Regimen (No.)</th>
<th>Complete Response, No. (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHAP (7)</td>
<td>4/7 (57)</td>
<td>All seven patients had received appropriate first-line treatment and had relapsed within 3 years of primary treatment.</td>
</tr>
<tr>
<td>ABVD (4)</td>
<td>3/4 (75)</td>
<td>All four patients had received ABV/COPP as primary treatment and had relapsed more than 3 years from primary treatment.</td>
</tr>
<tr>
<td>ABV/COPP (3)</td>
<td>2/3 (66)</td>
<td>Two patients had inadequate primary ABV/COPP and one had inadequate ABVD because of irregular attendance, and these relapses occurred within the first 2 years of default.</td>
</tr>
<tr>
<td>COPP (1)</td>
<td>1/1 (100)</td>
<td>Patient received six cycles of ABVD as primary treatment and relapsed at 1 year.</td>
</tr>
<tr>
<td>Oral cyclophosphamide (2)</td>
<td>1/2 (50)</td>
<td>Neither patient was fit for intensive chemotherapy.</td>
</tr>
</tbody>
</table>

Abbreviations: ABV/COPP, adriamycin, bleomycin, vinblastine, cyclophosphamide, vincristine, prednisone, and procarbazine; ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; COPP, cyclophosphamide, vincristine, prednisone, and procarbazine; DHAP, dexamethasone, ara-c, cisplatin.
chemotherapy, which could have negated any beneficial effect of IFRT. Many centers from the developing world have reported excellent outcomes when radiotherapy has been omitted from the treatment protocol.\textsuperscript{5,7,8} A treatment abandonment rate of 6.2\% was seen in our study, and this was similar to that which has been reported in other regional cancer centers in India.\textsuperscript{5} We did not find any significant differences between the ABV/COPP regimen and ABVD. However, these regimens were not compared prospectively in a randomized trial manner.

We did not investigate for subclinical organ dysfunction in our cohort of patients. Our patients received higher doses of anthracyclines (because of the six to eight cycles of treatment) compared with contemporary protocols, and only further long-term follow-up will clearly show the effects of treatment. Treatment-related toxicities could not be captured comprehensively because of the retrospective nature of the study.

It is challenging to offer second-line treatment in developing countries because of financial constraints and the reluctance of parents to accept treatment for their child after failure of the initial therapy. Our results suggest that sustained complete remission can be achieved in 70\% of patients if treated, and not all may require consolidation with high-dose chemotherapy. Patients who discontinue treatment with either ABVD or ABV/COPP and have progression of disease subsequently can be treated again effectively with either of these two regimens (\textbf{Table 3}).

This report has its limitations because it is retrospective. However, it is encouraging to note that OS is excellent in this cohort and that it reflects the real-world scenario in a developing country.

Our report illustrates that outcomes of pediatric patients with HL are excellent in developing countries despite the challenges in delivering optimal care. The results of second-line chemotherapy in patients with recurrence have been encouraging. In the future, a risk-adapted approach for treating pediatric HL in developing countries will be necessary, thereby reducing the long-term toxicities of the treatment without compromising cure.

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\textbf{AUTHOR CONTRIBUTIONS}

\textbf{Conception and design:} Venkatraman Radhakrishnan, Manikanadan Dhanushkodi, Trivadi S. Ganesan, Prasanth Ganesan, Tenali Gnana Sagar

\textbf{Collection and assembly of data:} Venkatraman Radhakrishnan, Manikanadan Dhanushkodi, Shirley Sundersingh, Ganesarajah Selvaluxmy, Rajaraman Swaminathan, Ranganathan Rama

\textbf{Data analysis and interpretation:} Venkatraman Radhakrishnan, Manikanadan Dhanushkodi, Trivadi S. Ganesan, Prasanth Ganesan, Shirley Sundersingh

\textbf{Manuscript writing:} All authors

\textbf{Final approval of manuscript:} All authors

\textbf{Accountable for all aspects of the work:} All authors

\textbf{AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST}

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/hwc or ascopubs.org/jco/site/ifc.

\textbf{Venkatraman Radhakrishnan}

No relationship to disclose

\textbf{Manikanadan Dhanushkodi}

No relationship to disclose

\textbf{Trivadi S. Ganesan}

No relationship to disclose

\textbf{Prasanth Ganesan}

No relationship to disclose

\textbf{Shirley Sundersingh}

No relationship to disclose

\textbf{Ganesarajah Selvaluxmy}

No relationship to disclose

\textbf{Rajaraman Swaminathan}

No relationship to disclose

\textbf{Ranganathan Rama}

No relationship to disclose

\textbf{Tenali Gnana Sagar}

No relationship to disclose

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\textbf{Affiliations}

All authors: Cancer Institute (WIA), Adyar, Chennai, India.
REFERENCES


Wilms Tumor Treatment Outcomes: Perspectives From a Low-Income Setting

Abstract

Purpose Wilms tumor is the commonest renal malignancy in childhood. Survival in high-income countries is approximately 90%, whereas in low-income countries, it is less than 50%. This study assessed treatment outcomes of patients with Wilms tumor at a Kenyan academic hospital.

Patients and Methods We conducted a retrospective medical record review of all children diagnosed with Wilms tumor between 2010 and 2012. Data on treatment outcomes and various sociodemographic and clinical characteristics were collected.

Results Of the 39 patients with Wilms tumor, 41% had event-free survival, 31% abandoned treatment, 23% died, and 5% had progressive or relapsed disease. Most patients presented at an advanced stage: stage I (0%), II (7%), III (43%), IV (40%), or V (10%). The most likely treatment outcome in patients with low-stage (I to III) disease was event-free survival (67%), whereas in those with high-stage (IV to V) disease, it was death (40%). No deaths or instances of progressive or relapsed disease were recorded among patients with low-stage disease; their only reason for treatment failure was abandonment of treatment. Stage of disease significantly affected treatment outcomes ($P = .014$) and event-free survival estimates ($P < .001$). Age at diagnosis, sex, duration of symptoms, distance to hospital, and health insurance status did not statistically significantly influence treatment outcomes or event-free survival estimates.

Conclusion Survival of patients with Wilms tumor in Kenya is lower compared with that in high-income countries. Treatment abandonment is the most common cause of treatment failure. Stage of disease at diagnosis statistically significantly affects treatment outcomes and survival.

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Introduction

Wilms tumor is the most common primary renal malignancy in children. It accounts for 5% of childhood malignancies.1 It is thought to arise from nephrogenic rests, which are foci of persistent metanephric cells.2 Survival rates have improved from 20% in the 1960s to approximately 90% currently in high-income countries; middle-income countries have survival rates of approximately 80%.2,3 This has been achieved through cooperative study groups as well as use of multimodal approaches to therapy. The two main study groups that have been involved are the National Wilms’ Tumor Study Group and the International Society of Pediatric Oncology (SIOP).2,4,5 Low-income countries, however, have survival rates between 20% and 50%.1-3 Reasons for the low survival in low-income countries include limited access to proper medical care as a result of lack of facilities for treatment, shortage of personnel, long distances to treatment centers, poor infrastructure, and limited public transport facilities. These factors lead to late presentation, which also affects outcomes. Other contributors to the low survival include lack of health insurance, abandonment of treatment, and lack of a multidisciplinary approach to the management of patients. Treatment includes surgery and chemotherapy, as well as radiotherapy for metastatic disease.2,3,5

The aims of our study were to assess the treatment outcomes of children presenting with Wilms tumor at a Kenyan academic hospital and to evaluate the influence of various sociodemographic and clinical characteristics (eg, age at diagnosis, sex, duration of symptoms, stage of disease, distance to hospital, and health insurance status) on treatment outcomes.

Patients and Methods

Setting

Kenya is situated in East Africa and is a low-income country with a population of approximately 43 million people.6 Most of the population (45%) lives below the poverty line.7 This study was carried out at Moi Teaching and Referral Hospital (MTRH), which...
is an academic hospital in Eldoret, a town 300 km northwest of the capital city Nairobi. The hospital has a capacity of approximately 800 beds, including 72 beds in the pediatric ward, of which 12 are dedicated to pediatric oncology. Approximately 120 pediatric oncology patients are seen in the hospital every year, in contrast to the expected number of 700 patients. One pediatrician is involved in the care of oncology patients. Two pediatric surgeons are involved in the surgical aspects of care. There is no radiotherapy facility in Eldoret; patients who require radiotherapy are referred to a center in Nairobi. Families pay for their hospital bills through health insurance or out of pocket. However, only approximately 10% of the Kenyan population have health insurance, which is provided by the government-owned and -controlled National Hospital Insurance Fund (NHIF) or through private insurance companies. Kenyan citizens can enroll with NHIF and pay a set monthly fee. Payments are dependent on level of income for those who are formally employed, whereas those who are self-employed or casual workers pay a monthly fee of approximately US$12. NHIF provides cover for inpatient care for the entire family in government-owned health facilities.

Patients with Wilms tumor are treated according to a protocol modeled on the SIOP approach. Treatment is started after imaging via computed tomography confirms an intrarenal tumor. All patients receive 6 weeks of preoperative chemotherapy with vincristine, dactinomycin, and doxorubicin. Vincristine is administered once per week; dactinomycin is administered in weeks 1, 3, and 5; and doxorubicin is administered in weeks 1 and 5 only. Patients are then scheduled for surgery in week 7 or 8 of treatment. Disease staging is performed intraoperatively, using imaging to detect lung or liver metastases. Staging guides the decision on postoperative treatment. Postoperatively, patients with stage I disease receive 4 weeks of vincristine and dactinomycin. Children with stage II or III disease receive 16 weeks of vincristine and dactinomycin; those with stage III disease are referred for radiotherapy as well. Children with stage IV disease, as well as those with anaplastic histology regardless of stage, receive vincristine, dactinomycin, and doxorubicin for 16 weeks. Patients with stage V disease receive the same preoperative chemotherapy outlined here; the decision on further treatment depends on preoperative imaging and findings at surgery.

**Study Design**

This was a retrospective medical record study. All children presenting with Wilms tumor at MTRH between January 1, 2010, and December 31, 2012, age between 0 and 16 years at diagnosis were included. It is important to note that we did not select patients for our analysis; rather, we included all patients who were diagnosed with Wilms tumor.

The names and inpatient numbers of patients diagnosed with Wilms tumor were extracted from the pediatric oncology database. Files were obtained from the medical record department. Sociodemographic and clinical characteristics were

<table>
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<th>Characteristic</th>
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<tr>
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<tr>
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<td>Luhya</td>
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<td>Kalenjin</td>
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<td>Luo</td>
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<td>Kikuyu</td>
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<td>13 (43)</td>
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<tr>
<td>V</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Health insurance status at diagnosis</td>
<td></td>
</tr>
<tr>
<td>NHIF</td>
<td>16 (41)</td>
</tr>
<tr>
<td>No NHIF</td>
<td>23 (59)</td>
</tr>
</tbody>
</table>

Abbreviations: MTRH, Moi Teaching and Referral Hospital; NHIF, National Hospital Insurance Fund; SD, standard deviation.
extracted from patients’ medical records using a data collection form.

Sociodemographic characteristics included age at diagnosis, sex, ethnicity, patient residence, and enrollment in NHIF. A patient’s residence was used to determine the distance from MTRH, which was subsequently categorized into distance of 100 km or less or more than 100 km.

Clinical characteristics included date of diagnosis, disease stage, time to event, and treatment outcome. Disease stage was determined using imaging to detect any lung or liver metastases, as well as through the information derived from intraoperative findings. For further analysis on outcomes, we grouped those with nonmetastatic stage I to III disease into low-stage and those with stage IV or V disease into high-stage groups. Treatment outcomes were classified as abandonment of treatment, death, progressive or relapsed disease, and event-free survival. Abandonment of treatment was defined as either not starting or not continuing planned treatment during 4 or more sequential weeks.11

Data Analysis

Data analysis and management were performed using SPSS software (version 20; SPSS, Chicago, IL). Frequency distributions, means, and medians were calculated. The relationship between treatment outcomes and sociodemographic or clinical characteristics was evaluated using $\chi^2$ and Fisher’s exact tests. The probability of event-free survival was estimated using the Kaplan-Meier method; estimates were compared using the log-rank test. Event-free survival was measured from date of Wilms tumor diagnosis to first treatment failure or date of last follow-up. Treatment failure included abandonment of treatment, death, and progressive or relapsed disease.

RESULTS

A total of 39 patients with Wilms tumor presented to the hospital during the study period. Girls comprised 52% of patients. Table 1 lists sociodemographic and clinical characteristics. Almost all patients (97%) were referred to MTRH from other health facilities. A majority (91%) were referred from secondary-level public health facilities, whereas the rest were referred by private clinics (3%), private hospitals (3%), or tertiary-level hospitals (3%). Before patients presented to MTRH, only 16% had received a possible diagnosis of Wilms tumor, and none had received any treatment specifically for Wilms tumor. A majority of patients presented at later stages. There was no patient with stage I disease. Children were diagnosed with: stage II (7%), III (43%), IV (40%), or V (10%) disease. Of the 39 patients, 54% lived more than 100 km from MTRH. At time of diagnosis, 39% of patients had NHIF. Of those who did not have NHIF at diagnosis, most (83%) registered while undergoing treatment at MTRH, bringing the total enrollment level to 90%.

The overall 3-year survival rate was 41%. Figure 1 shows the event-free survival estimate of all children with Wilms tumor.

As summarized in Table 2, the most common cause of treatment failure was abandonment of treatment (31%), and the second most common was death (23%). All deaths occurred within 4 months of diagnosis, with 78% of these children dying within the first 2 months. The least common cause of treatment failure was progressive or relapsed disease (5%).

Of 30 patients with documented stage of disease, 50% had low-stage (I to III) and 50% had high-stage (IV to V) disease. The most likely treatment outcome in patients with low-stage disease was event-free survival (67%), whereas in patients with high-stage disease, it was death (40%). No deaths or instances of progressive or relapsed disease occurred among patients with low-stage disease. As summarized in Table 2, differences in treatment outcomes between children with low- and high-stage disease were significant ($P = .014$). Figure 2 shows that event-free survival estimates
differed significantly between patients with stage II, III, IV and V disease (P < .001).

Other sociodemographic and clinical characteristics (i.e., age at diagnosis, sex, duration of symptoms, distance to hospital, and health insurance status) did not have a statistically significant influence on treatment outcomes or event-free survival estimates. Figures 3 and 4 illustrate that living at a shorter distance from MTRH and having health insurance at diagnosis led to better chances of survival, but this did not reach statistical significance (P = .063 and .358, respectively).

**DISCUSSION**

This study demonstrated a survival rate of 41% among patients diagnosed with Wilms tumor at MTRH between the years 2010 to 2012. This is a great improvement from the survival rate of 29% that was documented for those patients treated at the institution between the years 2000 and 2007.12 This improvement may be attributed to several factors. The hospital adopted the SIOP approach to the management of Wilms tumor during the timeframe of our study. In the previous study, some patients never received any preoperative chemotherapy, and mortality was high. In 2009, the hospital developed a protocol manual that was used to manage all patients with cancer. Use of protocols and establishment of a multidisciplinary team have been demonstrated to lead to better outcomes. We now have competent pediatric surgeons, psychological counselors, social workers, and pharmacists involved in the care of patients with Wilms tumor. A team of dedicated pediatric oncology nurses cares for the children, unlike in the past, when nurses were moved from the department every few months. This has increased nurses’ knowledge and experience, which has resulted in better patient outcomes.

**Table 2.** Treatment Outcomes in Children With Wilms Tumor and Influence of Disease Stage, Distance to Hospital, and Health Insurance Status (N = 39)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Treatment Abandonment</th>
<th>Death</th>
<th>Progressive or Relapsed Disease</th>
<th>Event-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall patient population</td>
<td>12 (31)</td>
<td>9 (23)</td>
<td>2 (5)</td>
<td>16 (41)</td>
</tr>
<tr>
<td>Disease stage (n = 30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low*</td>
<td>5 (33)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>High†</td>
<td>3 (20)</td>
<td>6 (40)</td>
<td>1 (7)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>P</td>
<td>.014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance to hospital, km</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 100</td>
<td>4 (22)</td>
<td>2 (11)</td>
<td>2 (11)</td>
<td>10 (56)</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>8 (38)</td>
<td>7 (33)</td>
<td>0 (0)</td>
<td>6 (29)</td>
</tr>
<tr>
<td>P</td>
<td>.074</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health insurance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHIF</td>
<td>4 (25)</td>
<td>4 (25)</td>
<td>0 (0)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>No NHIF</td>
<td>8 (35)</td>
<td>5 (22)</td>
<td>2 (9)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>P</td>
<td>.640</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NHIF, National Hospital Insurance Fund.

*Low indicates stage I to III disease.
†High indicates stage IV to V disease.
Supportive care has also improved over time through use of a protocol for management of febrile neutropenia and better availability of antibiotics. Nutritional care has improved significantly. Previously, cultural beliefs and associations with death prevented both the medical team and the families from using nasogastric feeding. Now most children do undergo nasogastric tube feeding, which allows feeding even when children have decreased appetite or mucositis. All patients were also actively encouraged to register with NHIF and were provided with assistance whenever possible. All these interventions have been achieved through collaboration with two partners in high-income countries: the Indiana University School of Medicine in the United States and the Vrije Universiteit Medical Center in the Netherlands. This collaboration has led to the transfer of knowledge among physicians, nurses, and other support staff, achieved through exchange visits, teleconferences in which patient care is discussed, and training workshops held in Eldoret every year.

High-income countries have reported high survival rates among children with Wilms tumor. In the United Kingdom, an overall survival rate of 88% was documented on 10-year follow-up.13 Middle-income countries also have good survival rates, with China reporting a survival rate of 81%.14 However, the survival rates are still low in low-income countries, especially in Africa. A 2-year survival rate of 25% was reported from an eight-center Wilms tumor treatment collaborative effort in Africa.15 In Malawi, the survival rate is 46%.16 These low survival rates have been attributed to several factors, including high treatment abandonment and treatment-related mortality.17

The rate of treatment abandonment was 31% in our study. This is a decrease from the 54% abandonment rate that we reported before in the same hospital for the period of 2007 to 2009, although the latter study examined all types of cancer.18 This figure is also lower than the 42% reported previously among patients with Wilms tumor at the same institution.12 In a study that examined several hospitals in Kenya, a 50% rate of patients lost to follow-up was reported among those with Wilms’ tumor, although this included both patients who abandoned therapy as well as patients who were lost to follow-up after finishing treatment.19 In Africa, Wilms tumor treatment abandonment rates vary between 14% and 48%.15 Abandonment in this setting is attributed to a lack of parental education on Wilms tumor by medical staff, parents’ misunderstanding of treatment protocols, and families’ financial difficulties.20 Abandonment of therapy contributes to a large extent to poor outcomes in pediatric oncology in low-income countries. In our study, abandonment was the only adverse outcome among those patients with stage II or III disease. If this phenomenon is addressed adequately, survival in this group could improve, approaching that reported in high-income countries.

A majority of patients of our study presented with late-stage disease. Those who had stage II disease had good outcomes, in contrast to those with later stages of disease. A multicenter study of Wilms tumor involving French-speaking countries in Africa reported that patients with stage III or IV disease comprised 41% of all patient cases.17 In South Africa, those with stage III or IV disease comprised 49% of patient cases.21 In both these studies, patients with stage V disease were excluded from analysis. This indicates that late presentation is still a major issue in low-income settings. It could possibly be explained by circumstances that lead to both patient and health care system delays. Patient delays usually result from outdated health beliefs, poor reputation of public hospitals, preference for alternative medicine, and financial difficulties coupled with lack of health insurance. Health care system delays result from unavailability of the qualified personnel or equipment required to make correct diagnoses.22,23 Disease stage has been documented as one of the most important prognostic factors. However, there are still huge differences when we compare...
outcomes in high- versus low-income countries. In the United Kingdom, an overall survival rate of 81% for stage IV disease was reported.\textsuperscript{13} In Africa, in the French-speaking collaborative group, children with stage IV disease had an overall survival rate of 49%, and in South Africa, the survival rate was 57%\textsuperscript{15,21}. Disparities in survival between high- and low-income countries are worse in the more advanced disease stages; however, most patients from low-income countries present with advanced disease. Therefore, to improve outcomes, we should concentrate not only on improving the standards of care but also on diagnosing patients with early-stage disease.

Increasing awareness of childhood cancer among health care workers is paramount. Having ultrasound machines as well as trained personnel in most primary care centers could lead to increased detection rates. This strategy could have the potential of increasing survival with less strain on the health care system.

Patients living more than 100 km from MTRH had lower chances of survival compared with those living nearer to the hospital, although this did not reach statistical significance. The most likely treatment outcome in patients within 100 km of MTRH was event-free survival, whereas in patients living farther from MTRH, it was abandonment of treatment. Distance and transport costs have been demonstrated to increase chances of abandonment and thereby decrease survival in pediatric oncology.\textsuperscript{24,25} In a previous study among families of children with cancer who abandoned treatment at MTRH, it was found that long distance to the hospital led to higher costs of transportation and affected the ability to keep appointments.\textsuperscript{18} Most Kenyan families use public transport to reach MTRH. However, Kenyan public transport is not well organized. The number and quality of roads are limited. There are no fixed routes, timetables, or fares.\textsuperscript{18} These infrastructural obstacles may ultimately affect the survival of children with Wilms tumor.

Although only 39% of families had health insurance before coming to MTRH, this number is higher than the national figure of 10%.\textsuperscript{26} Previous studies in the Kenyan setting have shown that having NHIF at diagnosis significantly decreases abandonment and improves childhood cancer survival.\textsuperscript{18,20} This taught our team that it is important to enroll patients in NHIF. In the pediatric oncology ward at MTRH, the physicians and nurses therefore now continually inform families about the need for NHIF. Particularly for children with potentially good prognoses, like those with Wilms tumor, medical staff make sure that families get NHIF. Support staff help families to collate all documents required for this purpose and direct them on which office to visit. Most families in our study subsequently enrolled in NHIF during hospitalization. This illustrates that if families are given the right information and are assisted in obtaining health insurance, many of them are willing to do so. The government should have mass media educational campaigns on the benefits and procedures of registering with NHIF.

The main limitations in this study were the small sample size and the fact that, because it was a retrospective medical record review, some data were missing. In conclusion, the survival rate of patients with Wilms tumor at MTRH improved between the years 2010 and 2012 as compared with 2000 to 2007. The main reason for treatment failure was abandonment of treatment. Disease stage at diagnosis significantly affected treatment outcomes and event-free survival estimates. Age at diagnosis, sex, duration of symptoms, distance to hospital, and having health insurance at diagnosis did not predict survival.

On the basis of the findings of our study, we acknowledge that abandonment of treatment needs to be addressed. Providing proper parental education and financial support would be useful strategies. To help reduce the number of children presenting with late-stage disease and improve access to conventional health care facilities, we recommend that the government initiate mandatory universal health insurance coverage. Health care workers should be trained on the clinical features of Wilms tumor. This should be done by
incorporating training on childhood cancers into the curricula of medical training institutions, as well as through continuous professional development for those who have already graduated. To reduce transportation difficulties for families living far from the hospital, establishing satellite clinics and family guesthouses near the hospital could be beneficial. Ultimately, all these interventions could improve survival of children with Wilms tumor.

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AUTHOR CONTRIBUTIONS

Conception and design: Festus Njuguna, Patel Kirtika, Gilbert Olbara, Steve Martin, Jodi Skiles, Terry Vik, Gertjan J.L. Kaspers, Saskia Mostert
Collection and assembly of data: Festus Njuguna, Hugo A. Martijn, Robert Tenge Kuremu, Peter Saula, Sandra Langat
Data analysis and interpretation: Festus Njuguna, Hugo A. Martijn, Gertjan J.L. Kaspers, Saskia Mostert
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Festus Njuguna
No relationship to disclose

Hugo A. Martijn
No relationship to disclose

Robert Tenge Kuremu
No relationship to disclose

Peter Saula
No relationship to disclose

Patel Kirtika
No relationship to disclose

Gilbert Olbara
No relationship to disclose

Sandra Langat
No relationship to disclose

Steve Martin
No relationship to disclose

Jodi Skiles
No relationship to disclose

Terry Vik
No relationship to disclose

Gertjan J.L. Kaspers
Consulting or Advisory Role: Jazz Pharmaceuticals, Boehringer Ingelheim
Travel, Accommodations, Expenses: Jazz Pharmaceuticals

Saskia Mostert
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Affiliations

Festus Njuguna, Robert Tenge Kuremu, Peter Saula, Patel Kirtika, Gilbert Olbara, and Sandra Langat, Moi University, Eldoret, Kenya; Hugo A. Martijn, Gertjan J.L. Kaspers, and Saskia Mostert, Vrije Universiteit Medical Center, Amsterdam, the Netherlands; and Steve Martin, Jodi Skiles, and Terry Vik, Indiana University School of Medicine, Indianapolis, IN.

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9. National Hospital Insurance Fund: www.nhif.or.ke/healthinsurance


Model for Estimating Power and Downtime Effects on Teletherapy Units in Low-Resource Settings

**Purpose** More than 6,500 megavoltage teletherapy units are needed worldwide, many in low-resource settings. Cobalt-60 units or linear accelerators (linacs) can fill this need. We have evaluated machine performance on the basis of patient throughput to provide insight into machine viability under various conditions in such a way that conclusions can be generalized to a vast array of clinical scenarios.

**Materials and Methods** Data from patient treatment plans, peer-reviewed studies, and international organizations were combined to assess the relative patient throughput of linacs and cobalt-60 units that deliver radiotherapy with standard techniques under various power and maintenance support conditions. Data concerning the frequency and duration of power outages and downtime characteristics of the machines were used to model teletherapy operation in low-resource settings.

**Results** Modeled average daily throughput was decreased for linacs because of lack of power infrastructure and for cobalt-60 units because of limited and decaying source strength. For conformal radiotherapy delivered with multileaf collimators, average daily patient throughput over 8 years of operation was equal for cobalt-60 units and linacs when an average of 1.83 hours of power outage occurred per 10-hour working day. Relative to conformal treatments delivered with multileaf collimators on the respective machines, the use of advanced techniques on linacs decreased throughput between 20% and 32% and, for cobalt machines, the need to manually place blocks reduced throughput up to 37%.

**Conclusion** Our patient throughput data indicate that cobalt-60 units are generally best suited for implementation when machine operation might be 70% or less of total operable time because of power outages or mechanical repair. However, each implementation scenario is unique and requires consideration of all variables affecting implementation.
In choosing the appropriate teletherapy machine for a particular region, it is important to investigate projected machine performance considering patient treatment needs, machine capabilities, and the framework of local infrastructure. As a first step, we have quantified the relative daily patient throughput of cobalt-60 units and linacs that deliver a range of treatment techniques under various infrastructure conditions in an effort to add quantitative data to the discussion of teletherapy machine implementation.

MATERIALS AND METHODS
Relative average daily patient throughput was modeled for six treatment scenarios (linac delivering conformal radiotherapy, step-and-shoot IMRT, dynamic IMRT, VMAT, and cobalt-60 unit delivering conformal radiotherapy with and without multileaf collimators [MLCs]) under three power outage conditions. Data from international organizations, peer-reviewed studies, clinical observations, and patient treatment plans were used to model daily operational time of the teletherapy units and patient treatment time. Machine availability for each scenario was calculated as the total number of working hours per day in which a power supply was available and the machine was otherwise in operable condition. Patient treatment time was calculated as described under Modeled Patient Population.

Machine Operability
Power outage scenarios. For the purpose of our study, it was assumed that although cobalt-60 units are functional during a power outage via generator-supplied power, linacs are inoperable during power outages. Using data from World Bank Enterprise Surveys, we recorded power outage frequency and duration in all 44 African countries for which data were available. African countries were used for this study because of the availability of data and the concentrated need for teletherapy. Data for multiple years for a single country were averaged, and the 44 data points were divided into three subgroups on the basis of frequency of outages. This discretization allowed for sampling of three power outage scenarios: many outages (an average of 9.1 to 31.5 outages per month), some outages (3.3 to 9.1 outages per month), and few outages (0 to 3.3 outages; Fig 1). Outage durations were sampled from the corresponding distribution of outage duration. The data were scaled from reported outages per month to daily values for power outages. In addition, each power outage was extended by 20 minutes to account for the time it takes to bring the machine back online after a power outage.

Machine downtime. To estimate machine downtime, we recorded fractional downtime in-house for 15 machines at The University of Texas MD Anderson Cancer Center over 16 months of operation, and daily machine downtimes were sampled from this distribution. To more closely reflect the machine operation and downtime characteristics of LMICs and low-resource settings in which onsite engineers and machine support staff may not be available, we created a second machine downtime distribution by scaling the collected data to reflect an average machine downtime of 8%, as reported for 30 linacs across 10 countries by van der Giessen et al. Data on cobalt-60 machine downtime were not available at our institution, nor were comprehensive analyses available in the literature. Those experienced with cobalt-60 machines suggested a downtime percentage of 1 week per 2 years of operation (1%); this value also reflects that reported in van der Giessen et al.

Modeled Patient Population
In general, the treatment time needed per patient per fraction varies by type of machine, site of disease, prescribed dose, and delivery technique. Our modeled population included patients assigned a cancer site, radiation prescription, and treatment modality on the basis of cancer incidence and standard radiation prescriptions. Treatment time was then calculated (see Patient treatment time).

Cancer incidence and radiation prescription. The vast diversity in cancer incidence among regions and countries indicates that teletherapy implementation should be undertaken with the projected patient population in mind. To reflect cancer incidence in the regions of power outage considered, we used published data on cancer incidence in eight African countries from Cancer Incidence in Five Continents, Volume X, from the International Agency for Research on Cancer. Nine cancer sites (breast, cervix, esophagus, head and neck, liver, lung, lymph node, prostate, and rectum) were identified, representing 40% to 80% of cancer incidence in each country. These percentages were averaged, normalized, and multiplied by the optimal fraction of patients receiving radiotherapy, as reported by Barton et al. Radiation prescriptions were assigned per site on the basis of current curative clinical schemes.
**Patient treatment time.** Patient treatment time was calculated as the sum of setup, image guidance (optional), and beam delivery times.

\[
\text{Treatment time} = \text{Setup} + \text{Image guidance} + \text{Beam delivery}
\]

It was assumed that the time needed for image guidance and setup was independent of the treatment machine, treatment technique, and cancer site. The distribution of patient setup times was acquired from clinical observations of 37 patient procedures. Image guidance time (2D-2D match), which was optional in patient treatment, was assumed to be 140 seconds,\(^{11}\) and this was verified with 31 clinical observations. Beam delivery time comprised beam-on and mechanical motion components.

\[
\text{Beam delivery time} = \text{Beam–on time} + \text{Mechanical motion time}
\]

Mechanical motion time included the time during which beam definition (field shape or beam angle) occurs. Beam-on time was calculated as the product of the prescribed dose (Gy), a percent depth dose correction factor (PDDC) which is applied for cobalt treatment only and scales the prescribed dose on the basis of the difference in percent depth dose characteristics of 6-MV linacs and cobalt-60 (PDDC, for cobalt-60 treatments only), a beam modulation factor (monitor units [MU]/Gy) which relates the number of monitor units needed to deliver the desired dose on the basis of treatment site and treatment technique, and the inverse dose rate (minutes/MU).

\[
\text{Beam–on time} = \text{Gy} \times \text{PDDC} \times \frac{\text{MU}}{\text{Gy}} \times \frac{\text{min}}{\text{MU}}
\]

Treatment modality and cancer site-specific distributions of beam modulation factor (all modalities) and mechanical motion times (step-and-shoot IMRT) were acquired from more than 1,000 patient plans. Mechanical motion times for other modalities were approximated by using the required machine parameters. Mechanical motion time for step-and-shoot IMRT was calculated as the sum of the time for MLC definition over each beam segment (acquired by using a treatment planning script on 126 patient plans treated on
Varian machines that incorporated segment order and leaf speed); it was assumed that gantry rotation time occurs simultaneously with MLC definition. For dynamic IMRT and conformal radiotherapy, mechanical motion time was set at 1 minute, under the assumption that beam angles span the full gantry extent and that gantry rotation occurs at one revolution per minute. For VMAT treatments, mechanical motion time was assumed to be 30 seconds, accounting for the collimator rotation between gantry arcs. Furthermore, total beam-on time for VMAT treatments was assumed to be at least 2 minutes or two arcs per treatment.

In addition, we considered two cobalt-60 treatment scenarios in which no MLCs were available, indicating the need for a therapist to add or change blocks. Through clinical observations, we estimated the time needed for one or three block changes per patient per fraction. One block change added 1 minute to the treatment time, and three block changes added 3.5 minutes to the treatment time.

For each treatment scenario, beam modulation factors and mechanical motion times were sampled from the distributions of treatment modality and cancer site incidence. If cobalt-60 was used, the prescribed dose was multiplied by a percent depth dose correction factor equal to 1.095, the average of the ratio of 6-MV and cobalt-60 depth doses under reference conditions from 1.5-cm to 10-cm depth. Finally, the inverse dose rate was used to calculate the beam-on time for each patient. The cobalt-60 dose rate decayed throughout the model duration, with an initial dose rate of 250 MU/minute corresponding to 100 MU/Gy under reference conditions. The linac dose rate was 600 MU/minute under reference conditions.

**RESULTS**

**Patient Treatment Time**

For each of the treatment scenarios, we determined the average time spent per treatment activity comprising the total average patient treatment time for each treatment scenario (Table 1). Shown are cobalt-60 units with MLCs during years 1, 5, and 8 of operation, in an effort to underscore the effect of source decay. Conformal radiotherapy during year 8 of cobalt-60 operation represented the longest average total treatment time, and step-and-shoot IMRT represented the second longest average total treatment time, largely because step-and-shoot IMRT required the longest average mechanical motion time (2.56 minutes).

Beam modulation factors which, for each treatment technique and site, indicate the number of monitor units needed to deliver the prescribed dose, were collected from over 1,000 patient treatment plans. In Table 2, beam modulation factors for each treatment site for each of the four treatment techniques are shown the mean and standard deviation of the distributions recorded.

**Patient Throughput and Power Outage Conditions**

Each of the treatment scenarios was considered under the three power outage conditions (many,

---

**Table 1.** Average Time Required for Each Treatment Activity by Treatment Technique

<table>
<thead>
<tr>
<th>Activity</th>
<th>Linac VMAT</th>
<th>Linac Dynamic IMRT</th>
<th>Linac Step-and-Shoot IMRT</th>
<th>Linac Cobalt-60 Y1</th>
<th>Linac Cobalt-60 Y5</th>
<th>Linac Cobalt-60 Y8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setup</td>
<td>3.21</td>
<td>3.21</td>
<td>3.21</td>
<td>3.21</td>
<td>3.21</td>
<td>3.21</td>
</tr>
<tr>
<td>Image guidance</td>
<td>2.33</td>
<td>2.33</td>
<td>2.33</td>
<td>2.33</td>
<td>2.33</td>
<td>2.33</td>
</tr>
<tr>
<td>Mechanical motion</td>
<td>0.50</td>
<td>1.00</td>
<td>2.56</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Beam-on</td>
<td>2.00</td>
<td>1.86</td>
<td>0.93</td>
<td>0.40</td>
<td>1.03</td>
<td>1.74</td>
</tr>
<tr>
<td>Total</td>
<td>8.04</td>
<td>8.41</td>
<td>9.03</td>
<td>6.95</td>
<td>7.57</td>
<td>8.28</td>
</tr>
</tbody>
</table>

**NOTE.** All data assume that multileaf collimators were used. Data are averaged across the top nine cancer sites for which radiotherapy is indicated in the eight African countries for which data were available.

**Abbreviations:** IMRT, intensity-modulated radiotherapy; Linac, linear accelerator; VMAT, volumetric-modulated arc therapy.

*Y indicates year of use of the cobalt-60 unit (ie, Y1 indicates year 1 of use).
some, or few power outages), assuming an average linac downtime distribution of 8%. The normalized daily patient throughput results are provided in Table 3. The average duration of daily power outages for each power outage condition is also reported.

Through 5 years of cobalt-60 operation, after which dose rate is 130 MU/minute under reference conditions, daily patient throughput was 94% relative to year 1. For cobalt-60 operation through 8 years, (87 MU/minute), relative throughput was 88%. Linacs delivering conformal radiotherapy with few power outages showed the highest relative daily patient throughput, and linacs delivering step-and-shoot IMRT with many power outages showed the lowest throughput.

When linac downtime percentages were sampled from the distribution of data collected at The University of Texas MD Anderson Cancer Center (average 1.7%), linac throughput across all treatment schemes increased by an average of 4%, but relative performance at or above baseline did not change.

Power outages affected daily patient throughput more dramatically than did treatment scenarios. Figure 2 shows patient throughput for linacs delivering each of the four treatment types and cobalt-60 units through 5 and 8 years of operation by average daily power outage duration. Daily throughput for linac conformal radiotherapy was found to be equal to that of cobalt-60 units through 5 years of operation with average daily power outages of 1.34 hours and equal to that of cobalt-60 units through 8 years of operation with average daily power outages of 1.83 hours, assuming an average linac downtime of 8%. When the average linac downtime was assumed to be 1.7%, equal average daily patient throughput for conformal radiotherapy on linac and cobalt-60 machines through 5 and 8 years of operation was achieved at 1.88 and 2.34 average daily hours of power outage, respectively. In addition, equal throughput was observed for linac VMAT and cobalt-60 units through 8 years of operation with an average of 0.49 hours of daily power outage.

Finally, when considering the availability of MLCs, daily throughput decreased dramatically when block changes were required. In Figure 3, daily patient throughput for cobalt-60 units through 8 years of operation requiring one block change and

Table 2. Beam Modulation Factors by Treatment Delivery Technique and Cancer Site of Prescription

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Conformal Radiotherapy</th>
<th>Step-and-Shoot IMRT</th>
<th>Dynamic IMRT</th>
<th>VMAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Mean</td>
<td>SD</td>
<td>No.</td>
<td>Mean</td>
</tr>
<tr>
<td>Breast</td>
<td>60</td>
<td>139</td>
<td>21</td>
<td>47</td>
</tr>
<tr>
<td>Cervical</td>
<td>35</td>
<td>114</td>
<td>17</td>
<td>69</td>
</tr>
<tr>
<td>Esophagus</td>
<td>48</td>
<td>113</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Head and neck</td>
<td>32</td>
<td>137</td>
<td>55</td>
<td>21</td>
</tr>
<tr>
<td>Lung</td>
<td>55</td>
<td>126</td>
<td>35</td>
<td>25</td>
</tr>
<tr>
<td>Prostate</td>
<td>39</td>
<td>113</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Rectum</td>
<td>33</td>
<td>142</td>
<td>18</td>
<td>26</td>
</tr>
</tbody>
</table>

NOTE. Shown are number of measurements recorded (No.). Data were not available for breast or cervical treatments using step-and-shoot intensity-modulated radiotherapy (IMRT); thus, for model purposes, breast conformal data and prostate step-and-shoot IMRT were used as surrogates, respectively. In addition, in modeling, esophagus distributions were used for lymphoma beam modulation factors. Abbreviations: SD, standard deviation; VMAT, volumetric-modulated arc therapy.

Table 3. Relative Daily Patient Throughput

<table>
<thead>
<tr>
<th>Treatment Scenario</th>
<th>Many Power Outages* (5.9)</th>
<th>Some Power Outages* (1.6)</th>
<th>Few Power Outages* (0.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobalt conformal radiotherapy</td>
<td>Baseline</td>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>Year 1</td>
<td>Baseline</td>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>Year 5</td>
<td>87</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>Year 8</td>
<td>76</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>Linac conformal radiotherapy</td>
<td>44</td>
<td>91</td>
<td>106</td>
</tr>
<tr>
<td>Linac VMAT</td>
<td>36</td>
<td>73</td>
<td>86</td>
</tr>
<tr>
<td>Linac dynamic IMRT</td>
<td>34</td>
<td>69</td>
<td>81</td>
</tr>
<tr>
<td>Linac step-and-shoot IMRT</td>
<td>30</td>
<td>62</td>
<td>73</td>
</tr>
</tbody>
</table>

NOTE. Initial cobalt dose rate is assumed to be 250 MU/min under reference conditions, and average linear accelerator (linac) downtime distribution is assumed to be 8% in an average patient population for which no image guidance was used.

Abbreviations: IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy.

*Average power outage duration per 10-hour working day (hours).
three block changes per patient per fraction are shown. Relative to cobalt-60 units through 8 years of operation using MLCs, the need for one block change reduced the throughput to 86% and the need for three block changes reduced the throughput to 63%. The relative reduction in throughput observed when three block changes were required for cobalt-60 units made the throughput equal to that of the linac step-and-shoot IMRT modality (which had the lowest relative throughput) with an average of 2.47 hours of daily power outages per 10-hour working day.

DISCUSSION

Thousands of teletherapy units are needed in LMICs and in low-resource settings. The choice of teletherapy unit is an important one, especially considering the cost (both upfront and continuing) and lifetime of teletherapy units. Furthermore, the technologies associated with and the uses and capabilities of a treatment machine, while presumably dynamic over time, can have an impact on the number of patients able to receive possibly lifesaving radiotherapy services. We have quantitatively explored the relative daily patient...
throughput characteristics of linac and cobalt-60 teletherapy units operating with many treatment techniques and under various infrastructure scenarios. Our results underscore and re-emphasize the importance of power infrastructure characteristics at the site of implementation. It is clear that a complete understanding of the power availability in the region of projected implementation is, without doubt, critical in estimating potential machine performance. Under scenarios of moderate power outages (fewer than 1.6 average hours of power outage per 10-hour working day), conformal treatment techniques delivered with MLCs on cobalt-60 units or linacs can be expected to achieve similar patient throughput. It is our hope that the results of this study can inform the reader who also has a knowledge of their individual clinic regarding the impact of machine type and treatment choices.

Machine implementation is a multifaceted and highly complex issue. It is impractical, and likely impossible, to completely model the projected machine performance over an extended period of time while considering all variables and scenarios that are likely to arise. As a partial acknowledgment of additional considerations, Table 4

Table 4. Limited List of Considerations for Identifying a Radiotherapy Machine Best Suited to Each Clinic’s Need

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Discussion and Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power outages and machine downtime</td>
<td>Discrete interruptions in machine operation not only limit average throughput but may interrupt treatment of patients, staff work times, and scheduling. In addition, sudden power cuts may be damaging to teletherapy machines or auxiliary equipment.</td>
</tr>
<tr>
<td>Service parts and personnel</td>
<td>Accessibility, geographical and otherwise, of service parts and personnel specific to the radiotherapy machine is essential to machine operation. Extended interruptions in treatment can dramatically decrease the efficacy of treatments and the treatment units to individual patients and to the population as a whole.</td>
</tr>
<tr>
<td>Image guidance and advanced techniques</td>
<td>Many types of image guidance and advanced techniques (eg, IMRT, VMAT, and MLCs) are clinically available, each with associated benefits. However, the addition of accessory technology to a radiotherapy machine may increase the mechanical stress and machine downtime. The advantages of such technologies whether they are an increase in patient load, dosimetric advantages, or otherwise, should be closely examined on a site-by-site basis. Furthermore, treatment times may vary depending on physician or clinical practice. For example, although we assumed a minimum of 2 minutes beam-on time for VMAT treatments, this might not be representative of true treatment times if one-arc treatments are available.</td>
</tr>
<tr>
<td>Dose rate and source exchange</td>
<td>Cobalt-60 sources will need replacement after a period of operation. This replacement time will depend upon the initial source strength (variable), financial concerns, and governmental and radioactive material concerns among others. The implications of operation with a decayed source reach beyond increased patient treatment time and decreases in patient throughput.</td>
</tr>
<tr>
<td>Capabilities of staff</td>
<td>The training and continued education of technologists, physicists, oncologists, nurses, and dosimetrists depends on the machine and its capabilities. Sufficiently trained staff is essential for the safe operation of radiotherapy equipment.</td>
</tr>
<tr>
<td>Adjunct equipment</td>
<td>Successful operation of radiotherapy services may indicate the need for additional equipment including but not limited to diagnostic and treatment planning imaging equipment, quality assurance equipment and tools, basic spare parts, treatment planning services, patient positioning and immobilization devices, a shielded bunker or the like, power stabilization equipment, and generators. Without some or all of these, treatment may need longer for completion or may be halted altogether.</td>
</tr>
<tr>
<td>Clinician and patient desires</td>
<td>Not to be overlooked are the wishes and desires of clinicians, staff, and patients. The choice of machine should be in agreement with current and future clinical operations. A machine that is not wanted or capabilities that are not fully understood will likely suffer in operation.</td>
</tr>
</tbody>
</table>

Abbreviations: IMRT, intensity-modulated radiotherapy; MLC, multileaf collimator; VMAT, volumetric-modulated arc therapy.
discusses scenarios of note and their implications. Our work mainly focuses on the effect of power outages and machine downtime on relative machine performance. This is a simple first step in an effort to clearly elucidate projected machine performance. A relative average daily throughput analysis was conducted according to data availability. Day-to-day variation in patient throughput may have impacts beyond patient throughput, including interruptions in treatment, staffing resources, and machine performance.

Considering treatment time, advanced treatment techniques, with the exception of MLCs, reduce patient throughput because of increased mechanical motion or beam-on times. Although it is beyond the scope of this investigation, the indication for implementation of these advanced techniques is debated.14,15 When considering cobalt-60 teletherapy units and the availability of MLCs, if physical block changes are needed, a substantial reduction in patient throughput is seen. If three block changes are needed per patient per fraction, throughput is decreased 37%, relative to operation with MLCs. Although block changes may not be indicated in all treatment regimens, as assumed here, our results indicate the critical role automatic beam shaping devices can play in maximizing patient throughput, but we do not consider the burden this may place on machine downtime.

In addition, although a scenario of operation without MLCs was considered only for cobalt-60 units, linacs will also be subject to throughput decreases if MLCs are not used. Often cited as a disadvantage of cobalt-60 teletherapy is the limited source strength available.2,4 We have shown that source decay (initial source strength 2.5 Gy/min at 80 cm) over 8 years represents an increase in patient treatment time of 1.5 minutes per treatment (or 20%). Although with lower initial source strengths and less frequent cobalt-60 source exchanges, patient treatment time can become prohibitively long as a result of increased beam-on time. Thus, the projected availability of cobalt-60 sources must be considered upon machine implementation.

Although the circumstances surrounding each scenario of machine implementation are unique, our analysis quantitatively compared the projected performance of cobalt-60 machines and linacs in low-resource settings. Power infrastructure is implicated as a key factor in the choice of teletherapy machine, but cobalt-60 source availability as well as the use of advanced treatment techniques, including IMRT, VMAT, and MLCs, must also be considered.

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**AUTHOR CONTRIBUTIONS**

Conception and design: Rachel McCarroll, Bassem Youssef, Beth Beadle, Geoffrey Ibbott, Christoph Trauernicht, Peter Balter, Laurence Court

Financial support: Rachel McCarroll, Geoffrey Ibbott, Laurence Court

Administrative support: Rachel McCarroll, David Followill, Geoffrey Ibbott, Laurence Court

Provision of study materials or patients: All authors

Collection and assembly of data: Rachel McCarroll, Bassem Youssef, Beth Beadle, Rex Cardan, Robin Famiglietti, David Followill, Peter Balter, Laurence Court

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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Rachel McCarroll
No relationship to disclose

Bassem Youssef
Travel, Accommodations, Expenses: Merck

Beth Beadle
No relationship to disclose

Maureen Bojador
No relationship to disclose

Rex Cardan
Honoria: Varian Medical Systems
Consulting or Advisory Role: Varian Medical Systems
Research Funding: Varian Medical Systems
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Travel, Accommodations, Expenses: Varian Medical Systems

Robin Famiglietti
No relationship to disclose

David Followill
No relationship to disclose

Geoffrey Ibbott
Stock or Other Ownership: Accuray (I)
Research Funding: Varian Medical Systems (Inst), Elekta (Inst)
Travel, Accommodations, Expenses: Elekta
Anuja Jhingran
No relationship to disclose

Christoph Trauernicht
No relationship to disclose

Peter Balter
Employment: University of Texas MD Anderson Cancer Center,
University of Texas School of Dentistry (I)

Honoraria: Sun Nuclear Corporation, International Atomic
Energy Agency

Speakers’ Bureau: Varian Medical Systems

Research Funding: Varian Medical Systems

Travel, Accommodations, Expenses: Sun Nuclear Corporation

Laurence Court
No relationship to disclose

Affiliations
Rachel McCarroll, Beth Beadle, Robin Famiglietti, David Followill, Geoffrey Ibott, Anuja Jhingran, Peter Balter, and Laurence Court,
The University of Texas MD Anderson Cancer Center; Rachel McCarroll The University of Texas Graduate School of Biomedical
Sciences at Houston, Houston, TX; Maureen Bojador, Benavides Cancer Institute, University of Santo Tomas Hospital, Manila,
Philippines; Rex Cardan, University of Alabama Birmingham, Birmingham, AL; Bassem Youssef, American University of Beirut
Medical Center, Beirut, Lebanon; and Christoph Trauernicht, Groote Schuur Hospital, Cape Town, South Africa.

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Cervical cancer is one of the most common cancers among women worldwide, and approximately 85% of new diagnoses occur in less-developed regions of the world. Global efforts in cervical cancer to date have focused on primary and secondary prevention strategies of human papillomavirus vaccination and cervical cancer screening. Cervical cancer screening is effective to reduce the incidence of cervical cancer and can result in diagnosis at earlier stages, but it will take time to realize its full impact. With expansion of screening programs, there is now a greater imperative to increase access to treatment for women who have cervical cancer, particularly in earlier stages of disease, when it is still curable. Resources for multimodality treatment can be limited—or even absent—in many less-developed regions of the world and may be associated with geographic, social, and financial barriers for the patient. However, there is evidence that, in many cases, less-invasive and less-resource-intensive treatment options are still effective. To this end, the National Comprehensive Cancer Network and American Society of Clinical Oncology have published guideline adaptations for specific resource constraints, and research about more conservative approaches to the treatment of cervical cancer continues. This review focuses on potential barriers and challenges to provision of safe and effective treatment of early-stage cervical cancer in lower-resource settings, and it suggests future directions for expansion of access to cervical cancer treatment around the world.

INTRODUCTION

Cervical cancer is the fourth most common cause of cancer in women worldwide and the most common cancer in women in eastern and middle Africa. Approximately 85% of the 528,000 new diagnoses of cervical cancer and 87% of the 266,000 deaths occur in less-developed regions of the world.1 Because of improvements in maternal health, deaths as a result of cervical cancer now outnumber those that are results of maternal mortality in most countries in Asia and Latin America and in some countries in Africa.2 Even with increasing availability of cervical cancer screening and vaccination around the world, prevalent occurrences will continue to be identified and to warrant treatment. In screened populations, greater than half of detected cancers diagnosed can be stage I or II, when less-radical treatment strategies are still an option.3,4 To address wide variations in the availability of resource-intense and highly technical interventions, such as radical surgery, chemotherapy, and radiation therapy, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) have published resource-stratified guidelines to delineate appropriate care options for women with cervical cancer. The objective of this review is to discuss barriers and challenges to treatment alternatives for early-stage cervical cancer—stages IA1 to IIA1—in lower-resource settings. Because many lower-resource settings are in Africa, this article largely focuses on the situation there; however, many of the principles and issues we raise also are applicable to many parts of Asia and Latin America.

CERVICAL CANCER PREVENTION

Cervical cancer can be prevented with human papillomavirus (HPV) vaccination and cervical cancer screening. Primary prevention with the HPV vaccine is expected to result in a significant decrease in the incidence of cervical cancer worldwide. Epidemiologic modeling has estimated that vaccine coverage of 90% could result in a decrease of up to 83% in incident cervical cancer occurrences worldwide.5 The HPV vaccine...
became available in 2006 and is available in approximately one third of low- and middle-income countries (LMICs), but many programs in low-income countries reach less than 10% of the target population.6 Although the vaccine is promising, differences in cervical cancer incidence that result from HPV vaccination will take decades to be realized.

In the shorter term, secondary prevention with cervical cancer screening has been shown to prevent malignancy when precancer is detected and treated. Furthermore, prevalent occurrences of invasive cancer are detected at earlier stages. In India, a cluster-randomized trial of 30,577 women compared a single round of visual inspection with acetic acid (VIA)–based screening versus no screening and found that, in the screened arm, 35% of cervical cancer occurrences were stage I, and 18% were stage II, compared with 0% and 6%, respectively, in the control arm.3 Cytology is the most commonly used screening method in developed countries, but see-and-treat VIA is used frequently in lower-resource settings.7 Greater than 50 low-income countries have introduced cervical cancer screening with VIA.8

Although the availability of cervical cancer screening programs has been increasing, coverage is still low. Most screening programs in low-income countries and the WHO African region are estimated to reach less than 10% of the population.5 Therefore, as screening programs scale, they likely will continue to identify a large number of prevalent invasive cancer occurrences that require treatment.

**RESOURCE-STRATIFIED GUIDELINES FOR THE TREATMENT OF CERVICAL CANCER**

Cervical cancer is clinically, rather than surgically, staged via the International Federation of Gynecology and Obstetrics (FIGO) system9 (Table 1). Treatment of early-stage invasive cervical cancer historically has included surgery, such as cold knife conization, simple hysterectomy, or radical hysterectomy with pelvic lymph node dissection.10,11 More advanced disease generally is treated with chemoradiation.11,12 However, radical surgery, chemotherapy, and/or radiation are not available in many parts of the world. They are expensive modalities and require highly trained personnel and quality assurance, which may not be realistic or feasible in some locations. For example, surgical treatment of locally advanced disease is typically a radical hysterectomy, which, in contrast to a simple hysterectomy, involves removal of parametrial tissue and an additional vaginal margin. The surgery is technically more difficult to perform, requires more specialized training, and carries a higher risk of operative (eg, bleeding, infection, and injury) and long-term (eg, bladder dysfunction and fistula) complications. As a result, there is increasing research on more conservative approaches to the treatment of cervical cancer.13 In lower-resource settings, options such as cold-knife conization, simple hysterectomy, or neoadjuvant chemotherapy followed by simple hysterectomy may provide more realistic options for cure.

The NCCN guidelines provide multiple options to treat each cervical cancer stage (Table 2), including options for fertility-sparing treatment in early stages.11 Treatment of stage IA disease generally is less invasive and can be adapted to lower-resource settings. However, patients in lower-resource settings are more likely to present at stages for which the recommended treatment modality is not readily available.14-16 Therefore, both the NCCN (in the NCCN Framework) and ASCO created resource-stratified guidelines for women with invasive cervical cancer (Table 2).17,18 Both guidelines outline recommendations for each of four resource levels: basic, limited, enhanced, and maximal. For example, although NCCN guidelines recommend a radical hysterectomy with pelvic lymph node dissection or chemoradiation with brachytherapy for stage IB1 disease, the NCCN Framework guidelines recommend a simple hysterectomy or radical hysterectomy with pelvic lymph node dissection for basic-level settings; ASCO recommends a simple hysterectomy with or without neoadjuvant chemotherapy at that same level.

**RESOURCES CURRENTLY AVAILABLE IN LOWER-RESOURCE SETTINGS**

**Surgery**

Adequate training and access to appropriate providers have been ongoing limitations in global health. Compared with high-income countries, which have 28.7 physicians per 10,000 people, low-income countries have only 2.5 physicians per 10,000 people.19 Low-income countries have an estimated 0.7 surgical providers per 100,000 people compared with 56.9 in high-income countries.20

There are fewer statistics on capacity for gynecologic surgery. A review of the loop electrosurgical excision procedure (LEEP) in lower-resource countries found that this procedure usually is performed by physicians.21 However, it is feasible

Table 1. 2014 FIGO Staging for Cancer of the Cervix Uteri

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded).</td>
</tr>
<tr>
<td>IA</td>
<td>Invasive cancer is identified only microscopically. Invasion is limited to measured stromal invasion, with a maximum depth of 5 mm and a maximum width of 7 mm.</td>
</tr>
<tr>
<td>IA1</td>
<td>Measured invasion of stroma ≤ 3 mm in depth and ≤ 7 mm in width</td>
</tr>
<tr>
<td>IA2</td>
<td>Measured invasion of stroma &gt; 3 mm and &lt; 5 mm in depth and ≤ 7 mm in width</td>
</tr>
<tr>
<td>IB</td>
<td>Clinical lesions confined to the cervix, or preclinical lesions greater than those defined as stage IA</td>
</tr>
<tr>
<td>IB1</td>
<td>Clinical lesions no greater than 4 cm in size</td>
</tr>
<tr>
<td>IB2</td>
<td>Clinical lesions &gt; 4 cm in size</td>
</tr>
<tr>
<td>II</td>
<td>The carcinoma extends beyond the uterus, but it has not extended onto the pelvic wall or to the lower third of vagina.</td>
</tr>
<tr>
<td>II A</td>
<td>Involvement of up to the upper two thirds of the vagina; no obvious parametrial involvement</td>
</tr>
<tr>
<td>II A1</td>
<td>Clinically visible lesion ≤ 4 cm</td>
</tr>
<tr>
<td>II A2</td>
<td>Clinically visible lesion &gt; 4 cm</td>
</tr>
<tr>
<td>II B</td>
<td>Obvious parametrial involvement but not onto the pelvic sidewall</td>
</tr>
<tr>
<td>III</td>
<td>The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall. The tumor involves the lower third of the vagina.</td>
</tr>
<tr>
<td>III A</td>
<td>Involvement of the lower vagina but no extension onto pelvic sidewall</td>
</tr>
<tr>
<td>III B</td>
<td>Extension onto the pelvic sidewall, or hydronephrosis/nonfunctioning kidney</td>
</tr>
<tr>
<td>IV</td>
<td>The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.</td>
</tr>
<tr>
<td>IVA</td>
<td>Spread to adjacent pelvic organs</td>
</tr>
<tr>
<td>IVB</td>
<td>Spread to distant organs</td>
</tr>
</tbody>
</table>

NOTE. Stages are defined in the FIGO Committee on Gynecologic Oncology: FIGO staging for carcinoma of the vulva, cervix, and corpus uter.9


Many professional societies and nongovernmental organizations have initiated independent volunteer-based efforts in different countries to expand this capacity through didactics and hands-on mentorship in Africa, Central America, and Asia.25-27 Although efforts by voluntary organizations to improve training of local providers are laudable, formal teaching programs within each country must be developed and supported locally, either by providing in-country training or by sending qualified candidates abroad.

Even when surgical services exist, they often are concentrated in referral hospitals in urban areas, which may result in barriers related to cost, transport, long wait times, poor referral networks, and inability to pay. Patients also may be hesitant to undergo surgery because of fear of the procedure, fear of anesthesia, and rumors of poor outcomes.29 Even if trained surgical personnel exist, surgical services may be intermittently available because of supply and medicine stockouts, power shortages, inconsistent water supply, and poor infrastructure.30

Radiation Therapy

There are inadequate personnel and equipment to meet the demand for radiation therapy in lower-resource settings.31 The worldwide standard for the number of radiation megavoltage machines is one per 700,000 to 800,000 people or per 350 to 400 patients with cancer.32 In a recent survey of radiotherapy capacity, the average number of teletherapy machines per million people was 0.21 for low-income countries compared with 8.6 for high-income countries.33 Of the 52 African countries in this survey, only 23 offered external-beam radiotherapy, and only 20 offered brachytherapy. Combined, these countries housed 88 cobalt-60 units and 189 linear accelerators; however, 60% of these machines were concentrated in South Africa (n = 92 machines) and Egypt (n = 76 machines). Most radiotherapy centers only provided basic services, such as palliation and simple curative treatments, on the basis of two-dimensional imaging and treatment planning.34 A separate survey of 17 countries in the Asia and Pacific region reported 0.09 to 7.39 megavoltage machines per million people.34 Only four countries—Australia, Japan, New Zealand, and Singapore—exceeded two machines per million people. In this survey, many departments reported treatment of patients without simulators or treatment-planning systems. Furthermore, radiation oncologists often had additional duties, such as medical

to train nonphysicians to perform the procedure safely, and such training may represent a task-shifting opportunity. A program in Kisumu, Kenya, has successfully trained and certified clinical officers (the equivalent of a physician assistant) to perform LEEPs.22 Data about capacity to perform simple hysterectomies, radical hysterectomies, and lymph node dissections in lower-resource settings are scarce. Many providers who currently perform hysterectomies in lower-resource settings are primary care physicians who have undergone only 1 year of surgical training. Radical hysterectomy is not available in many lower-resource settings or may be available only in large central hospitals.23,24
oncology, medical physics, or diagnostic radiology duties. In Latin America, the most recent survey is from 2004 and identified 470 radiotherapy centers in the region, which had 710 machines across 19 countries. The distribution of centers ranged from none to 151 per country surveyed.

Efforts to increase radiotherapy capacity in lower-resource settings have been increasing. The International Atomic Energy Agency has been involved in projects to establish and improve radiotherapy in countries around the world. The International Education Subcommittee of the American Society of Radiation Oncology has collaborated with sister societies around the world to foster education.

Because of the complexity in the establishment of safe infrastructure and the training of specialized teams that include radiation oncologists, physicists, therapists, and nurses, radiotherapy services likely will exist only in urban areas. In addition to the difficulty of obtaining transport,
patients may face barriers related to being away from home for extended periods of time for their course of radiotherapy. Radiotherapy also is expensive—the capital costs of a linear accelerator can be greater than 1 million US dollars (USD), and those of a cobalt machine can be up to $480,000 USD. The median annual cost of quality assurance and maintenance of a linear accelerator has been estimated as $41,000 USD; that of a cobalt machine, $6,000 USD. These costs do not include power, personnel, and building costs.37

Chemotherapy
In cervical cancer, chemotherapy can be used as neoadjuvant therapy, as adjuvant therapy, or as a sensitizing agent for radiation therapy. A recent study about national essential medicine lists from LMICs found that most lists contained multiple oncology medicines.38 However, it is unclear how this has translated into availability. Access likely is limited: the African Palliative Care Association has estimated that only 5% of patients with cancer in Africa receive chemotherapy. In Southeast Asia, an estimated 15% of patients from LMICs in the region have access to essential oncology medications.40

In addition to barriers, such as patient fear of chemotherapy, distance from infusion centers, and poor referral networks, patients in LMICs likely face difficulty with schedules and payments for chemotherapy. A study in Cameroon found that 24% of patients experienced a delay in receipt of chemotherapy because of finances, and 38% were unable to schedule or keep a chemotherapy appointment in a timely manner. A total of 40% of patients spent greater than $200 USD on the most recent round of chemotherapy.41 This is a significant fraction of the gross national income per capita of $1,026 USD to $4,035 USD that defines the World Bank classification of lower and middle income.42 The Clinton Health Access Initiative and American Cancer Society recognized cost as a major obstacle to timely and high-quality cancer care worldwide and established a partnership in 2015 to improve capacity for cancer treatment. With an initial focus on breast and cervical cancer, this initiative seeks to strengthen capacity at tertiary hospitals and optimize the market for cancer drugs (eg, chemotherapy) to expand access to quality and affordable treatment.43

Pathology
Adequate pathology services are crucial to provision of oncology care, both to confirm malignancy and to determine the best treatment. In addition to human resource and training requirements for clinical pathologists and laboratory technicians, sufficient infrastructure, equipment, maintenance contracts, and reagents to properly transport, fix, and process tissue for histologic analysis are vital. In sub-Saharan Africa, there are 84,133 to 9,264,500 people per pathologist, which is a much higher ratio than the 15,000 to 20,000 people per pathologist in the United Kingdom or the United States. Of 30 sub-Saharan African countries that reported data, immunohistochemistry was available in 16 and molecular diagnostics, in two.44 The scarcity of pathology services may be due in part to the perception that pathology services are restricted to services provided by laboratory technicians rather than by medically trained clinicians.45

In 2014, the African Strategies for Advancing Pathology group was created with the goal to develop “a robust framework for efforts to increase and improve pathology services within sub-Saharan Africa.”44 Other international partners also are investing in improvements to pathology capacity in lower-resource settings.46

Research Challenges
Many less-invasive treatment options for cervical cancer, such as those recommended in the NCCN Framework and ASCO resource-stratified guidelines, are supported by small observational studies. Because of a lack of high-level evidence for treatments feasible in more resource-limited settings, many recommendations are based on expert consensus.17,18 Although most of the disease burden is in more resource-limited areas, cervical cancer research is conducted disproportionately in resource-rich settings. Therefore, a major challenge to extension of access to cervical cancer treatment—particularly alternatives suitable for resource-limited settings—is a strong evidence base. Prospective studies with adequate sample size and power to evaluate the efficacy and feasibility of proposed treatment alternatives for early-stage cervical cancer are necessary. In the interim, there is an urgency to start implementation of innovative treatment strategies, because women with potentially curable cancer continue to die without any treatment.

Logistic and Social Challenges
It may take years to develop the human resources, implement the systems of care, and procure the supplies needed to provide the current resource-intense standard of care for cervical cancer. Even in settings where resources may be available,
access continues to be a challenge, and poor access can lead to delays in care and poorer outcomes.\textsuperscript{47} For example, a study in New Delhi reported a median of 41 days from registration to radiation therapy initiation; 25% of patients did not complete therapy.\textsuperscript{48} Many African countries, including Cameroon, Rwanda, and South Africa, have reported an interval of up to 7 months between request for care as a result of symptoms and treatment of cancer.\textsuperscript{41,49,50} Although more than half of the population in less-developed countries reside in rural areas,\textsuperscript{51} oncology services tend to exist in urban areas. This means that many patients must travel long distances for treatment and face competing pressures among cost of travel and treatment, family obligations, and work responsibilities.

At the tertiary-care level, multidisciplinary management will be essential to ensure continuity of care, use of appropriate treatment protocols, and management of adverse effects and complications from treatment. When patients present for care, systems should be put in place to ensure that patients receive a timely histologic diagnosis, are not lost to follow-up because of confusion about multiple treatment modalities, receive referrals for adjuvant therapy in a timely manner, and benefit from counseling to understand the nature of the illness and the rationale for treatment.

Progress to Date

Although the literature is dominated by reports of limitations in oncology services and barriers to implementation, it is important to acknowledge the progress that has been made. In 2012, the African Organization for Research and Training in Cancer launched the African Cancer Network Project. As part of the project, a partial list of cancer treatment institutions in Africa was compiled and included 102 centers.\textsuperscript{52} Some of these centers may already be, or could become, research and training hubs to help serve their regions, such as Uganda, Bangladesh, and Rwanda.\textsuperscript{53}

At a policy level, 79% of low-income countries and 84% of LMICs have a cancer policy, strategy, or plan. Although only 45% and 58%, respectively, have an operational policy with funding, the policy efforts represent aspirations to improve oncology services.\textsuperscript{54} Civil society is taking an active role through community awareness, early detection campaigns, and advocacy. Many efforts are survivor-led and focus on breast and cervical cancer.\textsuperscript{55}

**OPTIONS TO TREAT EARLY-STAGE CERVICAL CANCER IN LOWER-RESOURCE SETTINGS**

Early-stage cervical cancer spreads by local extension to the endocervix, uterine corpus, parametrium, and vagina. It also can spread via lymphatic channels to the pelvic lymph nodes, which confers a worse prognosis.\textsuperscript{56} This risk serves as the rationale in higher-resource settings for evaluation or treatment of the parametria and pelvic lymph nodes with radical hysterectomy and pelvic lymph node dissection in stages as early as IA1 with lymphovascular space invasion (LVSI). In a classic study of patients with stage I disease treated with radical hysterectomy and pelvic lymphadenectomy, tumor size, depth of invasion, and LVSI were independent prognostic factors for survival.\textsuperscript{57} The 3-year disease-free survival (DFS) rate was 85.6% with negative nodes and was 74.4% with positive nodes. DFS in patients with positive parametria was 69.6% and was 84.9% in patients with negative parametria. DFS was 69.1% in patients with positive margins and was 84.3% in patients with negative margins.\textsuperscript{57} Ideally, the goals of surgical therapy are to excise tissue at risk for disease, achieve negative margins, and determine the need for additional therapy. In well-resourced settings, the standard of care involves removal of any at-risk areas, including the parametria and pelvic lymph nodes; yet, many patients with early-stage disease do not have involvement of parametrium or nodes and could theoretically be cured with less-radical surgery. An increasing number of studies have provided evidence for less-radical surgery in patients with stage IA2 and IB1 disease,\textsuperscript{58-60} in whom the risk of parametrial involvement is approximately 2% and 6% to 10%, respectively and the risk of pelvic lymph node metastases is less than 15% (Table 3).\textsuperscript{51-64}

**LEEP**

In the absence of other services, a LEEP procedure could be used in stages IA1, IA2, and IB1 disease smaller than 2 centimeters. Studies of conservative treatment of stages IA1 to IB1 disease ranged in eligibility criteria and use of adjuvant treatment and may have included imaging modalities (eg, magnetic resonance imaging) that are not readily available in lower-resource settings. However, outcomes from these studies suggest their feasibility. An analysis of 1,409 patients with stage IA1 cervical cancer reported a 5-year survival of 98% versus 99% (hazard ratio, 0.65; 95% CI, 0.23 to 1.47) in women who underwent a cold knife conization versus those who underwent a hysterectomy.\textsuperscript{72} In IA2 disease, one study reported a 98% survival rate in 66 women who underwent a cold knife conization after a median follow-up time of 19 years. Twenty-eight of these patients underwent lymphadenectomy, and no positive lymph
nodes were identified.73 Maneo et al74 used cold knife conization and pelvic lymph node dissection to treat a selected group of patients with stage IB1 tumors smaller than 2 centimeters without evidence of enlarged lymph nodes or uterine involvement. After a median of 66 months, one recurrence was noted 34 months after initial treatment. No positive lymph nodes were found.74 Per the NCCN guidelines, a LEEP rather than a cold knife conization is acceptable if specimen integrity with adequate margins can be obtained. The procedure is relatively simple, can be done in the clinic, does not require a physician, and has established feasibility and safety in LMICs.22,75,76 To study this question more, two prospective studies through MD Anderson Cancer Center and the Gynecologic Oncology Group are underway to evaluate simple hysterectomy or cone biopsy with pelvic lymphadenectomy in early-stage cervical cancer.60,77

Neoadjuvant Chemotherapy

In larger tumors for which surgery may not be sufficient or worthwhile without other treatment modalities, neoadjuvant chemotherapy to reduce the tumor burden to enable surgical excision can be considered. This approach is recommended throughout the ASCO resource-stratified guidelines.

One application for this approach could be neoadjuvant chemotherapy followed by a cold knife conization, although the evidence is limited to small studies of highly selected women, some of whom ultimately underwent more radical surgery.78,79 Another application of neoadjuvant chemotherapy could be to downstage the tumor in more advanced disease before a less radical surgery, such as a simple hysterectomy. Few studies validate this approach, and they typically are limited to the fertility-sparing setting—for example, neoadjuvant chemotherapy followed by laparoscopic lymphadenectomy and vaginal simple trachelectomy.80 It is important to emphasize that neoadjuvant chemotherapy currently is not standard treatment and that the workup involved in determination of eligibility, in itself, can involve resources that are difficult to access in lower-resource settings. However, if resource-appropriate selection criteria can be established, the number of patients who may be able to obtain treatment would increase, particularly if more aggressive treatments are not easily accessible. Ultimately, the choice of surgical procedure should be tailored to the setting of each patient and should be predicated on what surgical care is safely available for the cancer stage of the patient and whether appropriate supplies, support systems, and facilities are available.

FUTURE DIRECTIONS

The current global effort to prevent and detect cervical cancer continues to scale. Screening programs ultimately will decrease cervical cancer

Table 3. Risk of Parametrial and Lymph Node Metastases by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Parametrial Involvement (%)</th>
<th>Pelvic Lymph Node Metastases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>IA2</td>
<td>2</td>
<td>0-13</td>
</tr>
<tr>
<td>IB</td>
<td>15-20</td>
<td>9-20</td>
</tr>
<tr>
<td>IB1</td>
<td>6-10</td>
<td>Approximately 15</td>
</tr>
<tr>
<td>IIA</td>
<td>11-17</td>
<td>29-33</td>
</tr>
</tbody>
</table>

NOTE. Risks collated from published data.56,61-71

Fig 1. Future directions to increase access to cervical cancer treatment in lower-resource settings include attention to clinical care, clinical training, quality management, and research.

| Clinical care | \- Develop local clinical protocols for care by using existing literature and international guidelines  
\- Define safe and simple procedures to track patient safety during and after treatment  
\- Establish minimal level of resources and supplies necessary to provide each treatment option (ie, pathology services, operating room backup, surgical/anesthesia backup)  
\- Designate local and/or regional high-volume centers of excellence, where trained providers can provide high-volume high-quality care |
| Clinical training | \- Develop training program on staging, tumor burden assessment, indications for available treatment options  
\- Continually evaluate time and resources necessary to acquire skills for management of early-stage cervical cancer  
\- Establish credentialing/certification metrics for providers who treat patients with cervical cancer  
\- Integrate basic competencies for identifying cervical cancer into medical school training  
\- Embed training programs, including for procedures, in centers of excellence |
| Quality management | \- Compile quality assurance measures for pathology and gynecology to be overseen by local regulatory experts (ie, supply requirements, clinical volume for competency, outcomes assessment)  
\- Strengthen tumor registries and patient-tracking systems to allow ongoing surveillance of patient outcomes |
| Research | \- Provide ongoing training opportunities for aspiring investigators  
\- Plan prospective studies to identify and evaluate treatment options appropriate for lower-resource settings |
incidence after the initiation of screening and also will downshift the stage distribution of occurrences if treatment becomes more widely available.\(^3\) As awareness and advocacy about cervical cancer increase, so does the imperative to provide access to treatment. In many situations, the default often is to do nothing, which means certain death. Some resources are available, but they are not yet available to the same degree as in high-income economies. Doing nothing should not be an option; therefore, researchers and policy makers should focus their activities on how best to balance the use of existing resources with the expected impact on quantity and quality of life (Fig 1). Clinicians should use existing international guidelines, such as the NCCN Framework and ASCO resource-stratified guidelines, to provide the maximally feasible treatment option. The medical and policy communities should measure outcomes to ensure that good care is being provided, identify areas for improvement, and prioritize research activities. Future research priorities in LMICs can focus on identification of more resource-appropriate alternatives to the current treatment paradigms and on strategies to better operationalize access to prevention and treatment.

In conclusion, although cervical cancer screening and prevention programs have been growing, cervical cancer still is prevalent, and treatment has not become widespread. Rather, women often are referred to palliative care and are condemned to death. Although the traditional standard of care for early-stage cervical cancer has been radical surgery or chemoradiation, there are data to suggest less-invasive, and therefore potentially more accessible, treatments. The NCCN Framework and ASCO have published resource-stratified guidelines with alternative treatment recommendations that can guide countries in applications of their available resources to cervical cancer treatment. For each patient, these guidelines should be tailored to the extent of the disease, the surgical procedures that can be safely performed, and other available treatment modalities. Although many gaps in oncology resources and barriers to treatment exist, there is increased political will and international attention to improving access to safe and effective treatment of cervical cancer.

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Emily S. Wu
No relationship to disclose
Jose Jeronimo
No relationship to disclose
Sarah Feldman
No relationship to disclose

Affiliations
Emily S. Wu, University of Washington; Jose Jeronimo, PATH, Seattle, WA; and Sarah Feldman, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

REFERENCES
Managing Pain in Patients With Cancer: The Chinese Good Pain Management Experience

**Purpose** The number of cancer cases in China has increased rapidly from 2.1 million in 2000 to 4.3 million in 2015. As a consequence, pain management as an integral part of cancer treatment has become an important health care issue. In March 2011, the Good Pain Management (GPM) program was launched to standardize the treatment of cancer pain and improve the quality of life for patients with cancer. With this work, we will describe the GPM program, its implementation experience, and highlight key lessons that can improve pain management for patients with cancer.

**Methods** We describe procedures for the selection, implementation, and assessment procedures for model cancer wards. We analyzed published results in areas of staff training and patient education, pain management in practice, analgesic drugs administration, and patient follow-up and satisfaction.

**Results** Pain management training enabled medical staff to accurately assess the level of pain and to provide effective pain relief through timely dispensation of medication. Patients with good knowledge of treatment of pain were able to overcome their aversion to opioid drugs and cooperate with nursing staff on pain assessment to achieve effective drug dose titration. Consumption of strong opioid drugs increased significantly; however, there was no change for weaker opioids. Higher pain remission rates were achieved for patients with moderate-to-severe pain levels. Proper patient follow-up after discharge enabled improved outcomes to be maintained.

**Conclusion** The GPM program has instituted a consistent and high standard of care for pain management at cancer wards and improved the quality of life for patients with cancer.
In 1986, the WHO published the Cancer Pain Relief guidelines \(^\text{11}\) for the management of cancer-related pain. These guidelines recommended the careful assessment of the patient’s complaint of pain, together with his psychologic state, and use of alternative methods of pain control and a three-step analgesic-ladder approach for the prescription of pain relief drugs, starting from nonopioids (step 1), to weak opioids (step 2), and, finally, to strong opioids (step 3). The analgesic effect of nonopioids, such as nonsteroidal anti-inflammatory drugs, are dose dependent, that is, their effectiveness increases with increasing dosage; however, incidence of their adverse effects also increases at the same time. \(^\text{12}\) Opioids are also effective pain relievers and are indispensable for the treatment of moderate-to-severe cancer pain. Weak opioids, such as codeine and tramadol, are prescribed for patients with mild-to-moderate pain when nonopioid analgesics no longer provide adequate relief. Strong and high-potency opioids, such as morphine, oxycodone, hydromorphone, methadone, fentanyl, and buprenorphine, are used as a last resort for severe pain of which adequate relief with weak opioids is not achieved. \(^\text{13}\) However, physicians are often reluctant to use strong opioids for fear of their adverse effects, in particular, addiction. \(^\text{14}\) When used appropriately, consumption of opioids in a country can be a good proxy for determining the quality of palliative cancer care. Morphine-equivalence (ME) consumption and PMI, which are derived from WHO guidelines, \(^\text{11}\) are used to assess the efficacy of the treatment of cancer pain. \(^\text{15}\) In 1983, the per-capita consumption of strong opioids, excluding methadone, in China was low compared with the global average (0.33 ME \(\times 2.22\) ME). Although consumption increased to 0.75 ME in 2001, it remained low compared with the global rate (14.95 ME). However, the situation is improving: per-capita consumption in China rose to 2.95 ME in 2013, or a nine-fold increase over 30 years. \(^\text{16}\)

The 2001 survey \(^\text{9}\) on cancer pain in China cited inadequate pain assessment, excessive state regulation on the prescription of opioids, inadequate staff knowledge of pain management, and lack of access to powerful analgesics as the main barriers to optimal management of cancer pain. In March 2011, the Ministry of Health of the People’s Republic of China launched the Good Pain Management (GPM) program to standardize the treatment of cancer pain, improve the quality of life for patients with cancer, and safeguard the quality and safety of health care services. \(^\text{17}\) The GPM program was initially targeted at oncology and terminal cancer treatment departments, pain specialist divisions, and palliative care wards at secondary and tertiary levels of general and cancer specialist hospitals. The program called for the creation of 150 such GPM model wards within a 3-year period as well as for playing a leading and exemplary role in improving and standardizing the quality of pain management. \(^\text{8,17}\) At the same time, standards for the selection and operation of the model wards, and importantly, the clinical management of pain were established to ensure treatment consistency and to raise the quality of pain management. \(^\text{18,19}\)

This work describes the implementation of the GPM program, specifically its assessment and compliance processes at the model wards. We discuss some of the initial outcomes of the GPM program and highlight key lessons from its implementation, which we would like to share among physicians with a view toward improving pain management for patients with cancer in China and elsewhere.

**METHODS**

Under the GPM program, the Ministry of Health Expert Group on the standardized treatment of cancer pain was formally established in March 2011 and was tasked with providing technical support and guidance for the creation of GPM wards and their related activities. Specific tasks included the development of cancer pain diagnosis and treatment guidelines; creation of standardized GPM demonstration wards; formulation of appraisal and auditing standards for GPM wards; preparation of training materials and organization of GPM-related training; provision of technical assistance to support the implementation of GPM wards; and, finally, analysis of outcomes and review of the GPM program.

The 41 members of the expert group comprised representatives from various disciplines involved in the management of cancer pain, including oncology, pain management, clinical pharmacy, nursing, hospice care, and opioids administration, and came from health care institutions at different geographical regions across the country. There were 26 oncologists, nine pain management specialists, three clinical pharmacists, and one specialist each from nursing, hospice care, and opioids administration. These members came from 19 cities and represented 33 hospitals and medical institutions across China.

**Selection of GPM Wards**

We developed a standard GPM assessment checklist in accordance with GPM guidelines \(^\text{20}\) to assist health administrators in evaluating and
nominating suitable cancer treatment wards for
the GPM program; to guide these selected model
wards in the implementation of GPM; and to audit
the model ward implementation for compliance
with GPM guidelines.17 Figure 1 describes the
structure of this GPM assessment checklist. Model
wards for the GPM program were selected from
oncology wards at cancer specialist hospitals and
pain specialist departments at the secondary and
tertiary levels of the health care system. Inclusion
criteria were based on the duration of clinical
practice, number of beds and admissions, annual
number of cases, and staff training. Oncology
wards were additionally assessed on their tech-
nical competence and ability to setup an indepen-
dent outpatient pain management service for their
patients (Table 1).19
At each nominated GPM hospital, a model ward
project panel was established to plan, oversee,
and coordinate its implementation among the
affected departments, namely, the oncology ward
(the model ward), the pharmacy, and anesthesi-
ology, as well as to ensure compliance through
regular audits. A project team then developed the
required protocols and carried out the imple-
mentation of the GPM program at these departments.
A medical affairs department was also created
within the hospital and was responsible for the
review of pain education activities for health care
professionals and patients and their families to
identify areas of concern for rectification. These
reviews also focused on the effectiveness of pain
treatment, quality of medical record-keeping,
analyses of cause of death, and patient quality
of life and post-treatment follow-up.
External audit teams at provincial and national
levels conducted audits for the certification of
model wards. Each audit team was composed of
an oncologist, a pain management specialist, a
nurse, a pharmacist, and an audit coordinator
who were selected from certified GPM wards. The
team performed an independent audit of the imple-
mentation for compliance by using the GPM
assessment checklist. This on-site audit, which
covered the model ward, outpatient pain clinic,
pharmacy, and hospital administration depart-
ment, was conducted through interviews of patients
and staff and inspection of medical documentation.
The audit team highlighted the shortfalls in imple-
mentation and recommended remedial courses of
action. Further audits were conducted annually at
the provincial level to ensure that certified wards
maintained their GPM standards.

**GPM Assessment Checklist**

The GPM assessment checklist used a point sys-
tem to guide the systematic implementation of the
program, with more points awarded to areas of
greater emphasis. A maximum of 100 points—10
points at the hospital level and 90 points at the

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Fig 1. Structure of the Good Pain Management (GPM) program assessment checklist.
department level—were awarded, with an additional 20 bonus points given for additional capabilities, such as pain management expertise, staff training, and medical research (Fig 1). In the assessment of model ward performance, which carried the highest number of points (73 points), emphasis was placed on pain assessment (16 points) and the standardized treatment of pain (43 points). Staff participation, including training and patient education, was also emphasized at hospital and departmental levels.

### Pain Assessment

The practice of cancer pain management, that is, pain diagnosis, treatment processes, and use of analgesic drugs, was standardized under the Standardized Diagnosis and Treatment Protocol for Cancer Pain (2011 Edition) document to ensure consistency in the classification of pain and assessment and treatment methodologies for patients with cancer. This document recommends that an overall patient pain assessment be completed within 8 hours upon admission and that regular pain assessments using the brief pain inventory be included as part of the nursing routine and carried out at regular intervals during patient stays. This pain assessment used a dynamic evaluation mechanism that measured the pain level, changes in the nature of pain, acute pain episodes, determinants of pain relief, and aggravation and adverse reactions to medication.

Quantitative pain assessment was performed by using the numerical rating scale. The numerical rating scale has a 0- to 10-point scale, where 0 equals no pain and 10 equals maximum pain. The verbal rating scale (VRS), simple pain assessment scale, or the visual analog scale was used for patients who had difficulty communicating their pain level, such as children, the elderly, or patients with communication difficulties, such as language or cultural differences. The VRS has a 4-point Likert-like scale: no pain, mild pain, moderate pain, and severe pain. These numerical and verbal scales were often used interchangeably, and the following equivalence was applied: 0 = no pain, 1 to 3 = mild pain, 4 to 6 = moderate pain, and 7 to 10 = severe pain. Improvement in pain relief was described by using a 5-point scale—no relief, mild relief, moderate relief, apparent relief, and complete relief.

### Table 1. Inclusion Criteria for the Good Pain Management Model Ward

<table>
<thead>
<tr>
<th>Criteria for Oncology Wards</th>
<th>Cancer Specialist Hospital</th>
<th>Pain Specialist Department</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of clinical practice</td>
<td>Tertiary</td>
<td>Secondary</td>
</tr>
<tr>
<td>No. of beds/admissions</td>
<td>Practiced clinical oncology for &gt; 5 years</td>
<td>Practiced clinical oncology for &gt; 5 years</td>
</tr>
<tr>
<td>Admits &gt; 50 patients</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Annual No. of cases</td>
<td>Treats &gt; 800 patient cases of advanced cancer</td>
<td>Treats &gt; 400 patient cases of advanced cancer</td>
</tr>
<tr>
<td>Outpatient oncology service</td>
<td>Set up an independent oncology outpatient service and performs pain diagnosis and treatment of &gt; 240 patient cases or 1,500 episodes annually</td>
<td>Set up an independent oncology outpatient service and performs pain diagnosis and treatment of &gt; 150 patient cases or 900 episodes annually</td>
</tr>
<tr>
<td>Technical competence</td>
<td>Achieves a technical competence on par with that of specialist departments of tertiary hospitals and is a leader among the tertiary hospitals of its province (region, municipality)</td>
<td>Technical competence is greater than that of other hospitals of the same level</td>
</tr>
<tr>
<td>Staff training</td>
<td>Capable of training more than five physicians who have the ability to diagnose and treat cancer pain, and more than six nurses skilled in cancer pain care each year</td>
<td>Equipped with the experience and ability to train medical personnel from medical institutions of the same level</td>
</tr>
</tbody>
</table>
Standardized Treatment of Pain

A system of patient informed consent was established, and patients and their families were informed of the purpose of pain management and its attendant risks, precautions, and possible adverse reactions before treatment of cancer pain. The prescription of analgesic therapy was based on the WHO three-step analgesic ladder\(^ {11} \) and was administered at regular intervals rather than on demand, with oral administration preferred over the transdermal route. Treatment was adjusted according to the patient’s changing pain condition. This personalized, case-by-case treatment plan for which treatment is based on patient condition and physical health—and was developed collectively by oncology, pain management, and pharmacy departments—was targeted to achieve a treatment efficiency of \( \geq 75\% \).\(^ {19} \)

Consumption of opioids (steps 2 and 3) drugs at hospitals was measured by the daily defined dose\(^ {21} \) or by their unit of prescription, for example, tablet, injection, or suppository. The combined use of opioids with nonsteroidal anti-inflammatory drugs was encouraged to enhance the analgesic effects and reduce opioid consumption. A patient who used opioids for the first time was given short-acting agents, for example, immediate-release morphine tablets. When long-acting opioids, such as sustained-release morphine or oxycodone tablets, were used, short-acting opioid analgesics were prepared as a rescue medication. Whereas adverse reactions to opioid drugs were mostly temporary or tolerable, the prevention and treatment of such reactions formed an important part of the pain treatment plan, and patients who experienced adverse effects were monitored for reduced renal function, hypercalciemia, metabolic abnormalities, and combination use of psychotropic drugs. Rescue medication for opioid-associated adverse events was also made available. In the event of excessive sedation or mental health disorders, the dosage of analgesic drugs was reduced.

Training and Education

The GPM program called for the establishment of a medical training system that would ensure that all cancer-related health care professionals received training in pain management at least once a year. Effectiveness of the training was assessed by testing their knowledge of pain assessment and management. Patients and their families were also provided information on cancer pain management through publicity and education seminars that were conducted on a regular basis as well as through education billboards. Patient knowledge of pain management was assessed through surveys.

Patient Follow-Up After Discharge

A follow-up system for discharged patients was established, with a targeted follow-up rate of \( \geq 70\% \).\(^ {19} \) Follow-up by telephone was performed within 1 week of discharge. Regular visits after discharge to conduct pain assessment were carried out to ensure that patients received sustained and effective treatment.

We hand-curated publicly available reports on the GPM program in medical journals and evaluated its implementation outcomes in the following areas: training and education of medical staff and patients; good pain management in daily practice; analgesic drug administration; and patient follow-up after discharge and evaluation.\(^ {25} \) Where the data were available, the significance of these outcomes was evaluated at the \( P = .05 \) level.

RESULTS

Of 150 GPM model wards to be established within 3 years of program inception, 100 were to be located at tertiary hospitals and 50 at secondary hospitals. At the end of 2012, 66 such wards successfully completed a series of assessments and were certified as GPM model wards.\(^ {8} \)

Training and Education of Medical Staff and Patients

Table 2 shows the observed outcomes of GPM training programs at four hospitals, measured through assessment of medical staff and patients on their knowledge of good pain management. Test scores for physicians and nursing staff on pain management and assessment knowledge were found to be significantly higher after the staff had completed their training \( (P < .05) \). In addition, nursing staff at the Shenzhen Nanshan People’s Hospital also reported a greater sense of professional accomplishment after their training\(^ {23} \).

Henan Cancer Hospital instituted a health education program for all admitted patients that covered knowledge of pain and its treatment, treatment and care routines for pain, and nonpharmacologic methods of pain relief and guidance on self-care postdischarge.\(^ {25} \) Nursing staff evaluated two groups of patients, GPM and control, on their knowledge of pain management at three levels: mastery, basic, or unsatisfactory. The difference in mastery levels between GPM and control groups was significant \( (P < .05) \).
Table 3 shows the impact of the GPM program on pain management before and after its implementation at four hospitals. VRS was the most commonly used method of pain assessment. After 2 weeks of treatment, remission rates for patients with moderate and severe pain at Tongji Hospital Cancer Centre were 24.3% (143 of 189) and 38.3% (29 of 47), respectively. These rates improved after a further 2 weeks to 72.0% (53 of 189) and 95.7% (2 of 47), respectively. At Sun Yat-sen University Cancer Centre, patients were divided into control and GPM groups. Complete (no pain) remission rate for the GPM group was significantly higher than that for the control group (54.5% [79 of 145] vs 33.7% [31 of 92]; P < .05). Similarly, for patients with moderate or severe pain, the remission rate was significantly higher for the GPM group (decreased to mild or none; 82.6% [81 of 98] vs 62.3% [48 of 77]; P < .05). The 1st Affiliated Hospital of Dalian Medical University used brief pain inventory scores to record the pre- and post-GPM at the most severe, least severe, average, and current pain levels in the previous 24 hours. Patients reported significant improvements in pain relief at all pain levels after GPM was adopted (P < .05). The Beijing Chest Hospital, which established a GPM pain clinic for outpatients in April 2012, assessed that 73.1% of its outpatients during the next 2 months (April to June 2012) had moderate-to-severe pain before treatment on a daily basis. After GPM treatment, this percentage dropped to 5.8% and approximately 65.2% of patients reported no pain.

Analgesic Drug Administration

Table 4 shows the consumption of strong (step 3) and weak (step 2) opioids before and after implementation of GPM at three hospitals. Morphine and oxycodone were the two most commonly prescribed strong opioids. Morphine sulfate (sustained-release tablets) was the most-used opioid at the Ganzhou and Hubei Cancer Hospitals.
and the second most-used opioid at the 2nd Affiliated Hospital of Zhejiang University. In addition, there was an increase in the postimplementation use of morphine sulfate, which ranged from 23.8% to 51.1%. Oxycodone (sustained-release tablets) was most consumed at the Zhejiang University Hospital and saw a three-fold (287.8%) increase in use post-GPM implementation. Consumption of weak opioids at the Ganzhou and Hubei Cancer Hospitals mostly decreased or was little changed after GPM implementation.

Patient Follow-Up After Discharge and Evaluation Ninghe County Hospital and the 1st People’s Hospital of Jingzhou in Hubei applied guideline-based pain treatment in at least eight in 10 patients after GPM implementation (Table 5).

Table 3. Good Pain Management in Daily Practice

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Period</th>
<th>No. of Patients; Sex; Age</th>
<th>Measurement Method (before/after)</th>
<th>Pain Score</th>
<th>Before GPM, No. (%)</th>
<th>After GPM, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tongji Hospital Cancer Centre, Wuhan, Hubei</td>
<td>April 2011</td>
<td>236; M/F, 142/94; 18-72 y</td>
<td>SPAS*/SPAS</td>
<td>Moderate pain</td>
<td>189 (80.1)</td>
<td>After 2 wks: 143 (60.6) After 1 mo: 53 (22.5)</td>
</tr>
<tr>
<td>Sun Yat-sen University Cancer Centre, Guangzhou, Guangdong</td>
<td>October 2008-April 2009</td>
<td>Control: 244; M/F, 144/100; median, 51 y; GPM: 231; M/F, 130/101; median, 52 y</td>
<td>VRS*/NRS†</td>
<td>No pain</td>
<td>152 (62.3)</td>
<td>183 (75.0)</td>
</tr>
<tr>
<td>1st Affiliated Hospital of Dalian Medical University, Liaoning</td>
<td>April 2012-March 2013</td>
<td>100; M/F, 56/44; 31-75 y</td>
<td>Pain level in last 24 h (BPI)</td>
<td>Most severe pain</td>
<td>9.34 ± 0.130</td>
<td>5.40 ± 0.278</td>
</tr>
<tr>
<td>Beijing Chest Hospital, Capital Medical University, Beijing</td>
<td>April-June 2012</td>
<td>138; M/F, 69/69; 40-81 y</td>
<td>VRS*/frequency‡</td>
<td>No pain/0</td>
<td>11 (8.0)</td>
<td>90 (65.2)</td>
</tr>
</tbody>
</table>

Abbreviations: BPI, brief pain inventory; GPM, Good Pain Management program; NRS, numerical rating scale; SPAS, simple pain assessment scale; VRS, verbal rating scale.

*VRS or SPAS: Standardized Diagnosis and Treatment Protocol for Cancer Pain (2011 Edition) guidelines, Ministry of Health, China. Compared with the BPI scale, no pain, 0; mild pain, 1 to 3; moderate pain, 4 to 6; and severe pain, 7 to 10.
†NRS or BPI: Scale 0 to 10 to indicate the degree of pain, with 0 being no pain and 10 maximum pain.
‡Frequency of pain was measured as the number of times per day pain was experienced.
Table 4. Analgesic Drugs (WHO Steps 2 and 3) Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Before GPM (DDD*)</th>
<th>After GPM (DDD*)</th>
<th>% Increase (decrease)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong opioids (step 3)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganzhou Cancer Hospital, Jiangxi, year<strong>29</strong>†</td>
<td>2012</td>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>Morphine sulfate sustained-release (tab)</td>
<td>4,610.0</td>
<td>6,968.0</td>
<td>51.1</td>
</tr>
<tr>
<td>Oxycodone sustained-release (tab)</td>
<td>4,674.0</td>
<td>4,192.5</td>
<td>(10.3)</td>
</tr>
<tr>
<td>Morphine hydrochloride (tab)</td>
<td>248.0</td>
<td>1,152.0</td>
<td>364.5</td>
</tr>
<tr>
<td>Fentanyl transdermal patches</td>
<td>864.3</td>
<td>900.0</td>
<td>4.1</td>
</tr>
<tr>
<td>Morphine hydrochloride injection</td>
<td>188.0</td>
<td>232.0</td>
<td>23.4</td>
</tr>
<tr>
<td>Hubei Cancer Hospital, Hubei, year<strong>30</strong>‡</td>
<td>2011</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>Morphine sulfate sustained-release (tab)</td>
<td>9,420.0</td>
<td>11,661.0</td>
<td>23.8</td>
</tr>
<tr>
<td>Morphine sulfate suppository</td>
<td>853.3</td>
<td>6,723.3</td>
<td>687.9</td>
</tr>
<tr>
<td>Oxycodone sustained-release (tab)</td>
<td>3,338.7</td>
<td>5,325.3</td>
<td>59.5</td>
</tr>
<tr>
<td>Fentanyl transdermal patches</td>
<td>5,583.3</td>
<td>4,666.7</td>
<td>83.6</td>
</tr>
<tr>
<td>Morphine hydrochloride (tab)</td>
<td>742.0</td>
<td>1,416.0</td>
<td>90.8</td>
</tr>
<tr>
<td>Morphine hydrochloride injection</td>
<td>520.0</td>
<td>773.3</td>
<td>48.6</td>
</tr>
<tr>
<td>Pethidine hydrochloride injection</td>
<td>179.8</td>
<td>78.8</td>
<td>(56.2)</td>
</tr>
<tr>
<td>2nd Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang year<strong>31</strong></td>
<td>Q2 2011 (tab)</td>
<td>Q2 2012 (tab)</td>
<td></td>
</tr>
<tr>
<td>Oxycodone sustained-release (10 mg tab)</td>
<td>1,422</td>
<td>5,515</td>
<td>287.8</td>
</tr>
<tr>
<td>Morphine hydrochloride sustained-release (10 mg tab)</td>
<td>231</td>
<td>322</td>
<td>39.4</td>
</tr>
<tr>
<td>Morphine hydrochloride sustained-release (30 mg tab)</td>
<td>162</td>
<td>255</td>
<td>57.4</td>
</tr>
<tr>
<td>Oxycodone sustained-release (40 mg tab)§</td>
<td>—</td>
<td>382</td>
<td>—</td>
</tr>
<tr>
<td>Morphine hydrochloride (10 mg tab)§</td>
<td>—</td>
<td>214</td>
<td>—</td>
</tr>
<tr>
<td><strong>Weak opioids (step 2)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganzhou Cancer Hospital, Jiangxi, year<strong>29</strong>†</td>
<td>2012</td>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>Bucinnazine hydrochloride (tab)</td>
<td>2,016.0</td>
<td>1,856.0</td>
<td>(0.08)</td>
</tr>
<tr>
<td>Bucinnazine hydrochloride injection</td>
<td>1,536.0</td>
<td>1,224.0</td>
<td>(20.3)</td>
</tr>
<tr>
<td>Tramadol hydrochloride sustained-release (tab)</td>
<td>786.0</td>
<td>594.0</td>
<td>(24.4)</td>
</tr>
<tr>
<td>Codeine phosphate (tab)</td>
<td>152.0</td>
<td>132.0</td>
<td>(13.1)</td>
</tr>
<tr>
<td>Tramadol hydrochloride injection</td>
<td>48.0</td>
<td>18.0</td>
<td>(62.5)</td>
</tr>
<tr>
<td>Butorphanol tartrate injection</td>
<td>33.0</td>
<td>38.0</td>
<td>15.2</td>
</tr>
<tr>
<td>Hubei Cancer Hospital, Hubei, year<strong>30</strong>‡</td>
<td>2011</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>Codeine phosphate (tab)</td>
<td>3,432.0</td>
<td>3,514.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Tramadol hydrochloride sustained-release (tab)</td>
<td>2,816.7</td>
<td>2,876.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Tramadol acetaminophen (tab)</td>
<td>1,296.7</td>
<td>966.7</td>
<td>(25.4)</td>
</tr>
<tr>
<td>Bucinnazine hydrochloride injection</td>
<td>753.8</td>
<td>656.8</td>
<td>(12.7)</td>
</tr>
</tbody>
</table>

Abbreviations: DDD, daily defined dose; GPM, Good Pain Management program; Q2, second quarter; tab, tablet.

*DDD in milligrams.

†GPM ward was established in December 2012; 100 narcotic prescriptions were randomly selected each month from 2011 to 2013 from the GPM ward, that is, a total of 3,600 prescriptions.

‡GPM ward was established in 2012; 100 prescriptions per month were randomly selected from the GPM ward.

§Oxycodone sustained-release 40 mg and morphine hydrochloride 10 mg tablets were not available before implementation of GPM.
that only 42 of patients (57%) had received guideline-based pain treatment before GPM implementation. Of the noncompliant cases, 16 involved irregularities in treatment process that were avoidable and three had errors in pain assessment. Remedial efforts included training seminars for medical staff on pain management guidelines and management of narcotic drug and adverse drug reaction. Pain assessment procedures were standardized by using the visual analog scale, and physician and nursing staff were required to conduct the assessment together. This resulted in an improved GPM-compliant treatment rate of 84% at 6 months after implementation.

Surveys of the patient satisfaction with nursing care outcome at model wards in the Jingzhou, Shenzhen, and Henan hospitals showed that more than nine in 10 patients were satisfied with the treatment they received (Table 5). At the Henan Cancer Hospital, there was a difference between the satisfaction rates of control and GPM groups after the GPM program was implemented ($P < .05$).

The 2nd Affiliated Hospital of Xi’an observed discharged patients at discharge and 1 month after discharge. Although pain profiles of control and GPM groups were similar at discharge, there was a difference in the pain profile of the GPM group at 1 month after discharge compared with control group ($P < .05$): the GPM group had achieved noticeably better pain management outcomes.

## DISCUSSION

Our study of the published results of GPM implementation covered approximately 19.7% (13 hospitals) of the 66 certified model wards under the first phase of the GPM program. We are aware that these results are limited and may not be fully representative of the current state of the program. However, the outcomes and patient experiences at these model wards, which are located in nine

### Table 5. Patient Satisfaction With Treatment and Postdischarge Follow-Up

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Period</th>
<th>Participants</th>
<th>Outcome Measure</th>
<th>Score</th>
<th>Before GPM, %</th>
<th>After GPM, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ninghe County Hospital, Tianjin&lt;sup&gt;32&lt;/sup&gt;</td>
<td>January-December 2011</td>
<td>74 patients</td>
<td>Patients administered guideline-based pain treatment</td>
<td>57</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>1st People’s Hospital of Jingzhou, Hubei&lt;sup&gt;33&lt;/sup&gt;</td>
<td>March-December 2013</td>
<td>113 patients</td>
<td>Patients administered guideline-based pain treatment</td>
<td>—</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Shenzhen Nanshan People’s Hospital, Guangdong&lt;sup&gt;23&lt;/sup&gt;</td>
<td>June 2012-May 2013</td>
<td>50 patients</td>
<td>Satisfaction with nursing care</td>
<td>78</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Henan Cancer Hospital, Henan&lt;sup&gt;25&lt;/sup&gt;</td>
<td>January-October 2012</td>
<td>Control, 51; GPM, 51</td>
<td>Satisfaction with nursing care after GPM</td>
<td>Very satisfied</td>
<td>29 (56.7)</td>
<td>47 (92.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fairly satisfied</td>
<td></td>
<td></td>
<td>12 (23.5)</td>
<td>3 (5.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not satisfied</td>
<td></td>
<td></td>
<td>10 (19.6)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>2nd Affiliated Hospital of Xi’an Jiaotong University, Xi’an&lt;sup&gt;34&lt;/sup&gt;</td>
<td>October 2012-June 2013</td>
<td>Control, 48; GPM, 48</td>
<td>At discharge*</td>
<td>Mild pain</td>
<td>22 (45.8)</td>
<td>23 (47.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate pain</td>
<td></td>
<td></td>
<td>19 (39.6)</td>
<td>17 (35.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe pain</td>
<td></td>
<td></td>
<td>7 (14.6)</td>
<td>8 (16.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 1 mo*</td>
<td>Mild pain</td>
<td></td>
<td>20 (41.7)</td>
<td>33 (68.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate pain</td>
<td></td>
<td></td>
<td>19 (39.6)</td>
<td>12 (25.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe pain</td>
<td></td>
<td></td>
<td>9 (18.7)</td>
<td>3 (6.2)</td>
</tr>
</tbody>
</table>

Abbreviation: GPM, Good Pain Management program.

*Measured by using the verbal rating scale and numerical rating scale using the brief pain inventory scale (of 0 to 10 to indicate the degree of pain, with 0 being no pain and 10 maximum pain as in the Standardized Diagnosis and Treatment Protocol for Cancer Pain (2011 Edition) guidelines issued by the Ministry of Health) and adjusted as follows: no pain, 0; mild pain, 1 to 3; moderate pain, 4 to 6; and severe pain, 7 to 10.
(26.5%) of the 34 provinces and municipalities in China, can provide an overview of the implementation of the GPM program across the country and provide useful learning points for pain practitioners who want to improve the level of care given to patients with cancer.

According to a face-to-face survey of 500 Chinese physicians who treated patients with cancer at 11 general hospitals in Sichuan, China, between December 2011 and December 2013, the main barriers to better pain management were reported as inadequate medical knowledge, pain assessment and its management, and patient reluctance to use opioids for fear of addiction, drug tolerance, and adverse effects. Compared with the earlier 2001 survey, excessive state regulation on the prescription of opioids and lack of access to powerful analgesics were no longer reported as barriers; however, inadequate pain assessment and staff knowledge of pain management remained as barriers to pain management. Our analysis of the available data on GPM model wards showed that, when given appropriate training in pain management standards and procedures, medical staff were able to accurately assess the level of pain of patients and to provide effective pain relief through correct and timely dispensation of pain medication. Appropriate training also gave nursing staff a greater sense of professional accomplishment, raised their awareness, and increased their learning motivation toward good pain management. The GPM program also saw an increased use of strong opioids, which led to higher pain remission rates, especially for patients with moderate-to-severe pain. Improved patient education at model wards also helped patients overcome their aversion to these drugs and increased their willingness to report pain symptoms. We also noticed that use of weak opioids decreased, although the underlying reasons may require further analysis. Within the GPM program, proper pain and drug use record-keeping were instituted at the model wards and this reduced the number of instances of inappropriate use of analgesic drugs. Good record-keeping helped provide relevant information on drug prescriptions for patients upon discharge. As the hospitals that implemented GPM continued to support patients after discharge, good record-keeping also helped to support patient follow-up monitoring and post-discharge treatment and enabled improved patient outcomes to be maintained for longer periods.

An on-site assessment of GPM model wards at 30 hospitals in the Zhejiang Province, China, was conducted in June and July 2012, the results of which lend credence to our views. Assessors found that nursing staff had conducted pain assessment in a timely manner and that patients who had a good knowledge of pain treatment were able to cooperate with the nursing staff on their pain assessment and drug dose titration. The 70% target rate for telephone follow-up after discharge was achieved by all but one hospital. The study also highlighted several areas for improvement: pain assessment was conducted too frequently, especially during the night, and may have affected the patient’s rest; the observational skills of nursing staff could be improved in such areas as visual (facial) pain assessment and adverse drug reaction; a need for pain assessment—in addition to the location of the pain and its intensity—must address the psychologic, emotional, social, and cultural aspects; and better storage and management of pain medication to ensure that it is available for timely dispensation when needed.

As each hospital conducted its own independent study of its GPM program, measured outcomes from one hospital could not be directly compared with those from other hospitals. Past records of pain parameters, such as pain score, opioid drug dose titration, dynamic changes in pain, and adverse reactions, may be incomplete as pain is one of the many symptoms of cancer. In addition, there was no uniform scale for pain measurement used across the hospitals. Whereas this may place some limitations on the interpretation of the success of the GPM program, we believe that the program delivered concrete and practical guidelines which have enhanced the diagnosis and treatment of cancer pain and, at the same time, improved the clinical management processes at these hospitals. This has encouraged the adoption of GPM practices at health care institutions in China.

By early 2016, 67 national wards and 769 provincial wards have been certified, as more hospitals implemented and adhered to the common set of guidelines for the establishment of GPM wards, procedures for pain assessment, and standards for pain treatment and management. This brings the total to 836 model wards, which far exceeds the 150 model wards initially planned for the GPM program—a testament to its success. The consistent and visible improvements to patient care brought about by the GPM program at the model wards has provided a useful benchmark for the degree of improvement that can be achieved in real-life practice.
AUTHOR CONTRIBUTIONS

Conception and design: Shi-Ying Yu, Jie-Jun Wang, Yu-guang Huang, Bing Hu, Kun Wang, Ping Ping Li, Yi-Long Wu, He-Long Zhang, Li Zhang

Provision of study materials or patients: Ping Ping Li, Qing-Yuan Zhang

Collection and assembly of data: Yu-guang Huang, Ping Ping Li, Qing-Yuan Zhang, Shu-Kui Qin

Data analysis and interpretation: Yu-guang Huang

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Shi-Ying Yu
No relationship to disclose

Jie-Jun Wang
No relationship to disclose

Yu-guang Huang
No relationship to disclose

Bing Hu
No relationship to disclose

Kun Wang
No relationship to disclose

Ping Ping Li
No relationship to disclose

Yi-Long Wu
Honorary: AstraZeneca, Eli Lilly, Roche, Pfizer

Consulting or Advisory Role: AstraZeneca, Roche, Merck, Boehringer Ingelheim

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He-Long Zhang
No relationship to disclose

Li Zhang
Research Funding: Eli Lilly, AstraZeneca, Novartis, Bristol-Myers Squibb, Boehringer Ingelheim

Qing-Yuan Zhang
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Shu-Kui Qin
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REFERENCES


Biologics play a key role in cancer treatment and are principal components of many therapeutic regimens. However, they require complex manufacturing processes, resulting in high cost and occasional shortages in supply. The cost of biologics limits accessibility of cancer treatment for many patients. Effective and affordable cancer therapies are needed globally, more so in developing countries, where health care resources can be limited. Biosimilars, which have biologic activity comparable to their corresponding reference drugs and are often more cost effective, have the potential to enhance treatment accessibility for patients and provide alternatives for decision makers (ie, prescribers, regulators, payers, policymakers, and drug developers). Impending patent expirations of several oncology biologics have opened up a vista for the development of corresponding biosimilars. Several countries have implemented abbreviated pathways for approval of biosimilars; however, challenges to their effective use persist. Some of these include designing appropriate clinical trials for assessing biosimilarity, extrapolation of indications, immunogenicity, interchangeability with the reference drug, lack of awareness and possibly acceptance among health care providers, and potential political barriers. In this review, we discuss the potential role and impact of biosimilars in oncology and the challenges related to their adoption and use. We also review the safety and efficacy of some of the widely used biosimilars in oncology and other therapeutic areas (eg, bevacizumab, darbepoetin, filgrastim, rituximab, and trastuzumab).

INTRODUCTION

Biologics are important components of the modern cancer treatment armamentarium and are recommended for the treatment of various types of cancers by National Comprehensive Cancer Network (NCCN) and American Society for Clinical Oncology (ASCO) guidelines because they improve clinical outcomes, including overall survival (OS). Although only 15% of the agents listed in the NCCN Drugs and Biologics Compendium are biologics, they account for the majority of drug-related expenditures in outpatient and hospital settings in the United States. According to a 2011 drug expenditure analysis, biologics accounted for approximately 55% of the total expenditure on antineoplastic drugs in the US health care system; among the biologics, bevacizumab (Avastin; Roche, Basel, Switzerland), rituximab (Rituxan/MabThera; Roche), and trastuzumab (Herceptin; Roche) accounted for more than half of the top 20 antineoplastic expenditures in outpatient clinics. Bevacizumab is approved for the treatment of colorectal, brain, lung, fallopian tube, renal, and other cancers; rituximab is approved for the treatment of CD20-positive non-Hodgkin lymphoma and leukemia; and trastuzumab is approved for the treatment of human epidermal growth factor receptor 2 (HER2)–positive breast cancer and metastatic gastric and gastroesophageal junction adenocarcinomas. Although effective, biologics are expensive because of the complex manufacturing and development processes, adding to the already high cost associated with cancer treatment.

Over the last few years, biosimilars have generated great interest worldwide as effective alternatives to biologics. The US Public Health Service Act [Section 351(i)] defines a biosimilar as a “biologic product that is highly similar to the reference biologic, notwithstanding minor differences in clinically inactive components.” Similarly, the European Union defines a biosimilar medicine as a medicinal product, which is a copy of a biologic product (the reference product) that has already received authorization. Biosimilars are also referred to as follow-on biologicals, similar biotherapeutic products, or subsequent-entry biologics. The term biogenerics is also used occasionally but should be avoided because it may imply that biosimilars are identical to the original compounds, as in the case of generic versions of small-molecule drugs.
Biosimilars have been integral to clinical practice in the European Union for almost a decade. In 2006, somatropin (ribosomal DNA origin) for injection (Omnitrope; SANDOZ, Basle, Switzerland) became the first biosimilar to be approved by the European Medicines Agency (EMA), followed by biosimilars for epoetin alfa (Epoetin Alfa Hexal; HEXAL, Holzkirchen, Germany), reference drug, Eprex/Erypo; JANSSEN PHARMACEUTICALS, Raritan, NJ) in 2007 and filgrastim (Zarxio; SANDOZ, reference drug, Neupogen; AMGEN, Thousand Oaks, CA) in 2009. In 2015, Zarxio became the first biosimilar to be approved by the US Food and Drug Administration (FDA). Several key oncology biologics have already lost or will soon lose market exclusivity (Table 1), and corresponding biosimilars are currently in various stages of development (Table 2).

Expanding patient access to effective therapeutic agents and reducing health care costs continue to be the two main driving factors behind the rapid development of biosimilars. As we discuss in detail in this review, many oncology biosimilars have demonstrated similar clinical efficacy to their reference drugs. Common examples include biosimilars for filgrastim, pegfilgrastim, rituximab, and trastuzumab. Efficacy and safety of some biosimilars have also been tested in real-world settings with encouraging results. Such studies have prompted regulatory bodies to adopt a more positive opinion of biosimilars, even in highly regulated markets, paving the way for future inclusion of biosimilars in oncology therapy. As a result, global biosimilar sales are expected to rise from US$2.29 billion in 2015 to US$6.22 billion by 2020.

**GUIDANCE ON BIOSIMILAR DEVELOPMENT**

To demonstrate biosimilarity, the WHO recommends conducting characterization and comparability studies on physicochemical properties, biologic activity, process- or product-related impurities, and product stability, in addition to nonclinical studies on in vitro and in vivo bioactivity, and clinical studies on pharmacokinetics (PKs) and pharmacodynamics (PDs), efficacy, and safety (Fig 1). According to a recent analysis, the leading biosimilar specialists in the world are located in the United States, Europe, and Israel, with other important players being India, China, and Brazil. Regulatory guidance for biosimilar development in these nations broadly follows similar principles, with a few minor differences; these guidelines have been summarized in Table 3. Approval of biosimilars by the FDA, Health Canada, and the EMA requires in vitro studies demonstrating similarity to a reference biologic in terms of quality and nonclinical and clinical studies demonstrating comparable PKs, efficacy, safety, and immunogenicity. The Biologics Price Competition and Innovation (BPCI) Act of 2009 authorizes the FDA to allow an abbreviated pathway for approval of biosimilars, which eliminates unnecessary testing of biosimilars in animals and humans, thus saving time, money, and manpower. The US Patient Protection and Affordable Care Act of 2010 also supports the abbreviated pathway.

In developing countries such as India, efforts are focused on developing biosimilars involving low development costs and risks. Consequently, comprehensive regulatory guidelines are in place to monitor the development and approval of biosimilar products in India. Currently, India is the world’s second-largest supplier of vaccines and fourth-largest supplier of pharmaceuticals and is emerging as a global leader in manufacturing and use of biosimilars. Many biosimilars have already been approved and marketed in India for various types of cancer (Table 4). Indian regulatory authorities have recently proposed revised guidelines for the development of biosimilars in India, requiring specific postmarketing single-arm safety studies to be conducted among at least 200 evaluable patients, followed by comparison of results with historical data on the reference drug. These phase IV studies should be completed within 2 years of marketing approval and should have safety as their primary end point, with efficacy and immunogenicity as secondary end points.

**PHARMACOECONOMIC IMPACT OF BIOSIMILARS IN ONCOLOGY**

The global annual economic burden of cancer, including costs associated with prevention, treatment, and disability-adjusted life-years lost

<table>
<thead>
<tr>
<th>Drug</th>
<th>United States</th>
<th>European Union</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Approval</td>
<td>Patent Expiration</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2004</td>
<td>2019</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>2004</td>
<td>2018</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>1998</td>
<td>2013</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>1991</td>
<td>2013</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>2002</td>
<td>2015</td>
</tr>
</tbody>
</table>
to cancer, was estimated at US$1.16 trillion in 2010.43,44 When longer-term costs to patients and their families were taken into account, this estimate increased to US$2.5 trillion.44 In developing countries such as India, where nearly 70% of the population pays for their own health care,45 patients are less likely to have access to expensive oncology treatments.46 Most often, the cost of cancer treatments exceeds the average per capita income by many multiples. For example, the cost of a typical trastuzumab course, prescribed during the treatment of metastatic breast cancer, is approximately 15 times the per capita monthly income of an average Indian.45 Similarly, trastuzumab treatment in Peru costs more than three times the gross domestic product per capita per disability-adjusted life-year and cannot be considered cost effective.47

Until a few years ago, pharmaceutical and economic market analysts often expected that biosimilars would cost up to 30% less than their reference drugs.10,48 For example, in the United States, the cost of filgrastim-sndz is 15% less than Neupogen, and this price difference is expected to increase further.49 Similarly, biosimilar recombinant human erythropoietin costs 25% to 30% less than its reference drug in the European Union.1 In recent years, however, cost savings as high as 70% have been observed with the use of biosimilars. For example, in Norway, an infliximab biosimilar was initially offered at a 39% discount over the originator drug, but it failed to gain a significant proportion of the market; subsequently, it was discounted by nearly 70% and now represents more than 50% of drug sales.50,51 Recently, a similar 70% discount was offered for the same biosimilar in Denmark.52 In India and Peru, a rituximab biosimilar (Reditux; Dr Reddy’s Laboratories, Hyderabad, India) was introduced for the same indications as the originator drug at a 50% lower price.53 These trends illustrate the potentially massive impact of biosimilars on oncology care at the levels of the patient and the industry as a whole.

The cost-saving potential of biosimilars will also vary according to the pricing of the original biologic, its sales, the degree of competition, and

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**Table 2. Examples of Most Widely Used Biosimilars in Various Stages of Development Globally**

<table>
<thead>
<tr>
<th>Original Drug</th>
<th>Biosimilar</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>ABP 215</td>
<td>Amgen, Thousand Oaks, CA</td>
</tr>
<tr>
<td></td>
<td>BCD-021</td>
<td>BIOCAD, Moscow, Russia</td>
</tr>
<tr>
<td></td>
<td>Bevacirel</td>
<td>Reliance Life Sciences, Mumbai, India</td>
</tr>
<tr>
<td>BI 695502</td>
<td>Boehringer Ingelheim, Ingelheim am Rhein, Germany</td>
<td></td>
</tr>
<tr>
<td>Cizumab</td>
<td>Hetero Drugs, Hyderabad, India</td>
<td></td>
</tr>
<tr>
<td>DRL_BZ</td>
<td>Dr Reddy’s Laboratories, Hyderabad, India</td>
<td></td>
</tr>
<tr>
<td>PF-06439535</td>
<td>Pfizer, New York, NY</td>
<td></td>
</tr>
<tr>
<td>SB8</td>
<td>Samsung Bioepis, Incheon, Republic of Korea</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>ABP 798</td>
<td>Amgen</td>
</tr>
<tr>
<td></td>
<td>BCD-020</td>
<td>BIOCAD</td>
</tr>
<tr>
<td>GP2013</td>
<td>Novartis, Basel, Switzerland</td>
<td></td>
</tr>
<tr>
<td>MabionCD20</td>
<td>Mabion, Konstantynów Łódzki, Poland</td>
<td></td>
</tr>
<tr>
<td>MK-8808</td>
<td>Merck, Kenilworth, NJ</td>
<td></td>
</tr>
<tr>
<td>PF-05280586</td>
<td>Pfizer</td>
<td></td>
</tr>
<tr>
<td>RTXM83</td>
<td>mAbxience, Lugano, Switzerland</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>ABP 980</td>
<td>Amgen</td>
</tr>
<tr>
<td></td>
<td>BCD-022</td>
<td>BIOCAD</td>
</tr>
<tr>
<td>CT-P6</td>
<td>Celltrion, Incheon, Republic of Korea</td>
<td></td>
</tr>
<tr>
<td>DRL_TZ</td>
<td>Dr Reddy’s Laboratories</td>
<td></td>
</tr>
<tr>
<td>MYL-1401O</td>
<td>Mylan, Amsterdam, the Netherlands</td>
<td></td>
</tr>
<tr>
<td>PF-05280014</td>
<td>Pfizer</td>
<td></td>
</tr>
<tr>
<td>SB3</td>
<td>Samsung Bioepis</td>
<td></td>
</tr>
</tbody>
</table>

---

**Fig 1. Approval process for biosimilars. Data adapted.**

---

**Table 2. Examples of Most Widely Used Biosimilars in Various Stages of Development Globally**

<table>
<thead>
<tr>
<th>Processes and product development</th>
<th>Analytics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicochemical characterization</td>
<td>Biologic characterization</td>
</tr>
<tr>
<td>Preclinical studies</td>
<td>Pharmacokinetics/pharmacodynamics, immunogenicity</td>
</tr>
<tr>
<td>Nonclinical validation</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>Analytic studies</td>
<td>Trials, registry studies, postmarketing experience</td>
</tr>
</tbody>
</table>
### Table 3. Key Points of Various Regulatory Guidelines on Biosimilar Development

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FDA¹,³¹</th>
<th>EMA²⁸,³²</th>
<th>Israel¹³</th>
<th>India¹⁴,¹⁵</th>
<th>China³⁵</th>
<th>Brazil³⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data requirements</td>
<td>Uses a risk-based, totality-of-evidence approach when evaluating biosimilarity; stepwise approach, including detailed structural and functional characterizations of the biosimilar and reference biologic, is recommended</td>
<td>Guiding principle is to establish similarity to ensure previously proven safety and efficacy of the reference biologic apply to the biosimilar; stepwise approach, including detailed structural and functional characterizations of the biosimilar and reference biologic, is recommended</td>
<td>Registrations of the biosimilar with FDA, EMA, Canada, Australia, New Zealand, Japan, or Swiss Agency for Therapeutic Products (Swissmedic) may constitute a basis for registration in Israel</td>
<td>Conduct of analytic and quality characterization studies, nonclinical studies (PDs, cell proliferation, immunogenicity, and one repeat dose toxicity), and clinical studies (PKs/PDs, comparative, immunogenicity) is required; for clinical studies, equivalence study design is preferred over noninferiority</td>
<td>Conduct of analytic and quality characterization studies, nonclinical studies (PKs/PDs, immunogenicity), and clinical studies (PKs/PDs, immunogenicity) is required</td>
<td>Conduct of analytic and quality characterization studies, nonclinical studies, nonclinical studies (PDs, cumulative toxicity), and clinical studies (PKs/PDs, comparative, immunogenicity) is required</td>
</tr>
<tr>
<td>Extrapolations</td>
<td>Extrapolations to different indications are permitted if mechanism of action and receptors involved for different indications are same; any differences do not necessarily preclude extrapolation and are considered in context of totality of evidence</td>
<td>Extrapolation is permitted based only on comparability data; if pivotal evidence for comparability is based on PDs and different mechanisms of action are relevant for the claimed indications (or uncertainty exists), then additional relevant data will need to be provided</td>
<td>Extrapolation to indications for which the biosimilar was not clinically tested is permitted provided the reference drug is registered for such indications on the basis of the totality of available information, including quality, safety, and efficacy data, with emphasis on mechanism of action</td>
<td>Extrapolations to different indications are permitted if mechanism of action and receptors involved for different indications are same</td>
<td>Extrapolations are considered on a case-by-case basis</td>
<td>Extrapolations to different indications are permitted if mechanism of action and receptors involved for different indications are same and safety and immunogenicity have been sufficiently characterized</td>
</tr>
<tr>
<td>Reference drug</td>
<td>Reference drug should be licensed by FDA</td>
<td>Reference drug should be registered in a country where approval for the biosimilar is sought; reference product registered in a different country may be used with some additional studies</td>
<td>Registration of the biosimilar will not be permitted if the reference drug is not registered in Israel</td>
<td>Reference drug should be licensed in India and be an innovator drug; if reference biologic is not marketed in India, then it should be licensed for 4 years postapproval in innovator jurisdiction in a country with well-established regulatory framework</td>
<td>Reference drug should be approved by Chinese regulatory agencies; another biosimilar (even if approved) cannot be considered as a reference drug</td>
<td>Reference drug should be registered in Brazil or another country with regulatory requirements similar to those of Brazil</td>
</tr>
<tr>
<td>Interchangeability</td>
<td>More-specific guidelines for demonstration of interchangeability are available</td>
<td>No provision for interchangeability in most EU geographies</td>
<td>Physician, upon consultation with the medical institution, is permitted to substitute a reference drug with its biosimilar for the same indications</td>
<td>Recommendations on interchangeability are not available</td>
<td>Recommendations on interchangeability are not available</td>
<td>Recommendations on interchangeability are not available</td>
</tr>
<tr>
<td>Other points</td>
<td>Full clinical program can be skipped if extensive structural and functional similarities are demonstrated; comparative clinical studies must demonstrate purity, potency, immunogenicity, and safety in a condition for which the reference biologic is approved</td>
<td>Standalone development of the product should be considered if significant differences between the biosimilar and reference biologic become apparent</td>
<td>Risk management plan or risk evaluation and mitigation strategies need to be submitted as part of the application for registration of a biosimilar</td>
<td>Amino acid sequence of the biosimilar and its reference must be same</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EMA, European Medicines Agency; EU, European Union; FDA, US Food and Drug Administration; PD, pharmacodynamic; PK, pharmacokinetic.
A recent cost-benefit analysis of various biosimilars was performed assuming a year-on-year originator growth of 10%, an increase in the share of originator sales exposed to biosimilar competition from 10% in year 1 to 20% in year 10, biosimilar market penetration of 60%, and a biosimilar price discount of 35% resulting from competition. Results indicated that potential direct cost savings of US$44.2 billion were expected over a 10-year period from 2014 to 2024 (Table 5). The highest

<p>| Table 4. Biosimilars Approved and Marketed in India |
|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|</p>
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Therapeutic Area</th>
<th>Approval or Launch Date in India</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darbepoetin alfa</td>
<td>Anemia, cancer, chronic kidney failure</td>
<td>2014</td>
<td>Cipla/Hetero Drugs</td>
</tr>
<tr>
<td>Cresp</td>
<td>Anemia, cancer, chronic kidney failure</td>
<td>2010</td>
<td>Dr Reddy’s Laboratories</td>
</tr>
<tr>
<td>Darbatitor</td>
<td>Anemia, cancer, chronic kidney failure</td>
<td>2014</td>
<td>Torrent Pharmaceuticals</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Anemia, cancer, chronic kidney failure</td>
<td>2010</td>
<td>Emcure</td>
</tr>
<tr>
<td>Ceriton</td>
<td>Anemia, cancer, chronic kidney failure</td>
<td>2010</td>
<td>Intas Pharmaceuticals</td>
</tr>
<tr>
<td>Epofit Erykine</td>
<td>Anemia, cancer, chronic kidney failure</td>
<td>2005</td>
<td>Claris Lifesciences</td>
</tr>
<tr>
<td>Epoitin</td>
<td>Anemia, cancer, chronic kidney failure</td>
<td>NA</td>
<td>Biocon</td>
</tr>
<tr>
<td>Relipoietin</td>
<td>Anemia, autologous blood transfusion, chronic kidney failure, HIV</td>
<td>2008</td>
<td>Reliance Life Sciences</td>
</tr>
<tr>
<td>Wepox</td>
<td>Anemia, cancer, chronic kidney failure</td>
<td>2001</td>
<td>Wockhardt</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Neutropenia</td>
<td>2013</td>
<td>Cadila Pharmaceutical</td>
</tr>
<tr>
<td>Colstim</td>
<td>Neutropenia</td>
<td>2013</td>
<td>Gennova Biopharmaceuticals (Emcure)</td>
</tr>
<tr>
<td>Emgrast</td>
<td>Cancer, neutropenia</td>
<td>2010</td>
<td>Dr Reddy’s Laboratories</td>
</tr>
<tr>
<td>Fegraplac</td>
<td>Cancer, hematopoietic stem-cell \n transplantation, neutropenia</td>
<td>NA</td>
<td>Intas Pharmaceuticals</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Neutropenia</td>
<td>2013</td>
<td>USV</td>
</tr>
<tr>
<td>Grafeel</td>
<td>Neutropenia, hematopoietic stem-cell \n transplantation, cancer</td>
<td>2001</td>
<td>Dr Reddy’s Laboratories</td>
</tr>
<tr>
<td>Lupifil</td>
<td>Neutropenia</td>
<td>2013</td>
<td>Lupin</td>
</tr>
<tr>
<td>Neukine</td>
<td>Neutropenia, hematopoietic stem-cell \n transplantation, cancer</td>
<td>2004</td>
<td>Intas Pharmaceuticals</td>
</tr>
<tr>
<td>Nufil</td>
<td>Cancer, neutropenia</td>
<td>NA</td>
<td>Biocon</td>
</tr>
<tr>
<td>Religrast</td>
<td>Neutropenia</td>
<td>2008</td>
<td>Reliance Life Sciences</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>Cancer, neutropenia</td>
<td>2013</td>
<td>Lupin</td>
</tr>
<tr>
<td>Neupeg</td>
<td>Cancer, neutropenia</td>
<td>2007</td>
<td>Intas Pharmaceuticals</td>
</tr>
<tr>
<td>Pegex</td>
<td>Cancer, neutropenia</td>
<td>2010</td>
<td>Gennova Biopharmaceuticals (Emcure)</td>
</tr>
<tr>
<td>Peg-Grafeel</td>
<td>Chemotherapy-induced febrile neutropenia</td>
<td>2011</td>
<td>Dr Reddy’s Laboratories</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Lymphoma, NHL</td>
<td>2015</td>
<td>Hetero Drugs</td>
</tr>
<tr>
<td>MABTAS</td>
<td>Lymphoma, NHL</td>
<td>2013</td>
<td>Intas Pharmaceuticals</td>
</tr>
<tr>
<td>Reditux</td>
<td>Leukemia, lymphoma, rheumatoid arthritis</td>
<td>2007</td>
<td>Dr Reddy’s Laboratories</td>
</tr>
<tr>
<td>Rituximab</td>
<td>NHL</td>
<td>2013</td>
<td>Zenotech Laboratories</td>
</tr>
<tr>
<td>RituxiRel</td>
<td>NHL, rheumatoid arthritis</td>
<td>2015</td>
<td>Reliance Life Sciences</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Breast cancer</td>
<td>2013</td>
<td>Biocon</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; NHL, non-Hodgkin lymphoma.
Table 5. Potential Cost Savings Likely to Be Offered by Various Biosimilars by 2024\textsuperscript{54}

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Potential Cost Savings (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF products</td>
<td>21</td>
</tr>
<tr>
<td>Long-acting insulins</td>
<td>15</td>
</tr>
<tr>
<td>Monoclonal antibody antineoplastics</td>
<td>13</td>
</tr>
<tr>
<td>Fast-acting insulins</td>
<td>11</td>
</tr>
<tr>
<td>Colony-stimulating factors</td>
<td>6</td>
</tr>
<tr>
<td>Interferons</td>
<td>6</td>
</tr>
<tr>
<td>Erythropoietin products</td>
<td>6</td>
</tr>
<tr>
<td>Immunostimulants (excluding interferons)</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviation: TNF, tumor necrosis factor.

cost savings are expected from anti–tumor necrosis factor products. However, more systematic strategies need to be used to estimate the magnitude of clinical benefit of biosimilars across geographies and economies; these could include the use of tools such as the European Society for Medical Oncology Magnitude of Clinical Benefit Scale.\textsuperscript{55} This scale is a validated and reproducible scale designed to assess the magnitude of clinical benefit for cancer medicines. This scale uses a rational, structured, and consistent approach to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from a new anticancer treatment. Use of such approaches can provide a more accurate estimate of the cost benefit of biosimilars.

CHALLENGES IN THE ADOPTION AND USE OF BIOSIMILARS

Although biosimilars hold the promise of being effective and safe alternatives to biologics, several challenges impede their adoption and use. For example, designing appropriate clinical trials with relevant end points for testing comparability can be difficult. Likewise, generating clinician and patient interest in enrolling for such trials is a challenge in itself, because novel drugs offer the possibility of increased disease control and therefore tend to foster the greatest interest.\textsuperscript{56} Other challenges include limited guidelines on extrapolation of approved indications for biosimilars, the possibility of immunogenicity events in patients during testing, interchangeability with the originator drug, appropriate formulation and manufacturing of biosimilars, limited awareness of the efficacy and safety of biosimilars among health care providers, and potential political barriers. These issues are discussed in greater detail in subsequent paragraphs.

Selection of End Points

The choice of end points is paramount when designing studies of biosimilars. For biologics, the NCCN recommends using sensitive end points such as overall response rate (ORR), OS, and/or progression-free survival (PFS).\textsuperscript{2} For biosimilars, end points should be relevant to the disease and sensitive enough to detect clinically relevant differences between the biosimilar and its reference drug.\textsuperscript{28} The EMA and FDA recommend using end points that can facilitate detection of differences but are not influenced by patient- or disease-related factors.\textsuperscript{28} According to EMA guidance on end point selection, a clinical end point that measures activity (eg, ORR) as a primary end point may be considered. Assessment of ORR at a certain time point or percentage change in tumor mass from baseline is also considered appropriate.\textsuperscript{32} OS, the preferred efficacy end point in oncology, may not be suitable to establish biosimilarity, because it can be influenced by factors that are unrelated to the differences between a biosimilar and its reference product; also, OS as an end point would require conducting much larger trials with longer follow-up periods.\textsuperscript{32}

It is important to validate the effectiveness of biosimilars not only through clinical trials but also in real-world settings. Although most regulatory authorities demand clinical trials that demonstrate safety and efficacy in a structured setting, reimbursement authorities may require data in real-world settings where patient selection is not restricted by strict inclusion and exclusion criteria.\textsuperscript{57} Real-world studies with encouraging results can also help build clinicians’ confidence in prescribing biosimilars.\textsuperscript{58} Manufacturers realize the emerging importance of real-world data, leading to more studies of this type being conducted to complement clinical trials.\textsuperscript{58}

Extrapolation of Approval to Other Indications

On the basis of data submitted for one indication, regulatory agencies generally determine whether extrapolation to all approved indications of the reference drug should be allowed. EMA guidelines state that if biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification.\textsuperscript{37} Furthermore, manufacturers do not need to demonstrate biosimilarity again with changes in manufacturing steps, provided that marketing authorization has already been granted. In terms of procuring FDA approval, the 351(k) pathway is more appropriate when approval is desired for many indications at once; this pathway, however, requires a more rigorous level of clinical study. In contrast, the 351(a) pathway is faster, but approval is usually
granted for fewer indications. Therefore, if the FDA requires rigorous clinical evidence for extrapolated indications in the 351(k) pathway, manufacturers may prefer the abbreviated 351(a) pathway. For example, tbo-filgrastim (Granix; Teva Pharmaceutical Industries, Petah Tikva, Israel) was filed through a 351(a) pathway and approved for one indication (neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy), which was not the most desired indication for that product. Had tbo-filgrastim been filed through the 351(k) pathway, it potentially would have been eligible to gain extrapolation for all five indications for filgrastim. Thus, it is important for manufacturers to have clear guidance on extrapolation of indications from the regulatory authorities to ensure appropriate filing.

In 2012, the Indian Department of Biotechnology laid out detailed guidelines and requirements for the development and approval of biosimilars for primary and extrapolated indications. Several aspects of these guidelines are similar to those in the United States and European Union. In Brazil, two pathways have been established to regulate the extrapolated prescription of biosimilars. In the individual pathway, the development process, dossier, quality issues, and requirements for clinical studies are reduced, but indications cannot be extrapolated. In contrast, extrapolations are allowed in the comparability pathway after satisfactory completion of rigorous phase I, II, and III clinical trials against the reference biologic. When possible, clarity should be obtained on extrapolations at the time of launch. If physicians are not well informed of the nonpermitted extrapolations, they may unduly lose trust in the efficacy of the biosimilar, causing lower-than-expected adoption rates.

Immunogenicity

Biologics and biosimilars have the potential to induce antibody responses, which may result in hypersensitivity reactions and other adverse events (AEs) as well as decreased activity. In particular, biosimilars with post-translational modifications are not exactly identical to reference biologics and can trigger an immune response. Immunogenicity may be influenced by patient-, disease-, and/or product-related factors. Patient- and disease-related factors can be derived from original product data. Therefore, evaluations should focus on product-related factors, such as differences in structure between the biosimilar and reference medicine, impurities in preparation of the biosimilar, and changes in storage and/or distribution conditions of the biosimilar. Even seemingly small differences in these factors can affect immunogenicity and pose a risk to patients. Thus, appropriate clinical studies with comprehensive efficacy and safety end points are necessary for each biosimilar, especially because analytic or animal data cannot predict immune response in humans.

Issues Related to Manufacturing

The consistent replication of biosimilar manufacturing and formulation processes is critical because even small alterations can have serious ramifications. For example, a minor change in the packaging process of a reformulation of epoetin alfa (Eprex; Janssen Pharmaceuticals) resulted in an increased rate of pure red-cell aplasia, prompting manufacturers to be more vigilant regarding any changes in formulations or manufacturing procedures. The experience of the manufacturers in the field of biologics and the robustness of their production and supply chain abilities are important to ensure adequate supply of biosimilars over time. A lag in supply could lead to dose delays or reductions or result in patients switching to an alternate drug.

Interchangeability

Interchangeability means that a biosimilar can be used as a substitute for the original drug without referring to the prescribing physician. Given the sensitivity related to the manufacturing of biosimilars, their interchangeability is more complicated than the bioequivalence and interchangeability of generic drugs. The BPCI Act of 2009 authorizes the FDA to designate interchangeable status to a biosimilar with its reference drug after successful completion of specific studies. These studies include analytic studies demonstrating similarity, animal studies including assessment of toxicity, and clinical studies including assessment of immunogenicity and PKs and PDs. To achieve interchangeable status, the BPCI Act further requires that the biosimilar and its reference use a similar mechanism of action and have the same route of administration, dosage form, strength, and indications, which should be previously approved for the reference drug. Finally, it should be ascertained that interchanging the original drug with its biosimilar does not increase risk in terms of safety or diminished efficacy. FDA recommendations on interchangeability of biosimilars were released in January 2017. According to this guidance, the FDA expects that the sponsors will submit data and information showing that the proposed biosimilar can be expected to produce the same clinical results as the reference
product in all of the licensed conditions of use of the reference product in any given patient. This, however, may vary depending on the nature of the product under consideration. Although these guidelines enlist a detailed and rigorous process for attaining interchangeable status, such status could help build the confidence of physicians in prescribing biosimilars.

Awareness Among Health Care Providers and Patients

In 2011, the NCCN conducted a survey among the attendees of its 16th annual conference in Hollywood, FL, to assess the awareness of biosimilars. The participants consisted of 277 health care providers, including physicians, nurses, pharmacists, and other practicing and nonpracticing clinicians. Results indicated that more than half of the respondents were either not at all familiar (36%) or slightly familiar (19%) with recent developments regarding biosimilars; only 7% were extremely familiar. Overall interest in prescribing, dispensing, or administering biosimilars was high (27%) to moderate (35%); others expressed the need for more information before they could make a decision. The survey concluded that there was suboptimal knowledge of biosimilars and a need for greater awareness and education regarding biosimilars among health care providers. Another survey conducted among US physicians identified a strong need for evidence-based education about biosimilars for physicians across specialties. Major knowledge gaps included a lack of proper understanding of the concept of totality of evidence, lack of clarity on permitted extrapolations, and unclear information on interchangeability and rules for pharmacy-level substitution of drugs. Pharmacists have also expressed low confidence in prescribing or interchanging biosimilars because of a lack of clear guidelines on naming conventions. According to an online survey conducted among members of the Academy of Managed Care Pharmacy and the Hematology/Oncology Pharmacy Association, US pharmacists prefer the use of a naming convention for biosimilars that includes a nonproprietary proper name with a designated suffix, with the exact same nonproprietary name as the reference drug being more preferable. These findings highlight the urgent need for establishing a proper naming convention for biosimilars to increase confidence in prescribing.

Likewise, awareness of biosimilars is also low among the patient population. A recent survey was conducted among patients, caregivers, patients involved in support or advocacy groups, and the general population based in either the United States or the European Union on their perceptions of biosimilar use. Results revealed that across all groups, awareness of biosimilars was low, and only 6% of the general population reported some knowledge of biosimilars. Awareness was significantly high only among patients involved in support or advocacy groups (20% to 30%; \( P < .05 \)). Gaps in knowledge about biosimilars, as identified by the survey, included safety, efficacy, and access. Limited awareness among providers and users could be a major reason for low adoption rates of biosimilars despite the availability of data on their clinical efficacy.

Potential Political Barriers?

There have been few political barriers to the development and accessibility of biosimilars. A biosimilar manufacturer, while offering price reductions, may not be able to offer as complete a package as an innovator (eg, patient assistance program). Furthermore, price competition alone may not be a sufficient offering, because the innovator drug manufacturer is likely to lower the price of the reference drug in response to the launch of a biosimilar. It is also notable that the patent monopoly may be further strengthened by the provisions of agreements such as the Trans-Pacific Partnership. The Trans-Pacific Partnership is a proposed trade deal between 12 Asia-Pacific countries, including the United States, that would expand and protect patent rights. This may have limitations in access to affordable health care.

CASE STUDIES OF SPECIFIC BIOSIMILARS

A recent review by Jacobs et al presented a grid that mapped the extent of similarity of various biosimilars and their reference drugs in the context of clinical, preclinical, or postmarketing studies. The observations emphasize the point that each study should be analyzed in the context of its setting and design. In the next few sections, we present experiences with a few select biosimilars that are most commonly prescribed during cancer treatment and a few other therapeutic areas. With these case studies (presented in alphabetic order), we aim to provide a broad picture of the overall developmental landscape of these biosimilars in a concise manner.

Bevacizumab Biosimilars

Some of the bevacizumab biosimilars in late stages of development globally include ABP 215 (Amgen), BCD-021 (BIOCAD, Moscow,
Filgrastim Biosimilars

The filgrastim biosimilar Zarxio (Sandoz) was approved in the European Union in 2009 and in the United States in 2015. The physicochemical properties and in vitro biologic activity of Zarxio were compared with those of Neupogen using a variety of assays. Results showed similar molecular structures, purity profiles, and equivalent biologic activity in terms of effect on cell proliferation.80 Results of a randomized, double-blind, two-way crossover phase I study in healthy participants showed similar PKs and PDs and safety profiles between the two drugs.81 Results of a double-blind, randomized phase III study evaluating Zarxio in 218 neutropenic patients receiving myelosuppressive chemotherapy showed no clinically meaningful differences in duration of severe neutropenia, incidence of febrile neutropenia, rate of hospitalization because of febrile neutropenia, incidence of infection, depth and time of absolute neutrophil count nadir, and time to absolute neutrophil count recovery. AE profiles were comparable between the two agents.19 In 2013, Zarxio sales surpassed those of Neupogen in the European Union.82

Another filgrastim biosimilar, Grafeel (Dr Reddy’s Laboratories), received regulatory approval in India in 2001. The EMA accepted the manufacturer’s proposal that the clinically important difference between a biosimilar and its reference filgrastim was the difference of more than 1 day of neutrophil count recovery. AE profiles were comparable between the two agents.19 A pegylated version of Grafeel (Peg-Grafeel) was introduced by Dr Reddy’s Laboratories in India in 2011 at a cost 25% lower than the price of the reference brand in India and 95% lower than the US price for pegfilgrastim, thereby increasing access to an affordable biosimilar for the treatment of neutropenia.83

Other filgrastim biosimilars that have been approved in various countries include Biograstim (CT Arzneimittel, Ulm, Germany), Filgrastim Hexal (Hexal), Grastofil (Aptex, North York, Ontario, Canada), MK-4214 (Merck, Kenilworth, NJ), Nivestim (Hospira, Lake Forest, IL), Ratiogranst (Ratiopharm, Ulm, Germany), and Tevagrasstim (Teva Pharmaceutical Industries).20,85-87 Many filgrastim biosimilars have been made available in India over the last 5 years by various pharmaceutical companies (Table 3).87

Rituximab Biosimilars

In 2007, the rituximab biosimilar Redlix (Dr Reddy’s Laboratories) became the first monoclonal antibody biosimilar to be licensed in India.40 It is one of the oldest rituximab biosimilars in use in the country for the treatment of non-Hodgkin lymphoma and rheumatoid arthritis. In a study conducted among 223 patients with diffuse large
B-cell lymphoma, it was observed that complete remission rates with the reference drug (MabThera; Roche) and Reditux were similar (75% and 82%, respectively; \( P = .294 \)). There were no significant differences in toxicity, tumor response rates, PFS, and OS. The results of this retrospective analysis further revealed that there were no differences in infusion reaction rate and grade 3 to 4 neutropenia.\(^{18} \) Most oncologists in India are now successfully using Reditux, leveraging the cost benefit it brings to patients.\(^{18} \)

Some of the other rituximab biosimilars in various stages of development include AMG 798 (Amgen)\(^{88} \), CT-P10 (Celltrion, Incheon, Republic of Korea)\(^{89} \), GP2013 (Sandoz), with nonclinical assessments complete\(^{90} \) and phase III trial completion expected in 2017\(^{89} \); MabionCD20 (Mabion, Konstancin-Lódzki, Poland), with phase III trial completion expected in 2016; MK-8808 (Merck)\(^{89} \); PF-05280586 (Pfizer), with nonclinical assessments complete\(^{89,91} \) and phase III trial completion expected in 2016; and RTXMO83 (mAbxience, Lugano, Switzerland).\(^{92} \)

Trastuzumab Biosimilars

In 2013, the trastuzumab biosimilar Hertraz (Biocon-Mylan, Bangalore, India; alternative name, MYL-1401O) was approved in India for the treatment of HER2-positive breast cancer based on a series of physiochemical and functional assays using Herceptin as the reference biologic.\(^{93} \) Results confirmed similarities in molecular structure and biologic activity between the biosimilar and its reference.\(^{94} \) Recently, Mylan (Amsterdam, the Netherlands) completed a double-blind, randomized safety and efficacy study (\( N = 500 \)) comparing MYL-1401O with Herceptin.\(^{95} \) In combination with taxane, MYL-1401O had no significant differences in efficacy compared with the reference as measured by ORR at week 24 (MYL-1401O plus taxane, 69.6%; Herceptin plus taxane, 64%).\(^{95} \) The ratio of ORR was 1.09; both 90% CI (0.974 to 1.211) and 95% CI (0.954 to 1.237) were within the predefined equivalence margins. Median PFS has not yet been reached (41 events for MYL-1401O vs 48 events for Herceptin). Safety was comparable; serious AEs (primarily neutropenia related) occurred in 38% of those in the MYL-1401O group compared with 36% in the Herceptin group. These results suggest that the proposed trastuzumab biosimilar MYL-1401O could be a new treatment option for HER2-positive metastatic breast cancer.\(^{95} \)

In 2014, a trastuzumab biosimilar called CT-P6 (Celltrion; alternative name, Herzuma) was approved in Korea for the treatment of early and advanced HER2-positive metastatic breast cancers and advanced metastatic stomach cancer, the same indications as its reference biologic, Herceptin.\(^{96} \) Results of a double-blind, randomized phase I/IIb study of 174 women with HER2-positive breast cancer and an Eastern Cooperative Oncology Group score of 0 or 1 showed that CT-P6 and trastuzumab had similar PK profiles. CT-P6 was well tolerated, with a safety profile comparable to that of trastuzumab.\(^{97} \) In a phase III trial, which enrolled 475 patients with breast cancer at 115 sites in 18 countries, safety and efficacy (ORR, median time to progression, and median time to response) of CT-P6 plus paclitaxel compared with trastuzumab plus paclitaxel were not significantly different. In fact, there were fewer infusion and hypersensitivity reactions with the biosimilar molecule (CT-P6 plus paclitaxel, 15.6%; trastuzumab plus paclitaxel, 26%).\(^{21} \)

Other trastuzumab biosimilars in various stages of development include ABP 980 (Amgen), BCD-022 (BIOCAD; ClinicalTrials.gov identifier NCT01764022), DRL_TZ (Dr Reddy’s Laboratories; Clinical Trials Registry India identifier CTRI/2015/08/006085), PF-05280014 (Pfizer), and SB3 (Samsung Bioepis), with phase III trials slated for completion in 2016, 2015, 2017, 2018, and 2016, respectively.\(^{98} \) A phase III, randomized, double-blind, multicenter, active-controlled study assessing the safety and effectiveness of ABP 980 in comparison with its reference drug (Herceptin) recently met its primary end point; no clinically meaningful differences between ABP 980 and Herceptin were identified.\(^{99} \) In this study, a total of 725 women with HER2-positive early breast cancer were randomly assigned to receive either ABP 980 or Herceptin.\(^{100} \) Safety profile and immunogenicity of the two drugs were comparable. The study is in its late stages, and the final results are expected in the near future.\(^{100} \)

In conclusion, the universal demand for affordable, effective cancer treatments and greater access to biopharmaceuticals is propelling the rapid development of biosimilars. Increasing availability of biosimilars will enhance treatment options, improve patient access, and potentially stimulate price competition with reference medicines. Over the next few years, the global biosimilars market is projected to grow at a compound annual growth rate of nearly 50%.\(^{101} \) Thus, biosimilars have the potential to revolutionize biologic therapies for cancer and other diseases. Clinical experiences with biosimilars have been promising thus far. However, greater education of
health care providers regarding appropriate use of biosimilars is needed. Coordinated interplay among various stakeholders, including patients, health care providers, drug manufacturers, payers, and regulatory agencies, can ensure that the promise of biosimilars is fully realized.

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97. Generics and Biosimilars Initiative: Phase I/IIb trial of CT-P6 shows comparability to trastuzumab. http://www.gabionline.net/Biosimilars/Research/Phase-I-IIb-trial-of-CT-P6-shows-comparability-to-trastuzumab
Primary Prevention of Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Guideline

Purpose To provide resource-stratified (four tiers), evidence-based recommendations on the primary prevention of cervical cancer globally.

Methods The American Society of Clinical Oncology convened a multidisciplinary, multinational panel of oncology, obstetrics/gynecology, public health, cancer control, epidemiology/biostatistics, health economics, behavioral/implementation science, and patient advocacy experts. The Expert Panel reviewed existing guidelines and conducted a modified ADAPTE process and a formal consensus-based process with additional experts (consensus ratings group) for one round of formal ratings.

Results Existing sets of guidelines from five guideline developers were identified and reviewed; adapted recommendations formed the evidence base. Five systematic reviews, along with cost-effectiveness analyses, provided evidence to inform the formal consensus process, which resulted in agreement of ≥ 75%.

Recommendations In all resource settings, two doses of human papillomavirus vaccine are recommended for girls age 9 to 14 years, with an interval of at least 6 months and possibly up to 12 to 15 months. Individuals with HIV positivity should receive three doses. Maximal and enhanced settings: if girls are age ≥ 15 years and received their first dose before age 15 years, they may complete the series; if no doses were received before age 15 years, three doses should be administered; in both scenarios, vaccination may be through age 26 years. Limited and basic settings: if sufficient resources remain after vaccinating girls age 9 to 14 years, girls who received one dose may receive additional doses between age 15 and 26 years. Maximal, enhanced, and limited settings: if ≥ 50% coverage in the priority female target population, sufficient resources, and cost effectiveness, boys may be vaccinated to prevent other noncervical human papillomavirus–related cancers and diseases. Basic settings: vaccinating boys is not recommended.

INTRODUCTION

The purpose of this guideline is to provide expert guidance on primary prevention of cervical cancer, via the reduction in human papillomavirus (HPV) infection by HPV vaccine administration, to clinicians, public health leaders, and policymakers in all resource settings. The target population is people at risk for HPV infection and related diseases. Cervical cancer is the most common of the severe outcomes of HPV infection. Other disease outcomes from HPV infection include genital warts, several other anogenital cancers, and oropharyngeal cancers, particularly at the base of the tongue and tonsil.1,2 This guideline focuses on the role of HPV infection in cervical cancer. Approximately 85% of incident cervical cancers occur in less developed regions, often overlapping with low- and middle-income countries (LMICs) around the world, and represent 12% of cancers among women in those regions. Eighty-seven percent of deaths resulting from cervical cancer occur in these less developed regions.3 Different regions of the world, both among and within countries, differ with respect to access to both primary and secondary prevention. As a result of these disparities, the American Society of Clinical Oncology (ASCO) Resource-Stratified Guidelines Advisory Group chose cervical cancer as a priority topic for guideline development.4,5 HPV causes virtually all cervical cancers and their immediate precursors everywhere in the world. The HPV 16 and HPV 18 subtypes are most associated with cervical cancer. It is estimated...
Primary Prevention of Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Guideline

**Guideline Question**
What is the optimal method for the primary prevention of cervical cancer?

**Target Population**
General population

**Target Audience**
Public health authorities, cancer control professionals, policymakers, obstetricians and gynecologists, pediatricians, other primary care providers, and lay public

**Recommendations**
Vaccination is the optimal strategy for primary prevention of infection by some types of human papillomavirus (HPV) that cause cervical cancer in the target population. There is no other preventive strategy for this cancer that can substitute for vaccination.

In maximal and enhanced resource settings:

For which cohorts is routine vaccination recommended in maximal and enhanced resource settings?

- **Recommendation A1a**
  Public health authorities, ministries of health, and primary care providers should routinely vaccinate girls, with the target age range being as early as possible, starting at 9 through 14 years of age (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

- **Recommendation A1b**
  Public health authorities may set the upper end of the target population higher than 14 years of age, depending on local policies and resources (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).

What numbers of doses and intervals are recommended in maximal and enhanced resource settings?

- **Recommendation A2a**
  For girls 9 to 14 years of age who are immune competent, a two-dose regimen is recommended (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

- **Recommendation A2b**
  The interval between two doses should be at least 6 months and may be up to 12 to 15 months (6 months: Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong. 12 to 15 months: Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: weak).

- **Recommendation A2c**
  Girls age ≥ 15 years at the time of the first dose or initiation (outside of target population) who receive vaccine should receive three doses (Type: informal consensus-based; Evidence quality: intermediate; Strength of recommendation: moderate).

(continued on following page)
Should catch-up for those outside the priority age groups for vaccination be offered for prevention of HPV infection in maximal and enhanced resource settings?

- **Recommendation A3**
  For females who have received one dose and are age > 14 years, public health authorities may provide additional doses or complete the series up to 26 years of age (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Should HPV vaccination of boys be recommended to reduce HPV infection in maximal and enhanced resource settings?*

- **Recommendation A4**
  For prevention of cervical cancer, if there is low vaccine coverage of the priority female target population (< 50%) in maximal or enhanced resource settings, vaccination may be extended to boys (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

For prevention of cervical cancer in maximal or enhanced resource settings where vaccine coverage of girls is ≥ 50%, vaccination of boys is not recommended (Type of recommendation: evidence based; Evidence quality: insufficient; Strength of recommendation: weak).

In limited resource settings:

For which cohorts is routine vaccination recommended in limited resource settings?

- **Recommendation B1a**
  Public health authorities, ministries of health, and primary care providers should vaccinate girls as early as possible, starting at 9 through 14 years of age (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

What numbers of doses and intervals are recommended in limited resource settings?

- **Recommendation B2a**
  For girls starting at 9 years of age who are immune competent, a two-dose regimen is recommended (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

- **Recommendation B2b**
  The interval between the doses should be at least 6 months and may be up to 12 to 15 months (6 months: Type of recommendation: evidence based; Evidence for quality: high; Strength of recommendation: strong. 12 to 15 months: Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Should catch-up for those outside the priority age groups for vaccination be offered for prevention of HPV infection in limited resource settings?

- **Recommendation B3**
  If there are sufficient resources remaining after vaccinating high-priority populations with an adequate target (minimum recommended coverage is ≥ 50% with two doses, with a target of 80%), for females who have received one dose and are age > 14 years, public health authorities may provide additional doses or complete the series up to 26 years of age (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

*(continued on following page)*
THE BOTTOM LINE (CONTINUED)

Should HPV vaccination of boys be recommended to reduce HPV infection in limited resource settings?*

- Recommendation B4
  For prevention of cervical cancer in limited resource settings where vaccine coverage of girls is ≥ 50%, vaccination of boys is not recommended.
  For prevention of cervical cancer, if there is low vaccine coverage of the priority female target population (< 50%) in limited resource settings, vaccination may be extended to boys (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

*Qualifying statement for A4 and B4. Extending vaccination to boys to prevent cervical cancer is not cost effective, unless there is low vaccine coverage of the priority female target population (< 50%). Vaccination may be extended to boys for other reasons, such to prevent other noncervical HPV-related cancers and diseases (eg, genital warts) and/or to reduce more rapidly circulating HPVs.

In basic resource settings:

For which cohorts is routine vaccination recommended in basic resource settings?

- Recommendation C1
  Public health authorities, ministries of health, and primary care providers should vaccinate girls in the priority target age group, starting as early as possible through 14 years of age (Type of recommendation: evidence based; Evidence quality: high. Strength of recommendation: strong).

What numbers of doses and intervals are recommended in basic resource settings?

- Recommendation C2a
  For girls starting at 9 years of age who are immune competent, a two-dose regimen is recommended (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

- Recommendation C2b
  The interval between the doses should be at least 6 months and may be up to 12 to 15 months (6 months: Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong. 12 to 15 months: Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Should catch-up for those outside the priority age groups for vaccination be offered for prevention of HPV infection in basic resource settings?

- Recommendation C3
  High coverage of priority populations should be emphasized. Where coverage of the primary targeted group of females is high (≥ 50%) and resources allow, the age group may be expanded upward in catch-up efforts (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Should HPV vaccination of boys be recommended to reduce HPV infection in basic resource settings?†

- Recommendation C4
  For prevention of cervical cancer in basic resource settings where vaccine coverage of girls is ≥ 50%, vaccination of boys is not recommended.
  For prevention of cervical cancer, if there is low vaccine coverage of the priority female target population (< 50%) in basic resource settings, vaccination may be extended to boys (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

(continued on following page)
that complete coverage with HPV vaccines in the female population could reduce up to 90% of cervical cancer incidence worldwide with the existing vaccines, on the basis of reported worldwide HPV genotype distribution.6-8 There are three prophylactic HPV vaccines approved and recommended in the United States, Europe, and many regions and countries; the bivalent (2vHPV; against HPV 16 and 18),9 quadrivalent (4vHPV; against HPV 6, 11, 16, and 18),10-12 and nine valent (9vHPV; against HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58).13-15 These vaccines prevent (for those who are HPV naïve) and reduce the burden of infection of HPV types that are included in the vaccines (HPV vaccine types) overall. Although there is some cross-protection inferred by the bivalent and quadrivalent vaccines for HPVs that are phylogenetically related to the vaccine HPV types (eg, 45 for 18, 31 and 33 for 1616,17), the duration of this cross-protection remains unclear. As a partial result of failures within different health care systems at levels of prevention (eg, vaccination and screening) and disease treatment and management, there are large regional
and global disparities in cervical cancer incidence and mortality.

ASCO has established a process for resource-stratified guidelines, which includes mixed methods of guideline development, adaptation of the clinical practice guidelines of other organizations, and formal expert consensus. This article summarizes the results of that process and presents the practice resource-stratified recommendations, which are based in part on expert consensus and adaptation from existing guidelines (described in Results and Appendix Table A1, online only).

In developing resource-stratified guidelines, ASCO has adopted its framework from the four-tier resource setting approach (basic, limited, enhanced, maximal; Table 1) developed by the Breast Health Global Initiative and modifications to that framework based on the Disease Control Priorities 3.18,19 ASCO uses an evidence-based approach to inform guideline recommendations.

### GUIDELINE QUESTION

This clinical practice guideline addresses the overarching clinical question: What is the optimal method for primary prevention of cervical cancer in each resource stratum?

### METHODS

These recommendations were developed by an Expert Panel with multinational and multidisciplinary representation (Appendix Table A2, online only).

<table>
<thead>
<tr>
<th>Setting</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Basic</td>
<td>Core resources or fundamental services that are absolutely necessary for any public health or primary health care system to function; basic-level services typically are applied in a single clinical interaction; vaccination is feasible for highest-need populations</td>
</tr>
<tr>
<td>Limited</td>
<td>Second-tier resources or services that are intended to produce major improvements in outcome, such as incidence and cost effectiveness, and are attainable with limited financial means and modest infrastructure; limited-level services may involve single or multiple interactions; universal public health interventions feasible for greater percentage of population than primary target group</td>
</tr>
<tr>
<td>Enhanced</td>
<td>Third-tier resources or services that are optional but important; enhanced-level resources should produce further improvement in outcome and increase the number and quality of options and individual choice (perhaps ability to track patients and links to registries)</td>
</tr>
<tr>
<td>Maximal</td>
<td>May use guidelines of high-resource settings</td>
</tr>
</tbody>
</table>

High-level or state-of-the-art resources or services that may be used or available in some high-resource countries and/or may be recommended by high-resource setting guidelines that do not adapt to resource constraints but that nonetheless should be considered a lower priority than those resources or services listed in the other categories on the basis of extreme cost and/or impracticality for broad use in a resource-limited environment

NOTE. Data adapted.18,19 To be useful, maximal-level resources typically depend on the existence and functionality of all lower-level resources.

The Expert Panel met via teleconference and in person and corresponded through e-mail. On the basis of consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and submitted to a peer-reviewed journal for editorial review and consideration for publication. This guideline was partially informed by the ASCO-modified Delphi Formal Expert Consensus methodology, according to which the Expert Panel was supplemented by additional experts recruited to rate their agreement with the drafted recommendations. The entire membership of experts is referred to as the consensus panel (the Data Supplement provides a list of members). All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee before publication. This guideline adaptation was also informed by the ADAPTE methodology20 and consensus processes used together as an alternative to de novo guideline development. Adaptation of guidelines is considered by ASCO in selected circumstances, when one or more quality guidelines from other organizations already exist on the same topic. The objective of the ADAPTE process is to take advantage of existing guidelines to enhance the efficient production, reduce duplication, and promote the local uptake of quality guideline recommendations.

Table 1. Framework of Resource Stratification: Primary Prevention
The ASCO adaptation and formal consensus processes begin with a literature search to identify candidate guidelines for adaptation. The Panel used literature searches (1966 to 2015, with additional searches for literature published in specific areas [date parameters, 2005 to 2015]), existing guidelines and expert consensus publications, some literature suggested by the Panel, and clinical experience as guides. Adapted guideline manuscripts are reviewed and approved by the ASCO Clinical Practice Guideline Committee. The review includes two parts: methodologic review and content review. The methodologic review was completed by ASCO senior guideline staff (Methodology Supplement). The content review was completed by the Expert Panel. In addition, staff reviewed the methodologies of systematic reviews with the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) instrument.

The guideline recommendations were crafted, in part, using the GLIDES (Guidelines Into Decision Support) methodology and accompanying BRIDGE-Wiz software. Detailed information about the methods used to develop this guideline is available in the Methodology and Data Supplements at www.asco.org/rs-cervical-cancer-primary-prev-guideline.

The ASCO Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update.

This is the most recent information as of the publication date. For updates and the most recent information and to submit new evidence, please visit www.asco.org/rs-cervical-cancer-primary-prev-guideline and the ASCO Guidelines Wiki (www.asco.org/guidelineswiki).

Guideline Disclaimer

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Guideline and Conflict of Interest

The Expert Panel was assembled in accordance with ASCO’s Conflict of Interest Policy Implementation for Clinical Practice Guidelines (“Policy,” found at http://www.asco.org/wc). All members of the Expert Panel completed ASCO’s disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker’s bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, a majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

As part of the systematic literature review, PubMed, Standards and Guidelines Evidence directory, Cochrane Systematic Review, and National Guideline Clearinghouse databases were searched for
guidelines, systematic reviews, and meta-analyses published between 1966 and January 2015. Inclusion criteria identified publications that were (1) on the primary prevention of cervical cancer, (2) developed by multidisciplinary content experts as part of a recognized organizational effort, and (3) published between 1966 and 2015. Searches for cost-effectiveness analyses (CEAs) were also conducted. Articles were excluded from the systematic review if they were (1) meeting abstracts or (2) books, editorials, commentaries, letters, news articles, case reports, or narrative reviews.

A total of nine guidelines and seven systematic reviews were found in the literature search, and their currency, content, and methodology were reviewed. On the basis of content and methodology reviews, the Expert Panel chose guidelines from five public health authorities or guideline developers (the WHO,24 the US Advisory Committee on Immunization Practices [as adopted by the Centers for Disease Control and Prevention (CDC)],7-9,25 the National Advisory Committee on Immunization [NACI; Canada],26 German guidelines,27 and Immunize Australia28), four systematic reviews, and one quantitative review25,29-32 on the primary prevention of HPV infection as the evidentiary basis for the guideline recommendations, along with CEAs. Appendix Table A1 lists links to the guidelines. While this ASCO guideline was nearing publication, the CDC announced a forthcoming change in recommendations regarding doses.33

This ASCO guideline reinforces selected recommendations offered in the WHO, CDC, NACI, German, and Immunize Australia guidelines and acknowledges the effort put forth by the authors and aforementioned societies to produce evidence-based and/or consensus-based guidelines informing practitioners and institutions providing primary prevention of HPV infection. The identified guidelines were published between 2014 and 2015. The Data Supplement includes an overview of these guidelines, including information on the clinical questions, target populations, development methodologies, and key evidence.

GUIDELINES ON PRIMARY PREVENTION OF HPV INFECTION

Clinical Questions and Target Populations of Guidelines Adapted by ASCO

The guidelines adapted in part by ASCO are listed in Appendix Table A1. The WHO guideline, based on the WHO Strategic Advisory Group of Experts (SAGE) systematic review, pertained to the 4vHPV and 2vHPV vaccines, with a target population of preadolescent and adolescent girls age 9 to 13 years (primary population), including those who were immunocompromised (ie, HIV positive), as well as men who have sex with men (MSM). The primary clinical question was the appropriate number of doses.24,32,34 The 2015 CDC guidelines focused on the 9vHPV vaccine, with a target population of US girls and boys age 11 or 12 years, including catch-up (ie, extending the target age range) for females age 13 to 26 years and males age 13 to 21 years who have not received or completed a vaccine series. The CDC stated that men age 22 to 26 years may also receive the vaccine. In the United States, all three vaccines are available.15 This was the highest-quality guideline found on the 9vHPV vaccine (based on AGREE II [Appraisal of Guidelines for Research and Evaluation II] assessment; Methodology Supplement). The clinical questions concerned the age of initial target populations and ages for older populations who had not previously received vaccinations. A previous CDC guideline (2014) examined the 4vHPV vaccine for males and females and included populations (including ages) similar to those in the more recent CDC guideline; its clinical question concerned the routine use of the 4vHPV vaccine for boys.11 This 2014 guideline was preceded by 2010 and 2011 recommendations for boys.12,35 Another previous CDC guideline was on the 2vHPV vaccine, for US females only, age 11 to 26 years, including primary and catch-up populations.9

The German guideline concerned the 4vHPV and 2vHPV vaccines, with a target population of girls (both 4vHPV and 2vHPV) and boys (4vHPV) starting at age 9 years. The summary was in English, and the full guideline was in German; the clinical questions were not explicitly stated in the English-language summary.27 The 2015 Canadian guideline, which was largely based on the WHO SAGE systematic review, had a target population of females and males age 9 to 26 years, as well as immunocompromised persons and MSM, and covered the 4vHPV and 2vHPV vaccines.26 The clinical questions regarded schedule, number of doses, and boosters. The 2016 Australian guideline population included males, females, MSM, and immunocompromised persons. The clinical questions were not available; however, the guideline target population was girls and boys age 12 to 13 years.28
Summary of Guidelines Adapted by ASCO: Development Methodologies and Key Evidence

The WHO SAGE methods included systematic and nonsystematic reviews of published and gray literature and critical appraisal with GRADE (Grading of Recommendations Assessment, Development and Evaluation). This guideline received a rating of 82% on the AGREE II (Methodology Supplement). The most important evidence underlying recommendations on the number of doses came from the WHO SAGE systematic review, which included not only randomized clinical trials (RCTs) but also observational studies and publications from the gray literature (defined as preserved and collected but non–peer-reviewed unpublished literature).36,32

The primary systematic review examined studies that compared two versus three doses of 2vHPV and 4vHPV vaccines and found randomized evidence from four RCTs (two on 2vHPV and two on 4vHPV; one was later reclassified as a cohort study; Appendix Table A3, online only)37; participants were girls age 9 to 18 years (the trials were referred to as Canada1 BCGov01,38-41 Canada/German1 HPV-048,42-45 Europe [ClinicalTrials.gov identifier: NCT00552279; Esposito et al46], and India [ClinicalTrials.gov identifier: NCT00923702]; since the SAGE review, the India study was published in a peer-reviewed journal that stated the authors reanalyzed the results as an observational cohort study).37,47 There were also four nonrandomized comparisons within RCTs and nonrandomized comparative studies (Canada1,38-41 Canada.Germany1,42-45墨西哥,48 and multinational44,45,49; Table 2 in WHO SAGE Appendix 132), plus other noncomparative, nonrandomized data. The primary outcomes were immunologic, although SAGE also looked at clinical outcomes if studies reported them. All guidelines except the WHO and NACI guidelines presumed the target intervention included three doses of the vaccines.

The Canadian NACI conducted a literature search to update the WHO SAGE literature search and found three observational studies. Otherwise, the NACI guideline used the WHO SAGE evidence base to support its clinical practice guideline, which received 64% on the AGREE II (Methodology Supplement). Its methodology included a committee vote on the NACI recommendations.

CDC guidelines are based on systematic reviews. The CDC adopted the GRADE methodology for critical appraisal of evidence in 2011 and first used it for its guidelines on HPV vaccination for males. Key evidence included clinical trial data (prelicensure, including RCTs, immunogenicity, and immunobridging studies) and cost-effectiveness modeling data. The 2014 recommendations on 4vHPV were based on four RCTs on efficacy and safety guidance from seven clinical trials. The AGREE scores for the CDC 2010 to 2015 guidelines ranged from 42% to 52% (Methodology Supplement).

The German guideline used mixed methods, including evidence based, clinical (informal) consensus, clinical experience, and formal consensus in a nominal group process. This guideline received a rating of 52% on AGREE II. The evidence base primarily came from 28 studies. The Immunize Australia guideline recommendations were based on methods involving an evidence base, expert review, and public comment. The guideline refers to using the highest-quality evidence available and other guidelines. The AGREE score was 54% (Methodology Supplement).

Results

The outcomes or endpoints in most studies reviewed by the guidelines included immunogenicity, HPV infection, cervical intraepithelial neoplasia (CIN; cervical cancer precursor lesions), and safety.

Results of ASCO Methodologic Review

The methodologic review of the guidelines was completed by two ASCO guideline staff members using the Rigour of Development subscale of the AGREE II instrument. The score for the Rigour of Development domain is calculated by summing the scores across individual items in the domain and standardizing the total score as a proportion of the maximum possible score. Detailed results of the scoring and the AGREE II assessment process for this guideline are available in the Methodology Supplement.

Final Recommendations

The recommendations were developed by a multinational, multidisciplinary group of experts using evidence from existing guidelines and clinical experience as a guide. The ASCO Expert Panel underscores that health care practitioners who implement the recommendations presented in this guideline should first identify the available resources in their local and referral facilities and endeavor to provide the highest level of care possible with those resources.
Maximal and Enhanced Resource Settings

These recommendations were modified from the following guidelines: WHO, CDC, and Canadian guidelines.

For which cohorts is routine vaccination recommended in maximal and enhanced resource settings?

Recommendation A1a. Public health authorities, ministries of health, and primary care providers should routinely vaccinate girls, with the target age range being as early as possible, starting at 9 through 14 years of age (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation A1b. Public health authorities may set the upper end of the target population higher than 14 years of age, depending on local policies and resources (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).

What numbers of doses and intervals are recommended in maximal and enhanced resource settings?

Recommendation A2a. For girls 9 to 14 years of age who are immune competent, a two-dose regimen is recommended (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation A2b. The interval between two doses should be at least 6 months and may be up to 12 to 15 months (6 months: Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong. 12 to 15 months: Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: weak).

Recommendation A2c. Girls age ≥ 15 years at the time of the first dose or initiation (outside of target population) who receive vaccine should receive three doses (Type: informal consensus based; Evidence quality: intermediate; Strength of recommendation: moderate).

Source guidelines and discussion. Vaccination is the optimal strategy for primary prevention for the majority of HPV genotypes that cause cervical cancer in the target population. There is no other preventive strategy that can substitute for vaccination. Vaccination does not protect against all oncogenic HPV types. In trial conditions, the 9vHPV vaccine showed > 96% efficacy in the reduction of persistent infection and cervical, vaginal, and vulvar precursor or preneoplastic lesions for the five additional types included in the vaccine (ie, 31, 33, 45, 52, and 58).15 Protection from infection is improved with higher vaccination coverage.

The lower end of the age range (9 years) is supported by the WHO, CDC (on 9vHPV), German, and Canadian guidelines and by licensure by regulatory authorities (eg, European Medicines Agency [EMA]); this is based on immunogenicity data for girls and boys from age 9 years onward. The upper end of the age range recommendation is based on the WHO position paper34 and the NACI Canadian guidelines.26 In some countries, the upper end ranges from 15 to 16 years.

The RCTs establishing the benefit of vaccination were conducted with three doses. Subsequently, research has investigated the use of two doses with immunogenicity end points. The most important evidence underlying recommendations on the number of doses came from the WHO SAGE systematic review, as described in Summary of Guidelines Adapted by ASCO. The NACI guideline agrees with the WHO recommendations. The data should be evaluated in the future when there is > 4 years of follow-up. There are now data with end points of immunogenicity for 9vHPV (unpublished data). The EMA has stated that 9vHPV can be administered on a two-dose schedule for boys and girls age 9 to 14 years.13

In most clinical trials and guidelines, the interval between the first and second vaccine doses was 6 to 12 months.24,34 The maximum interval between two doses that is still effective is not known. Research comparing the upper end of the interval of 12 months with other intervals has not been conclusive and is ongoing (eg, ClinicalTrials.gov identifier: NCT02568566). A WHO position paper suggested an interval of no greater than 12 to 15 months so that girls complete all doses before they are sexually active, noting that they do not recommend a maximum interval.34(p489)
Although this guideline specifically regards cervical cancer, there is also an additional benefit of HPV vaccination in preventing other HPV-related cancers, such as other anogenital and potentially oropharyngeal cancers. This guideline does not make recommendations or review evidence regarding these other cancers.

The source guidelines reviewed safety data, and this subject is discussed in detail in Special Topic C. The ASCO Expert Panel also endorses the recently published International Papillomavirus Society statement on the safety of the vaccines.

Should catch-up for those outside the priority age groups for vaccination be offered for prevention of HPV infection in maximal and enhanced resource settings?

Recommendation A3. For females who have received one dose and are age > 14 years, public health authorities may provide additional doses or complete the series up to 26 years of age (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Source guidelines and discussion. The purpose of catch-up strategies is to address the temporary situation in which some persons are older than the priority target populations. Vaccination up to age 26 years is supported by all three CDC guidelines reviewed, the 2015 Canadian guideline, and evidence reviewed by the WHO. In addition to evidence discussed in these guidelines, Couto et al conducted a high-quality meta-analysis of trials published before October 2012, including 13 RCTs, on catch-up vaccination for women age ≥ 16 years, without language restrictions. Included studies were conducted in the United States, Canada, South America, Europe, and Asia and compared the vaccine with placebo or no vaccine. Although the systematic review looked for studies with a variety of outcomes, there were limited data of the effect of vaccination on mortality. For HPV-associated CIN grade ≥ 2 (CIN2+), the pooled risk ratio (RR) was 0.80 (95% CI, 0.62 to 1.02). For HPV-related CIN, the intention-to-treat pooled RR was 0.54 (95% CI, 0.44 to 0.67). All RRs are based on 4 years of follow-up. The RR for pooled outcomes of adverse events was 0.99 (95% CI, 0.91 to 1.08). (This systematic review received a 9.5 AMSTAR rating.)

Increasing the upper age limit of the cohort in which catch-up vaccination is implemented should be based on relative cost effectiveness from high-quality CEAs for each setting or region. CEAs should include (1) an incremental cost-effectiveness ratio (ICER) analysis that is practicable to apply according to the resource setting of a country and (2) at least a two-way sensitivity analysis to include paramount parameters that may act as cost drivers in the model used in references. The CHEERS checklist provides parameters for such criteria.

Should HPV vaccination of boys be recommended to reduce HPV infection in maximal and enhanced resource settings?

Recommendation A4. For prevention of cervical cancer, if there is low vaccine coverage of the priority female target population (< 50%) in maximal or enhanced resource settings, vaccination may be extended to boys (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

For prevention of cervical cancer in maximal or enhanced resource settings where vaccine coverage of girls is ≥ 50%, there are insufficient data to recommend for or against vaccination of boys (Type of recommendation: evidence based; Evidence quality: insufficient; Strength of recommendation: weak).

Qualifying statement. Extending vaccination to boys to prevent cervical cancer is not cost effective, unless there is low vaccine coverage of the priority female target population (< 50%). Vaccination may be extended to boys for other reasons, such as to prevent other noncervical HPV-related cancers and diseases (eg, genital warts) and/or to reduce more rapidly circulating HPVs.

Source guidelines and discussion. The scope of this guideline extends only to the prevention of cervical cancer; it does not review literature on the prevention of other cancers (eg, oropharyngeal cancer and/or other HPV-related cancers in males). In current practice in the United States, the CDC recommends vaccinating boys starting at 11 or 12 years of age with 4vHPV or 9vHPV. If boys are vaccinated, the age could be as young as 9 years; guidelines vary with regard to the earliest starting age, because they consider noncervical cancers as well as cervical cancer. In addition, the German, Canadian, and Australian guidelines also support vaccinating boys in maximal settings, with the 4vHPV vaccine (the CDC recommends 9vHPV).

There can be direct benefit in vaccinating male recipients with regard to prevention of male cancer and benefits to female populations by lowering the incidence of HPV-related cervical cancer via herd
protection, depending on the coverage level for girls, although it would be less cost effective than increasing vaccine coverage of girls. Predictive models suggest that when coverage in girls is low, including boys might add some benefit to cervical cancer prevention. However, this benefit will be lower than that achieved with increasing girls’ coverage to 80%. A recent meta-analysis of model-predicted outputs from 16 independent transmission models, all representing developed countries, reaffirmed previous findings that there is greater impact by increasing coverage in girls than extending coverage to boys and that the health benefit and cost effectiveness of including boys are maximized when vaccination coverage in girls is low. If the coverage in girls has reached 50%, the benefit of adding boys is marginal for cervical cancer prevention (based on CEAs), and the benefit may only apply to reducing the risk of noncervical cancers. Of note, CEAs have been based on theoretic or market prices of the vaccine and not in real government-paid prices. Thus, the benefit of vaccinating boys may be larger than previously estimated. For the goal of reducing cervical cancer, the priority should be providing vaccination to the maximum portion of the target population of girls.

In the opinion of the ASCO Expert Panel, if public health authorities have sufficient resources to devote to the prevention of less common HPV-related cancers other than cervical cancer, the HPV vaccine may be offered to boys. The number of doses would follow the age-related recommendations for females in this guideline.

**Limited Resource Settings**

The recommendations for the limited resource setting concerning age cohort and number of doses are the same as those for the higher-resourced settings.

**For which cohorts is routine vaccination recommended in limited resource settings?**

**Recommendation B1a.** Public health authorities, ministries of health, and primary care providers should vaccinate girls as early as possible, starting at 9 through 14 years of age (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of Doses in Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-14 (target completion before 15th birthday)</td>
<td>2</td>
</tr>
<tr>
<td>15-26 (catch-up)</td>
<td>3 (if first dose after 14; if first dose before 15, can complete through age 26 years)</td>
</tr>
</tbody>
</table>

**What numbers of doses and intervals are recommended in limited resource settings?**

**Recommendation B2a.** For girls starting at 9 years of age who are immune competent, a two-dose regimen is recommended (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

**Recommendation B2b.** The interval between the doses should be at least 6 months and may be up to 12 to 15 months (6 months: Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong. 12 to 15 months: Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).

**Should catch-up for those outside the priority age groups for vaccination be offered for the prevention of HPV infection in limited resource settings?**

**Recommendation B3.** If there are sufficient resources remaining after vaccinating high-priority populations with an adequate target (minimum recommended coverage is ≥ 50% with two doses, with a target of 80%), for females who have received one dose and are age > 14 years, public health authorities may provide additional doses or complete the series up to 26 years of age (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

**Should HPV vaccination of boys be recommended to reduce HPV infection in limited resource settings?**

**Recommendation B4.** For prevention of cervical cancer in limited resource settings where vaccine coverage of girls is ≥ 50%, vaccination of boys is not recommended. For prevention of cervical cancer, if there is low vaccine coverage of the priority female target population (< 50%) in limited resource settings, vaccination may be extended to boys (Type of recommendation: evidence based; Evidence quality: intermediate. Strength of recommendation: moderate).

**Qualifying statement.** Extending vaccination to boys to prevent cervical cancer is not cost effective, unless there is low vaccine coverage of the priority female target population (< 50%). Vaccination may be extended to boys for other reasons, such as to prevent other noncervical HPV-related cancers and diseases (eg, genital warts) and/or to reduce more rapidly circulating HPV.
**Source guidelines and discussion.** These recommendations follow the WHO guideline. The ages for boys in limited resource settings should be the same as those for girls in limited resource settings. The exceptions to these recommendations and contraindications are listed in the product specifications and may be affected by lack of resources to deliver the vaccine appropriately (eg, equipment, cold chain, and so on). High coverage of priority target populations should be emphasized, taking into account any relevant sociocultural factors. If there are more resources than are typically found in limited resource settings, the age group of females offered vaccines may be expanded. There is some evidence on the efficacy of vaccination in boys to prevent cervical cancer; however, CEAs are contradictory, and most CEAs conducted in LMICs have found vaccinating boys has only a marginal benefit over vaccinating girls with regard to reducing the risk of cervical cancer, and therefore, reaching female populations should be the priority. Specific CEA publications related to the issue of vaccination of males are discussed in this guideline, in Further Discussion and in Cost Implications.

**Basic Resource Settings**

Recommendations for the basic resource setting are modified from the WHO guideline.

**For which cohorts is routine vaccination recommended in basic resource settings?**

**Recommendation C1.** Public health authorities, ministries of health, and primary care providers should vaccinate girls in the priority target age group, starting as early as possible through 14 years of age (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

**What numbers of doses and intervals are recommended in basic resource settings?**

**Recommendation C2a.** For girls starting at 9 years of age who are immune competent, a two-dose regimen is recommended (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

**Recommendation C2b.** The interval between the doses should be at least 6 months and may be up to 12 to 15 months (6 months: Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong; 12 to 15 months: Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).

**Should catch-up for those outside the priority age groups for vaccination be offered for prevention of HPV infection in basic resource settings?**

**Recommendation C3.** High coverage of priority populations should be emphasized. Where coverage of the primary targeted group of females is high (>50%) and resources allow, the age group may be expanded upward in catch-up efforts (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

**Should HPV vaccination of boys be recommended to reduce HPV infection in basic resource settings?**

**Recommendation C4.** For prevention of cervical cancer in basic resource settings where vaccine coverage of girls is ≥50%, vaccination of boys is not recommended.

For prevention of cervical cancer, if there is low vaccine coverage of the priority female target population (<50%) in basic resource settings, vaccination may be extended to boys (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

**Qualifying statement.** Extending vaccination to boys to prevent cervical cancer is not cost-effective, unless there is low vaccine coverage of the priority female target population (<50%). However, if resources allow for efforts to reduce non-cervical cancers and diseases and/or reduce more rapidly circulating HPVs, vaccination may be extended to boys.

**Source guidelines and discussion.** Recommendations for basic resource settings are based on the WHO guideline. In these settings, girls’ HIV status may be unknown at the age of vaccination. Therefore, authorities providing vaccine to girls with unknown HIV status should follow the age-related recommendation. The highest priority is to have high coverage of young girls. If the country or region has a certain amount of resources, these should be devoted first to increasing coverage of girls. Decisions regarding boys depend on prevalence, coverage, resources, and CEAs. In addition, sociocultural issues in some settings may affect policy decision making. Providing catch-up vaccination should not be performed at the expense of achieving high coverage in the recommended priority cohort. Therefore, only if priority populations are vaccinated with sufficient coverage (ie, >50% with a target of 80%) and additional resources remain should authorities offer catch-up.
Further Discussion on Vaccinating Boys (all settings)

Source guidelines and discussion. Vaccine coverage is essential to reducing HPV prevalence (circulating HPVs) in the target populations. In basic and limited settings, the highest priority is to have high coverage of girls while still promoting safe sex to reduce transmission of the virus to non-vaccinated girls. Resources should be devoted to reach >80% coverage of girls. In higher-resource settings, the extension and purposes of vaccinating boys should depend on the coverage level of the primary target population. If there is low coverage of girls (<50%), vaccination may be extended to boys. If there is high coverage of girls, the recommendation is not to vaccinate boys, except in maximal and enhanced settings, where male vaccination may be offered to prevent other noncervical HPV-related cancers and diseases.

Vaccinating boys can also reduce the viral pool and may contribute to reducing the spread of HPV infections in the population. Thus, vaccination of boys may consequently reduce the overall burden of cervical cancer, as well as other HPV-related diseases, in the female population. However, modeling suggests this benefit is quite limited once a moderate level of coverage among girls has been achieved (C. Wheeler and V. Tsu, personal communication, August 2016). In addition, boys and young men can themselves benefit from the prevention of HPV-related infections and disease (e.g., reduction of genital warts and male anogenital cancers). As mentioned, reviewing the benefits of HPV vaccines for outcomes in diseases other than cervical cancer was outside the scope of this guideline.

Performing a CEA is advisable to determine whether a particular resource setting may be able to extend HPV vaccination to boys. CEAs need to take into account the comments presented in this guideline; that is, duration of protection becomes less important as vaccinated cohorts move into the initial decade of sexual activity, because transmission is blocked if enough individuals are immune, and there is not a reservoir of infectious virus in the population, providing males and females are vaccinated. For example, a recent systematic review of CEAs (building on three other systematic reviews of CEAs) found vaccinating males was not cost effective for the prevention of cervical cancer in higher-income countries.\textsuperscript{29} It was only cost effective if other HPV-related diseases were included in analyses, which might still be the case in many developing countries. The overall societal impact may occur not only in cervical cancer, because many other diseases and cancers are also highly attributable to HPV. This systematic review included studies that reported ICERs in developed countries,\textsuperscript{29} all with three-dose series. The comparators were primarily female-only vaccination strategies. Outcomes included cervical cancer only, cervical cancer and genital warts, all HPV-related diseases, and anal cancer and/or genital warts for MSM. End points used for comparison were ICERs representing quality-adjusted life-years (QALYs). Seventeen studies were reviewed, including one on MSM, which found a value of $17,970 per QALY gained (for anal and genital outcomes) as a result of vaccinating males at 12 years of age. For cervical cancer only, vaccinating both sexes resulted in $28,713 to $554,317 per QALY gained.\textsuperscript{29} Higher ICERs obtained for both sexes might still be acceptable if HPV-related diseases are prevalent in a country, whereby the burden of HPV-related disease management would definitely be higher than the cost of primary prevention achieved by vaccinating both sexes.

Special Populations

These recommendations are modified from the WHO and Canadian guidelines.

What vaccination strategy is recommended for women who are HIV positive or immunosuppressed for other reasons (all resource settings)?

Recommendation D. Females who are HIV positive or immunosuppressed for other reasons should follow the same age recommendations but should receive three doses (Type of recommendation: evidence based; Evidence quality: insufficient; Strength of recommendation: weak).

Source guidelines and discussion. This recommendation is based on the WHO guideline and also agrees with the Canadian and Australian guidelines. A two-dose scheme is not recommended in this population, because of insufficient data on immunogenicity. If girls’ HIV status is unknown, authorities should provide vaccine to girls following the age-related recommendation for the basic setting. Data on the safety of a three-dose schedule in HIV-positive females and males and in HIV-infected children age 7 to 12 years showed no evidence of harm.\textsuperscript{34} Most importantly, girls in this population should receive antiretroviral treatment of HIV.

What vaccination strategy is recommended for women who are pregnant (all resource settings)?

Recommendation E. HPV vaccination is not recommended for pregnant women (Type of
recommendation: evidence based; Evidence quality: insufficient; Strength of recommendation: weak).

Source guidelines and discussion. This recommendation is based on the WHO and Immunize Australia guidelines. HPV vaccination is not recommended during pregnancy, because of lack of sufficient evidence of safety; however, there is no evidence of harm.54,55 It is not necessary to perform a pregnancy test before vaccination or to terminate a pregnancy subsequent to vaccination. Women who have received one or two doses should receive the second and/or third dose at the completion of the pregnancy. There is no need to restart the complete vaccination program.

What vaccination strategy is recommended for women receiving treatment for cervical cancer precursor lesions (CIN2+; eg, conization, loop electrosurgical excision procedure, or cryotherapy; all resource settings)?

Recommendation F. No recommendation (insufficient data).

Discussion. There are insufficient data to recommend that women in this population be offered vaccination or not based on their history of HPV infection and/or treatment of cervical cancer precursor lesions. Reports in women who had received HPV vaccines before or after excisional treatment of high-grade cervical disease have shown mixed results, with some studies demonstrating no effect.56-58 In the absence of consistent and persuasive evidence that women with a history of HPV-related abnormalities have any risk for future new infection that is different from women of a similar age, HPV vaccination should be offered according to the age- and resource-related recommendations as given in this guideline. HPV status, including HPV testing or history of HPV-related abnormalities (eg, abnormal cytology results or cervical biopsies), is not part of the decision making for offering HPV vaccine. The likelihood of infection with HPV 16 or 18 increases with the severity of cervical abnormality, and the overall benefit of vaccination would decrease. Women should be advised that results from clinical trials do not indicate the vaccine will have any therapeutic effect on existing HPV infection or cervical lesions.10 Women who receive treatment for precursor lesions and their physicians should follow routine post-treatment follow-up recommendations.4,5,59,60

An article published after the guidelines were adapted presented results from a randomized trial of the bivalent vaccine; some participants had HPV infections, but there were no differences in infection outcomes or efficacy.61,62 Other articles that did not meet the inclusion criteria included a retrospective case-control study of a patient who had undergone loop electrosurgical excision procedure.63 A greater percentage of nonvaccinated women had recurrences of CIN grade 2 to 3, and a multivariate analysis showed a lack of vaccination was prognostic for recurrence. Finally, a nonprespecified and retrospective analysis of results from the double-blind, placebo-controlled RCTs FUTURE I and II54 included women who had been enrolled in the trials without screening and regardless of HPV infection status. There was a statistically significant decreased risk of cervical disease (after previous treatment for cervical disease). Overall, the results of studies of women treated for precursor lesions were negative, were retrospective, included small numbers of patient cases, and/or showed mixed results. Larger, prospective studies would be needed before the Panel discusses making a recommendation for this population.

SPECIAL COMMENTARY

Topic A

In vaccinated cohorts, what is recommended for secondary prevention in terms of cost-effectiveness ratios for the combined strategies?

Vaccination does not replace screening. Until additional data are gathered, vaccinated cohorts will need to be screened. The testing algorithm and interval between screening tests are still under evaluation in many countries. It is likely that the initial change for screening of vaccinated women will be to increase the age at which screening is initiated. Screening after vaccination is discussed in detail in the ASCO Screening Resource-Stratified Guideline.5

Topic B

Is there a need to have a registration system (ie, enrollment, refusal, or surveillance of potential adverse effects) to evaluate the impact and coverage of the strategies?

There is a need for monitoring the implementation of vaccines in terms of coverage and outcomes detected by screening and cancer registries. Strengthened systems for monitoring immunization adverse events are essential for tracking potential adverse effects, especially rare or late-occurring events. The rationale for screening and cancer registries is the need for data over
time to track longer-term outcomes, especially cervical cancer outcomes, and the duration of immunity and protection. Surveillance with linkage of screening and vaccination information should occur to inform the safe, effective, and rational integration of these two complementary prevention strategies. In basic and limited resource settings, public health providers need to document the percentage of eligible girls and boys vaccinated. All countries or regions should have basic coverage data documenting the percentage of eligible girls and boys vaccinated. As countries and regions introduce HPV vaccination, they need to update the WHO Expanded Programme on Immunization, with recording of doses administered and collection of reported adverse events. In limited resource settings, policymakers and public health authorities need to move toward population-based cancer registries for at least one region in the country. In enhanced resource settings, policymakers and public health authorities should implement a surveillance system to monitor HPV infections and HPV-related precancers. In countries with more resources, policymakers and public health authorities should implement countrywide, regional, and state surveillance systems. Surveillance systems can rule out false associations and identify rare adverse events in the postvaccine licensure period.57

Several entities conduct routine adverse event reporting, including VAERS, the EMA, Japan, and others.

- After monitoring reports to VAERS, the CDC and US Food and Drug Administration analyzed reports of serious adverse events and deaths, as well as postmarketing data, and found no causal link to HPV4 vaccination.11 The Morbidity and Mortality Weekly Report also refers to other analyses of adverse event reporting, including those from Denmark, Sweden, and France, and reports there have been no findings of any causal link between 4vHPV vaccination and autoimmune, venous thromboembolic, neurologic, or other conditions.
- The EMA reviewed publications, clinical trial data, postmarketing data, and reports and found no evidence that HPV vaccines may cause complex regional pain syndrome or postural orthostatic tachycardia syndrome. There is no evidence of higher incidence of these syndromes among vaccinated or unvaccinated girls.65,66
- The WHO Global Advisory Committee for Vaccine Safety reviewed safety data, most recently in December 2015, and found no safety signals warranting changes in WHO recommendations.58
- The International Papillomavirus Society assessed reviews by the WHO, US Food and Drug Administration, CDC, EMA, International Federation of Gynecology and Obstetrics, UK Medicines & Healthcare Products Regulatory Agency, and Australian Therapeutic Goods Administration and other publications and concluded that there is no evidence that neurologic disease, autoimmune diseases, or deaths are vaccine attributable and emphasized there have been no deaths associated with HPV vaccines.50

**Topic C: Safety**

The safety profile of HPV vaccines has been assessed extensively in RCTs and by robust pharmacovigilance in the postlicensure setting using both passive and active vaccine surveillance. Passive surveillance is the voluntary reporting in daily practice by vaccinated persons (or others) and medical professionals to manufacturers and national surveillance systems, such as the US Vaccine Adverse Event Reporting System (VAERS) and the Australian Therapeutic Goods Administration databases or multinational databases, such as the WHO Global Individual Case Safety Reports Database System and the Scientific and Technical Evaluation of Vaccinational Programs in the European Union. Active surveillance is the implementation of systematic procedures to actively seek and identify clinically significant events that occur within a defined period and/or population and include large postlicensure studies sponsored by the manufacturer or national regulatory authorities. As with all serious vaccine adverse events, it is important that appropriate investigations be carried out promptly to determine whether the event is caused by the vaccine and whether any remedial action is needed. The key challenge faced in pharmacovigilance is to distinguish real adverse events from background conditions that would occur regardless of vaccination. Population-based data on incidence of potential adverse events before vaccination allow analysis of observed and expected rates in vaccinated populations.56,57

- After monitoring reports to VAERS, the CDC and US Food and Drug Administration analyzed reports of serious adverse events and deaths, as well as postmarketing data, and found no causal link to HPV4 vaccination. The Morbidity and Mortality Weekly Report also refers to other analyses of adverse event reporting, including those from Denmark, Sweden, and France, and reports there have been no findings of any causal link between 4vHPV vaccination and autoimmune, venous thromboembolic, neurologic, or other conditions.
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This guideline agrees with the International Papillomavirus Society policy statement on the safety of HPV vaccines.

**Topic D: Children and Adolescents With History of Sexual Abuse**

Offering HPV vaccine in an age-appropriate manner to children and adolescents with a history of sexual abuse is recommended by the CDC, and this population may receive vaccines according to the age- and resource-stratified recommendations in this guideline. There has been a special concern about vaccinating children and adolescents with a history of sexual abuse, given that they may be at higher risk for HPV infection as a result of the cervical, vaginal, or anal trauma associated with forced penetration. The CDC includes this population in its 2016 Immunization Schedules for three doses starting at 9 years of age: “administer HPV vaccine beginning at age 9 years to children and youth with any history of sexual abuse or assault who have not initiated or completed the 3-dose series.”67(p1407) This subject is also discussed in a review by Garland et al.68 Given the strong evidence in support of vaccinating girls as young as age 9 years across all resource settings (basic to maximal and enhanced), girls with a history of sexual abuse would be covered without the need to directly associate vaccination with history of abuse. With regard to vaccinating boys with a history of sexual abuse, the evidence is less clear but is consistent with the overall recommendation that if resources allow, boys with a history of sexual abuse should be vaccinated as young as age 9 years.

**UPTAKE**

ASCO published “American Society of Clinical Oncology Statement: Human Papillomavirus Vaccination for Cancer Prevention” in April 2016,69 which includes specific literature-informed recommendations to promote HPV vaccination. It has been well established that health care provider recommendation is the strongest predictor of HPV vaccination.70-73 Primary care providers and pediatricians are in a unique position to promote HPV vaccination, given their longstanding relationship with their child and adolescent patients and their parents. Once informed and educated about the importance of HPV vaccination by a trusted source (usually their children’s health care provider), parents are more likely to vaccinate their children. Therefore, at all levels (basic through maximal), education of primary care physicians and pediatricians about the cancer-preventive properties of HPV vaccination and its safety could provide the highest return on investment in cervical cancer primary prevention. Secondary strategies to promote uptake, particularly in settings where cost is not the primary barrier, include reminders (for providers and parents); promotion of HPV vaccination with other vaccines (eg, Tdap); and dissemination of consistent evidence-based, culturally relevant messages among parents, agents of change (eg, teachers or pastors), and providers, particularly with regard to the effectiveness and safety of the vaccine in preventing HPV-related cancers.69,74,75 Furthermore, it has been shown that active vaccination policies at the country level are an important policy-level strategy. Mortensen et al76 found that in countries with active vaccination policies (United Kingdom and Italy), parents tended to trust the national vaccination programs, whereas in countries with passive vaccination strategies (Germany and France), parents needed greater assurance from health care providers and public health workers.

**COST IMPLICATIONS**

In low-resource settings, cost remains the primary barrier to HPV vaccination. Currently, the lowest pricing ($4.50) is available to countries receiving support from the Global Alliance for Vaccines and Immunization, with 54 countries eligible as of early 2016.77 There are many published CEAs on HPV vaccines. An ASCO literature search focusing on high-quality systematic reviews of published CEAs was conducted. Among systematic reviews found was a 2013 review by Fesenfeld et al30 of CEAs specifically on vaccination and focusing on LMICs. Twenty-five studies were found. The authors comment that delivery and program costs are an important part of total cost, and one group of CEAs found these costs formed an estimated 40% of the cost per girl (assuming the vaccine cost per dose was the international dollar 10 to 25). All but one study of girls found vaccination would be cost effective in most cases. Vaccination is usually second in line of cost effectiveness after routine screening, but this needs high coverage of the female population. Many countries are not able to implement an effective call–recall system for screening as a result of limited resources and logistic barriers. Findings of studies in boys were contradictory. The authors state that if results are pooled, the price relative to the income of a country spent on health is an important factor, unless regions are able to obtain support from donors (usually through a successful public–private partnership) to implement mass vaccination.
Kiatponsan et al78 published a CEA after Fesenfeld et al30 on two countries in east Africa. It was specific to 9vHPV and used a static natural history disease simulation model. It compared the cost effectiveness of 9vHPV with 2vHPV or 4vHPV for a population of females starting at 9 years of age and included some societal costs. In one country, the ICER for 9vHPV was below per-capita gross domestic product compared with existing vaccines. This showed that the strategy is cost effective.

For maximal resource settings, Armstrong31 published a review of CEAs with US-based models published before February 22, 2010. Eleven studies were included. All the studies included screening as a comparator, unlike in the report by Fesenfeld et al.30 Three of the studies included boys. Model types and assumptions varied, but all found HPV vaccination of girls versus screening alone is cost effective (ICER < $100,000 per QALY gained), especially if the interval was > 1 year.

CEAs support the recommendations in this guideline for, at minimum, vaccination of girls age 9 to 14 years. In the near future, screening will have to accompany vaccination.

LIMITATIONS OF RESEARCH AND FUTURE DIRECTIONS

There were limitations to the evidence informing some of the recommendations, resulting in part from the relatively recent introduction of the vaccine. There were limited published data on

- The impact on invasive cervical cancer outcomes
- The upper age range for the priority target population of girls starting at 9 years of age
- The optimal upper end of the interval (which starts at 6 months)
- Two versus three doses of 9vHPV
- CEAs of vaccinating boys in limited and basic settings
- Pregnant women
- Women who have or are receiving treatment for CIN2+
- Vaccination of women age ≥ 26 years
- Effectiveness studies on two doses for women who are HIV positive or immunosuppressed

Therefore, the Expert Panel suggests research be conducted on these topics. ASCO believes that cancer and cancer prevention clinical trials are vital to inform medical decisions and improve cancer care. All patients should have the opportunity to participate.

ADDITIONAL RESOURCES

Additional information, including data supplements, evidence tables, and clinical tools and resources, can be found at www.asco.org/rs-cervical-cancer-primary-prev-guideline and www.asco.org/guidelineswiki. Patient information is available there and at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

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Published online on jgo.org on March 17, 2017.
systems, which may include data supplements, slide sets, patient versions, frequently asked questions, and clinical tools and resources, are available at www.asco.org/rs-cervical-cancer-primary-prev.

ACKNOWLEDGMENT

We thank Jean Rene Clemenceau, MD, Noelle LoConte, MD, William Tew, MD, Muhieddine Seoud, MD, the Consensus Ratings Panel, and the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines Committee for their thoughtful reviews of and insightful comments on this guideline document and Shannon McKernin for her assistance on the manuscript and derivatives. The Expert Panel and ASCO staff dedicates this guideline to the memory of Xavier Castellsagué, our dearly departed colleague and Expert Panel member.

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Table A1. Adapted Guidelines and Links

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<th>Guideline</th>
<th>Link</th>
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Abbreviations: ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; NACI, National Advisory Committee on Immunization.

**Table A3.** SAGE Review of Two- Versus Three-Dose RCTs

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<tr>
<th>Study</th>
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<th>4vHPV</th>
<th>2vHPV</th>
<th>Reported GMCs</th>
<th>Reported Seroconversion or Positivity</th>
<th>Reported Clinical Outcomes</th>
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<td>India</td>
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<td>Europe</td>
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<td>X</td>
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<td></td>
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NOTE. Data adapted.32

Abbreviations: 2vHPV, bivalent human papillomavirus vaccine; 4vHPV, quadrivalent human papillomavirus vaccine; GMC, geometric mean concentration; RCT, randomized controlled trial; SAGE, Standards and Guidelines Evidence.

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**Table A2.** Expert Panel Membership

<table>
<thead>
<tr>
<th>Member</th>
<th>Affiliation</th>
<th>Expertise</th>
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</thead>
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<tr>
<td>Silvina Arrossi, PhD (co-chair, writing subcommittee)</td>
<td>NCI, Buenos Aires, Argentina</td>
<td>Demography/public health</td>
</tr>
<tr>
<td>Silvia de Sanjose, MD, MPH, PhD (co-chair, writing subcommittee)</td>
<td>Institut Català d’Oncologia, Barcelona, Spain</td>
<td>Epidemiology</td>
</tr>
<tr>
<td>Isaac Folorunso Adewole, MBBS, FMCOG</td>
<td>Ministry of Health, Abuja, Nigeria</td>
<td>Obstetrics/gynecology, gynecologic oncology</td>
</tr>
<tr>
<td>Neerja Bhatia, MD</td>
<td>All India Institute of Medical Sciences, New Delhi, India</td>
<td>Obstetrics/gynecology</td>
</tr>
<tr>
<td>Xavier Castellsague, MD, MPH, PhD (deceased)</td>
<td>Institut Català d’Oncologia, L’Hospitalet de Llobregat, Spain</td>
<td>Epidemiology</td>
</tr>
<tr>
<td>Linda O’Neal Eckert, MD (writing subcommittee)</td>
<td>University of Washington, Seattle, WA</td>
<td>Obstetrics/gynecology, ACOG representative</td>
</tr>
<tr>
<td>Sharifa Ezat, MD, MPH, PhD</td>
<td>Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia</td>
<td>Health economics</td>
</tr>
<tr>
<td>Tamika Felder</td>
<td>Cervivor, Upper Marlboro, MD</td>
<td>Patient advocacy</td>
</tr>
<tr>
<td>Suzanne Garland, MBBS, MD (writing subcommittee)</td>
<td>University of Melbourne, Victoria, Australia</td>
<td>Sexual health, infectious diseases, clinical microbiology and infectious diseases, clinical vaccine trials</td>
</tr>
<tr>
<td>Doudja Hammouda, MD</td>
<td>Institut National de Santé Publique, Algiers, Algeria</td>
<td>Epidemiology</td>
</tr>
<tr>
<td>Ryo Konno, MD, PhD</td>
<td>Jichi Medical University, Saitama Medical Center, Saitama, Japan</td>
<td>Gynecologic oncology</td>
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<tr>
<td>Gilberto Lopes, MD, MBA</td>
<td>Sylvester Comprehensive Cancer Center, Miami, FL</td>
<td>Medical oncology, health economics</td>
</tr>
<tr>
<td>Emmanuel Mugisha, MPH, PhD</td>
<td>PATH, Kampala, Uganda</td>
<td>Public health</td>
</tr>
<tr>
<td>Raúl Murrilo, MD, MPH</td>
<td>International Agency for Research on Cancer, Lyon, France</td>
<td>Cancer epidemiology and prevention, cancer and chronic disease control</td>
</tr>
<tr>
<td>Isabel C. Scarinci, PhD, MPH</td>
<td>University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL</td>
<td>Behavioral science</td>
</tr>
<tr>
<td>Margaret Stanley, OBE</td>
<td>University of Cambridge, Cambridge, United Kingdom</td>
<td>Virology, epithelial biology, pathology</td>
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<tr>
<td>Vivien Tsu, MPH, PhD</td>
<td>PATH, Seattle, WA</td>
<td>Epidemiology, implementation science</td>
</tr>
<tr>
<td>Cosette M. Wheeler, PhD</td>
<td>University of New Mexico, Albuquerque, NM</td>
<td>Molecular epidemiology, diagnostics, public health, pathology, clinical trials</td>
</tr>
</tbody>
</table>

NOTE. American Society of Clinical Oncology staff: Sarah Temin, MSPH.
Abbreviation: ACOG, American College of Obstetricians and Gynecologists.

**Purpose** To provide resource-stratified, evidence-based recommendations on the secondary prevention of cervical cancer globally.

**Methods** ASCO convened a multidisciplinary, multinational panel of oncology, primary care, epidemiology, health economic, cancer control, public health, and patient advocacy experts to produce recommendations reflecting four resource-tiered settings. A review of existing guidelines, a formal consensus-based process, and a modified ADAPTE process to adapt existing guidelines were conducted. Other experts participated in formal consensus.

**Results** Seven existing guidelines were identified and reviewed, and adapted recommendations form the evidence base. Four systematic reviews plus cost-effectiveness analyses provided indirect evidence to inform consensus, which resulted in ≥75% agreement.

**Recommendations**

- Human papillomavirus (HPV) DNA testing is recommended in all resource settings; visual inspection with acetic acid may be used in basic settings.
- Recommended age ranges and frequencies by setting are as follows: maximal: ages 25 to 65, every 5 years; enhanced: ages 30 to 65, if two consecutive negative tests at 5-year intervals, then every 10 years; limited: ages 30 to 49, every 10 years; and basic: ages 30 to 49, one to three times per lifetime. For basic settings, visual assessment is recommended as triage; in other settings, genotyping and/or cytology are recommended. For basic settings, treatment is recommended if abnormal triage results are present; in other settings, colposcopy is recommended for abnormal triage results. For basic settings, treatment options are cryotherapy or loop electrosurgical excision procedure; for other settings, loop electrosurgical excision procedure (or ablation) is recommended. Twelve-month post-treatment follow-up is recommended in all settings.
- Women who are HIV positive should be screened with HPV testing after diagnosis and screened twice as many times per lifetime as the general population.
- Screening is recommended at 6 weeks postpartum in basic settings; in other settings, screening is recommended at 6 months. In basic settings without mass screening, infrastructure for HPV testing, diagnosis, and treatment should be developed.

**INTRODUCTION**

The purpose of this guideline is to provide expert guidance on secondary prevention with screening for cervical cancer to clinicians, public health authorities, policymakers, and laypersons in all resource settings. The target population is women in the general population at risk for developing cervical cancer (specific target ages depend on the resource level).

There are large disparities regionally and globally in incidence of and mortality resulting from cervical cancer, in part because of disparities in the provision of mass screening and primary prevention. Different regions of the world, both among and within countries, differ with respect to access to prevention and treatment.

Approximately 85% of incident cervical cancers occur in less developed regions (also known as low- and middle-income countries [LMICs]) around the world, representing 12% of women’s cancers in those regions. Eighty-seven percent of deaths resulting from cervical cancer occur in these less-developed regions. Some of the regions in the world with the highest mortality rates include the WHO Southeast Asia and Western Pacific regions, followed by India and Africa. As a result of these disparities, the ASCO Resource-Stratified Guidelines Advisory Group
Guideline Question
What are the optimal method(s) for cervical cancer screening and the management of women with abnormal screening results for each resource level (ie, basic, limited, enhanced, maximal)?

Target Population
Women who are asymptomatic for cervical cancer precursors or invasive cervical cancer

Target Audience
Public health authorities, cancer control professionals, policymakers, obstetricians/gynecologists, primary care providers, lay public

Methods
A multinational, multidisciplinary Expert Panel was convened to develop clinical practice guideline recommendations on the basis of a systematic review of existing guidelines and/or an expert consensus process.

Authors’ note: It is the view of ASCO that health care providers and health care system decision makers should be guided by the recommendations for the highest stratum of resources available. The guidelines are intended to complement, but not replace, local guidelines.

Key Recommendations

Primary Screening
- Human papillomavirus (HPV) DNA testing is recommended in all resource settings.
- Visual inspection with acetic acid may be used in basic settings.
- The recommended age ranges and frequencies in each setting are as follows:
  - Maximal: 25-65 years, every 5 years
  - Enhanced: 30-65 years, if two consecutive negative tests at 5-years intervals, then every 10 years
  - Limited: 30-49 years, every 10 years
  - Basic: 30-49 years, one to three times per lifetime

Exiting Screening
- Maximal and enhanced: ≥ 65 years with consistently negative results during past ≥ 15 years
- Limited and basic: ≤ 49 years, resource-dependent; see specific recommendations

Triage
- In basic settings, visual assessment for treatment may be used after positive HPV DNA testing results.
  - If visual inspection with acetic acid was used as primary screening with abnormal results, women should receive treatment.
- For other settings, HPV genotyping and/or cytology may be used.

After Triage
- Women with negative triage results should receive follow-up in 12 months.
- In basic settings, women should be treated if there are abnormal or positive triage results.

(continued on following page)
chose cervical cancer as a priority topic for guideline development.

The primary goal of cervical cancer screening should be—and the emphasis of these guidelines is—the accurate detection and timely treatment of intraepithelial precursor lesions of the cervix at a population level for the purpose of cervical cancer prevention, rather than cancer control as for many other cancers. This is because these precursor lesions are readily found and diagnosable and are easily and effectively treated through outpatient services with minimal adverse events or sequelae. Earlier detection of cervical cancer at a lesser stage is also a benefit of screening, resulting in reduced morbidity and mortality. However, many low-resource settings have little capacity in terms of surgery and radiotherapy to treat women with invasive cervical cancer. Therefore, the ASCO Expert Panel that developed this guideline (Appendix Table A1) emphasizes the timely detection and treatment of cervical precancerous lesions before they become invasive. To achieve this, a high screening coverage and an organized screening program are necessary.

Human papillomavirus (HPV) causes virtually all cervical cancer and its immediate precursors everywhere in the world. High-quality screening programs can lower the incidence of cervical cancer by up to 80%. In the past three decades, mass

THE BOTTOM LINE (CONTINUED)

- In limited settings, women with abnormal results from triage should receive colposcopy, if available, or visual assessment for treatment, if colposcopy is not available.
- In maximal and enhanced settings, women with abnormal or positive results from triage should receive colposcopy.

Treatment of Women With Precursor Lesions
- In basic settings, treatment options are cryotherapy or loop electrosurgical excision procedure (LEEP).
- In other settings, LEEP (if high level of quality assurance) or ablation (if medical contraindication to LEEP) is recommended.
- Twelve-month post-treatment follow-up is recommended for all settings.

Special Populations
- Women who are HIV positive or immunosuppressed for other reasons should be screened with HPV as soon as diagnosed and screened twice as many times in a lifetime as the general population.
- The management of abnormal screening results for women with HIV and positive results of triage is the same as in the general population.
- Women should be offered primary screening 6 weeks postpartum in basic settings and 6 months postpartum in other settings.
- Screening may be discontinued in women who have received a total hysterectomy for benign causes with no history of cervical dysplasia or HPV. Women who have received a subtotal hysterectomy (with an intact cervix) should continue receiving routine screening.

Qualifying Statement
In basic settings without current mass screening, infrastructure for HPV testing, diagnosis, and treatment should be developed.

Additional Resources
More information, including a Data Supplement, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/rs-cervical-cancer-secondary-prev-guideline and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net.

ASCO believes that cancer and cancer prevention clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.
screening in high-resource settings has achieved these reductions in cervical cancer incidence. A cervical cancer prevention program will affect the incidence and mortality rates only if women with positive screening results complete proper evaluation and treatment to prevent the progression to invasive cancer. Therefore, one of the critical evaluation indicators for any population-based program is the rate of completion of management and treatment in women who require it, which should ideally be 100%.

In 2013 and 2014, WHO published guidelines on the screening and treatment of precursor lesions for women in all settings; this guideline reinforces those recommendations. The screening modalities addressed by WHO and this guideline, include cytology (also known as Papanicolaou, or Pap, test), visual inspection (eg, visual inspection with acetic acid [VIA]), and HPV DNA testing (screening). For evaluation of positive results, the WHO guidelines include colposcopy, and for treatment, the guidelines recommend loop electrosurgical excision procedure (LEEP) of the transformation zone and ablative treatments. The screening tests are sometimes used and have been studied alone and in combination. This ASCO guideline also addresses screening in the vaccination era, self-sampling, and emerging screening technologies. In some settings that have established mass screening, cytology is the primary screening mode; in other settings, providers add HPV DNA testing (cotesting).

In low-resource settings, where screening may not currently be available, there is usually a shortage of pathologists, laboratories, colposcopists and other health providers, which limits the establishment of a traditional screening program. For example, some countries in sub-Saharan Africa have no pathologists and/or laboratories. However, HPV DNA testing, which is more effective than the traditional cytology screening test, may be introduced without pathology and laboratories. Therefore, less infrastructure is needed compared with cytology testing (see Cost and Policy Implications).

As HPV vaccination becomes more widespread and the rate of HPV infection decreases, public health authorities must decide on screening policies. Although prophylactic HPV vaccination may be the ultimate cervical cancer prevention strategy, current HPV vaccines prevent infections but do not treat pre-existing infections and conditions. Moreover, bivalent and quadrivalent HPV vaccines provide only partial protection against cervical cancer. Therefore, even if universal female HPV vaccination could be rapidly deployed, there would still be several generations of at-risk, HPV-infected women who would not benefit from—and would unlikely be targeted for—HPV vaccination. Without robust screening, millions of women will die of cervical cancer before the impact of HPV vaccines on cervical cancer is observed. Thus, secondary prevention by cervical cancer screening will be needed for the foreseeable future. (See Special Commentary on vaccination and screening for an in-depth discussion.)

The diagnosis of cervical cancer precursors is based on the pathologist’s judgment of the thickness of the transformed epithelium in biopsied or excised tissue, which is graded (in order of increasing severity) as negative or as cervical intraepithelial neoplasia (CIN) grade 1 (CIN1; up to one-third thickness of epithelium), grade 2 (CIN2; up to two-thirds thickness), or grade 3 (CIN3; two-thirds thickness or greater). Other abnormal results may include atypical squamous cells (ASC), ASC of undetermined significance (ASC-US), and adenocarcinoma in situ (AIS), the glandular equivalent of CIN3 and the precursor to adenocarcinoma. In this guideline, the term precursor lesions refers to CIN2 or greater (≥ CIN2), defined as a diagnosis of CIN2 (the standard-of-care threshold that triggers treatment), CIN3, or AIS. CIN1 is not considered a precursor lesion; most cases of CIN1 regress within 6 years. CIN2 is considered an equivocal precancerous diagnosis; that is, some instances of CIN2 are CIN1 or HPV infection, and therefore, treatment of all CIN2 may represent overtreatment.

ASCO has established a process for resource-stratified guidelines, which includes mixed methods of guideline development, adaptation of the clinical practice guidelines of other organizations, and formal expert consensus. This article summarizes the results of that process and presents resource-stratified recommendations that are based, in part, on formal consensus and adaptation from existing guidelines on the screening, triage of screening results, and treatment of women with cervical cancer precursor lesions (these guidelines are listed in Results and Appendix Table A2).

ASCO uses an evidence-based approach to inform guideline recommendations. In developing resource-stratified guidelines, ASCO has adopted its framework from the four-tier approach (basic, limited, enhanced, maximal; Table 1) developed by the Breast Health Global Initiative and made modifications to that framework on the basis of

GUIDELINE QUESTIONS

This clinical practice guideline addresses the following four overarching clinical questions: (1) What is the best method(s) for screening for each resource stratum? (2) What is the best triage strategy for women with positive results or other abnormal (e.g., discordant HPV/cytology) results? (3) What are the best management strategies for women with precursors of cervical cancer? (4) What screening strategy should be recommended for women who have received HPV vaccination?

METHODS

These recommendations were developed by an ASCO Expert Panel with multinational and multidisciplinary representation (Appendix Table A1). The Expert Panel met via teleconference and in person and corresponded through e-mail. On the basis of the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and submitted to a peer-reviewed journal for editorial review and consideration for publication. This guideline was partially informed by ASCO’s modified Delphi Formal Expert Consensus methodology, during which the Expert Panel was supplemented by additional experts recruited to rate their agreement with the drafted recommendations. The entire membership of experts is referred to as the Consensus Panel (Data Supplement provides a list of members). All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee before publication.

The guideline development process was also informed by the ADAPTE methodology as an alternative to de novo recommendation development. Adaptation of guidelines is considered by ASCO in selected circumstances, when one or more quality guidelines from other organizations already exist on the same topic. The objective of the ADAPTE process is to take advantage of existing guidelines to enhance efficient production, reduce duplication, and promote the local uptake of quality guideline recommendations.

The ASCO adaptation and formal expert consensus processes begin with a literature search to identify literature including candidate guidelines for adaptation. The panel used literature searches (from 1966 to 2015, with additional searches for literature published in specific areas), existing guidelines and expert consensus publications, some literature suggested by panel members, and clinical experience as guides.

Adapted guideline manuscripts are reviewed and approved by the Clinical Practice Guideline Committee. The review includes the following two parts: methodologic review and content review. The

Table 1. Four-Tiered Resource Settings for Secondary Prevention

<table>
<thead>
<tr>
<th>Setting</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>Core resources or fundamental services absolutely necessary for any public health/primary health care system to function; basic-level services typically are applied in a single clinical interaction; screening is feasible for highest need populations.</td>
</tr>
<tr>
<td>Limited</td>
<td>Second-tier resources or services that produce major improvements in outcomes, such as incidence and cost effectiveness, but that are attainable with limited financial means and modest infrastructure; limited-level services may involve single or multiple interactions; universal public health interventions are feasible for a greater percentage of the population than primary target group.</td>
</tr>
<tr>
<td>Enhanced</td>
<td>Third-tier resources or services that are optional but important; enhanced-level resources may produce further improvements in outcome but increase the number and quality of screening/treatment options and individual choice (perhaps ability to track patients and links to registries).</td>
</tr>
<tr>
<td>Maximal</td>
<td>May use high-resource setting guidelines; high-level/state-of-the art resources or services that may be used in some high-resource countries and/or may be recommended by high-resource setting guidelines that do not adapt to resource constraints; this should be considered lower priority than in the other settings on the basis of cost impracticality for limited-resource environment.</td>
</tr>
</tbody>
</table>

NOTE. Data adapted 16,17
former was completed by two ASCO staff members and the latter by members of the Expert Panel convened by ASCO.

The guideline recommendations were crafted, in part, using the Guidelines Into Decision Support methodology and accompanying BRIDGE-Wiz software (Yale, New Haven, CT). Detailed information about the methods used to develop this guideline is available in the Data and Methodology Supplements at www.asco.org/rs-cervical-cancer-secondary-prev-guideline.

The ASCO Expert Panel and guidelines staff will work with the Steering Committee to keep abreast of any substantive updates to the guideline. On the basis of the formal review of the emerging literature, ASCO will determine the need to update this guideline.

This is the most recent information as of the publication date. Visit the ASCO Guidelines Wiki at (www.asco.org/guidelineswiki) to submit new evidence.

Guideline Disclaimer
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Guideline and Conflict of Interest
The Expert Panel was assembled in accordance with ASCO’s Conflict of Interest Policy Implementation for Clinical Practice Guidelines (“Policy,” found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO’s disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria; consulting or advisory role; speaker’s bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS
Literature Search
As part of the systematic literature review, the PubMed, SAGE, Cochrane Systematic Review, and National Guideline Clearinghouse databases were searched for literature and guidelines, systematic reviews, and meta-analyses that were about screening for, or treatment of, precursor lesions; developed by multidisciplinary content experts as part of a recognized organizational effort; and published between 1966 and 2015. Literature searches based on prespecified criteria as well as updates of literature searches with terms used by other guidelines were conducted, and a title screen was completed and abstract review begun. However, because several high- and moderate-quality guidelines were found, the full text review and data extraction steps of the systematic review were not completed. Searches for cost-effectiveness analyses (CEAs) were also conducted and titles, abstracts, and full
texts were reviewed. Forty-one CEAs were found (this guideline cites three from these results, and panel members suggested an additional study23). Articles were excluded from the systematic review if they were meeting abstracts, books, editorials, commentaries, letters, news articles, case reports, or narrative reviews.

Methods and Results of the ASCO Updated Literature Search

A search for new evidence was conducted by ASCO guidelines staff to identify relevant randomized clinical trials, systematic reviews, meta-analyses, and guidelines published since the Cancer Care Ontario (CCO) and WHO guidelines were completed. Following the strategies described in the WHO guidelines, PubMed and EMBASE databases were searched from 2011 to December 2014 in July 2015. The search was restricted to articles published in English, and the ASCO guideline inclusion criteria were applied to review of the literature search results. Titles were reviewed; as described earlier, evidence reviews conducted for other societies’ guidelines were used as the evidence base.

Sixteen guidelines were found in the search, and their currency, content, and methodology were reviewed. On the basis of content and methodology assessments, the Expert Panel chose seven guidelines as the evidentiary basis for the guideline recommendations; these guidelines were from the American Cancer Society (ACS)/American Society for Colposcopy and Cervical Pathology (ASCCP)/American Society for Clinical Pathology (ASCP)24,25; a second ASCCP-led effort26; another US-based multisociety group’s guideline, referred to here as Huh et al6; a European guideline, referred to as von Karsa et al5; and two guidelines from the WHO.28,29 (Note that at the time of this writing, the US Preventive Services Task Force was updating its guidelines.30) Appendix Table A2 contains links to and the Data Supplement provides an overview of the guidelines, including information on their clinical questions, target populations, development methodology, and details of key evidence.

ASCO Methodologic Review

The methodologic review of the guidelines was completed by two ASCO guideline staff members using the Rigor of Development subscale of the Appraisal of Guidelines for Research and Evaluation II instrument.31 The score for the Rigor of Development domain is calculated by summing the scores across individual items in the domain and standardizing the total score as a proportion of the maximum possible score. Detailed results of the scoring and the Appraisal of Guidelines for Research and Evaluation II assessment process for this guideline are available in the Methodology Supplement.

FINAL RECOMMENDATIONS

The recommendations were developed by a multinational, multidisciplinary group of experts using evidence from existing guidelines, supplementary literature, and clinical experience as guides. The ASCO Expert Panel underscores that public health officials and health care practitioners who implement the recommendations presented in this guideline should first identify the available resources in their local and referral facilities and endeavor to provide the highest level of care possible with those resources.
Maximal-Resource Setting

In maximal-resource settings, cervical cancer screening with HPV DNA testing should be offered every 5 years from ages 25 to 65 years. On an individual basis, women may elect to receive screening until 70 years of age (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Women who are \( \geq 65 \) years of age who have had consistently negative screening results during the past \( \geq 15 \) years may cease screening. Women who are 65 years of age and have a positive result after age 60 should be reinvited to undergo screening 2, 5, and 10 years after the last positive result. If women have received no or irregular screening, they should undergo screening once at age 65 years, and if the result is negative, they should exit screening (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

If the results of the HPV DNA test are positive, clinicians should then perform triage with reflex genotyping for HPV 16/18 (with or without HPV 45) and/or cytology as soon as HPV test results are known (Type: evidence based; Evidence quality: high; Strength of recommendation: strong). If triage results are abnormal (ie, \( \geq \) ASC-US or positive for HPV 16/18 [with or without HPV 45]), women should be referred to colposcopy, during which biopsies of any acetowhite (or suggestive of cancer) areas should be taken, even if the acetowhite lesion might appear insignificant. If triage results are negative (eg, primary HPV positive and cytology triage negative), then repeat HPV testing at the 12-month follow-up (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

If HPV test results are positive at the repeat 12-month follow-up, refer women to colposcopy. If HPV test results are negative at the 12- and 24-month follow-ups or negative at any consecutive HPV test 12 months apart, then women should return to routine screening (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Women who have received HPV and cytology cotesting triage and have HPV-positive results and abnormal cytology should be referred for colposcopy and biopsy. If results are HPV positive and cytology normal, repeat cotesting at 12 months. If at repeat testing HPV is still positive, patients should be referred for colposcopy and biopsy, regardless of cytology results (Type: formal consensus based; Evidence quality: intermediate; Strength of recommendation: strong).

If the results of the biopsy indicate that women have precursor lesions (\( \geq \) CIN2), then clinicians should offer LEEP (if there is a high level of quality assurance [QA]), or where LEEP is contraindicated, ablative treatments may be offered. (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

After women receive treatment of precursor lesions, follow-up should consist of HPV DNA testing at 12 months. If 12-month results are positive, continue annual screening; if not, return to routine screening (Type: formal consensus based; Evidence quality: intermediate; Strength of recommendation: moderate).

Source guidelines and discussion. The age range for HPV testing was modified from guidelines by Huh et al\(^6\) that based the age of initiation on the Addressing the Need for Advanced HPV Diagnostics (ATHENA) RCT used for US Food and Drug Administration registration.\(^{33}\) Adding the years 25 to 29 to the starting age recommended by CCO and WHO (30 years) is from the evidence that HPV testing benefits women who are HPV negative, including those age 25 to 29 years.\(^6\) Screening is not recommended for women under the age of 25 given the lack of evidence of the benefit of decreased cancer risk and the potential harms of screening and overtreatment. For example, as described in the Huh et al\(^6\) guideline, there is a lower 3-year cumulative incidence rate for women whose results were high-risk HPV type (hrHPV) negative. The age of cessation at 65 years is suggested on the basis of existing guidelines. In general, the criteria for exiting screening are determined primarily on resource availability and the average life span of women in each setting, which is matched with the current knowledge of the HPV infection-to-dysplasia process. As life expectancy in maximal resource settings (eg, Organization for Economic Cooperation and Development countries) increases, and where estimated incidence rates for women ages 60 to 64 and 65 to 69 years are similar (16.6 and 16.1 per 100,000, respectively),\(^1\) women and their doctors may make individualized decisions to extend screening up to 70 years of age. For example, women who are 65 to 70 years old, have received screening, and have a history of positive screening (HPV, cytology, or VIA) test results in the last 5 years may be reinvited to screening until 70 years of age.
The choice of HPV DNA testing is supported by evidence of its effectiveness as a screening test and by several existing guidelines from developers including WHO, von Karsa et al, Huh et al, and CCO. HPV DNA testing is more sensitive than cytology. The interval of 5 years is based on the WHO, CCO, and European guidelines (CCO recommendations were specific to women older than age 30 years). There have been 10 RCTs on primary HPV testing. (The CCO guideline cites seven RCTs published between 2007 and 2010, including New Techniques in Cervical Cancer [NTCC], A Randomized Controlled Trial of HPV Testing in Primary Cervical Screening [ARTISTIC], Population-Based Screening Study Amsterdam [POBASCAM], Swedescreen, Finnish Public Health Trial [FPHT], Sankaranarayanan et al, and Canadian Cervical Screening Trial [CCCaST].) The Huh et al guidance cites pooled analyses of European RCTs (Dillner et al, which included seven prospective studies, and Ronco et al, which included four of the trials in CCO that had data from two rounds of screening [ARTISTIC, POBASCAM, NTCC, and Swedescreen published between 2007 and 2012]), the Vrije Universiteit Medisch Centrum-Salto (VUSA)-Screen study, the ATHENA RCT, and a Kaiser database. Ronco et al mentioned FOCAL, listed as ongoing by CCO, which was not included in the Huh et al guidance. Selected RCT data have been extracted in the Data Supplement.

Cotesting is an option, as recommended by the ACS/ASCCP/ASC pathology guideline; however, the added value on the basis of increased costs is limited. Evidence for this statement is found in the Huh et al guideline and a 2014 publication including CEA from the ARTISTIC trial, which found that strategies using primary HPV screening were more cost-effective than those using cotesting (eg, the rate of primary HPV screening with cytology triage and repeat HPV at 12 or 24 months was 22% for vaccinated cohorts and 18% in unvaccinated cohorts).

In maximal-resource settings, mass screening should be available to the entire target population and should aim to cover at least 80% of women age 25 to 70 years. Readers should note that there are more than 100 molecular tests for the detection of HPV; however, population-based screening programs should only use HPV tests that show clinical utility (which ASCO considers the highest level of evidence for biomarkers), are properly validated, and are approved by national and/or international regulatory agencies, such as US Food and Drug Administration approval, European Union CE marking, WHO endorsement/prequalification, or other country- or regional-level regulatory agencies. The tests should also have confirmed good manufacturing practices.

Women who are 65 to 70 years of age and do not have a history of ≥ CIN3 do not need to be offered screening if they have had two or more consecutive negative HPV test results or three or more negative cytology test results and only negative test results in the past 15 years.

If there are positive results from colposcopy, the options for the treatment of women with precursor lesions include LEEP, which is the first choice in maximal and enhanced settings, and various ablative treatments including cryotherapy, cold coagulation, or laser, which should all meet a high level of QA metrics (listed in Table 2). Cryotherapy is not recommended in the maximal setting. LEEP is preferred, in part, because it provides tissue for a histopathologic diagnosis. However, LEEP technology and training may not be available in lower resource settings and/or have contraindications. The Massad et al and WHO guidelines, citing RCTs and Cochrane reviews, and a more recent (2013) Cochrane review showed minimal differences between treatments. The WHO guideline states there is low evidence of treatment versus no treatment, mostly pooled results of non-comparative, nonrandomized studies. There are no RCTs specifically on HPV after LEEP. There is a paucity of prospective, comparative data on other treatment and follow-up strategies to guide recommendations on post-treatment follow-up. Therefore, on the basis of formal consensus, this guideline recommends follow-up HPV DNA testing at 12 months after one of these treatments.

Enhanced-Resource Setting

In enhanced-resource settings, cervical cancer screening with HPV DNA testing should be offered to women 30 to 65 years of age every 5 years (ie, second screen 5 years from the first; Type: evidence based; Evidence quality: high; Strength of recommendation: strong). If there are two consecutive negative screening test results, subsequent screening should be extended to every 10 years (Type: formal consensus based; Evidence quality: intermediate-low; Strength of recommendation: moderate).

Women who are ≥ 65 years of age who have had consistently negative screening results during the past ≥ 15 years may cease screening. Women who are 65 years of age and have a positive result after age 60 years should be reinvited to undergo
<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Criteria</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEEP</td>
<td>The results of VIA or VILI or colposcopy positive, not suspicious for cancer unless LEEP for biopsy and not treatment, can identify full extent of external lesions, etc., &gt; 12 weeks postpartum</td>
<td>Jhpiego&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Sufficient training of provider, with ability to handle complications</td>
<td>WHO&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Absolute contraindications to LEEP</td>
<td>ASCO Expert Panel</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>WHO&lt;sup&gt;39&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Acute cervicitis</td>
<td>ASCO Expert Panel</td>
<td></td>
</tr>
<tr>
<td>Bleeding or coagulation disorders</td>
<td>ASCO Expert Panel</td>
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</tr>
<tr>
<td>Patient unwillingness</td>
<td>ASCO Expert Panel</td>
<td></td>
</tr>
<tr>
<td>Relative contraindications to LEEP</td>
<td>ASCO Expert Panel</td>
<td></td>
</tr>
<tr>
<td>Patient &lt; 3 months postpartum</td>
<td>ASCO Expert Panel</td>
<td></td>
</tr>
<tr>
<td>Recurrence in a postcervical conization case</td>
<td>ASCO Expert Panel</td>
<td></td>
</tr>
<tr>
<td>Young patient with a small cervix</td>
<td>ASCO Expert Panel</td>
<td></td>
</tr>
<tr>
<td>Strong suspicion of microinvasive cancer</td>
<td>ASCO Expert Panel</td>
<td></td>
</tr>
<tr>
<td>Ablation</td>
<td>Lesion covers &lt; 75% of cervix, lesion does not enter endocervical canal, patient does not have positive ECC, entire lesion can be visualized and covered by the cryotherapy probe, no suspicion for invasive cancer</td>
<td>WHO&lt;sup&gt;29&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: ECC, endocervical curettage; LEEP, loop electrosurgical excision procedure; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol’s iodine.

### Table 2. Quality Assurance Criteria for Treatment of Precursor Lesions

If HPV test results are negative at the 12- and 24-month follow-ups or negative at any consecutive HPV test 12 months apart, then women should return to routine screening (Type: evidence based; Evidence quality: high; Strength of recommendation: strong). If the results of colposcopy and biopsy indicate that women have precursor lesions (≥ CIN2), then clinicians should offer LEEP (if there is a high level of QA) or, where LEEP is contraindicated, ablative treatments may be offered (Type: evidence based; Evidence quality: high; Strength of recommendation: strong). After women receive treatment of precursor lesions, follow-up should consist of HPV DNA testing at 12 months. If 12-month results are positive, continue annual screening; if not, return to routine screening (Type: formal consensus based; Evidence quality: intermediate; Strength of recommendation: moderate).

**Source guidelines and discussion.** In enhanced-resource settings, which refer to most programs in urban areas of middle-income countries, public health authorities may narrow the screening age range to 30 to 65 years; this is in agreement with the CCO guidelines. There is insufficient evidence on the best age of cessation.\(^{44}\) The extension to 10 years after negative tests is based on the von Karsa et al\(^{5}\) guideline.

The cost analysis study by Beal et al\(^{21}\) (2014) was conducted from the perspective of Mexican health care institutions and compared the following four screening plus triage strategies: cytology alone, hrHPV with reflex cytology, hrHPV with molecular triage, and cotesting with molecular triage. The study found that when the base case was cytology alone, hrHPV with molecular triage had the lowest incremental cost-effectiveness ratio (ICER) (–819 $–108.99 $–537 for hrHPV with molecular triage, hrHPV with cytology triage, and cotesting, respectively), with a cost at US$91.5 million (2013 US dollars). This strategy resulted in fewer women undergoing colposcopy. (Note that Mexico’s 2013 gross national income per capita was $15,620 [World Bank data, gross national income per capita, purchasing power parity].\(^{45}\)

As with the maximal-resource setting recommendations, if a woman has a history of positive screening (HPV, cytology, or VIA) test results in the past 5 years, she should be reinvited to screening. The interval may increase to 10 years in enhanced settings after two negative tests and is a modification of the von Karsa et al\(^{5}\) guidelines, which give the upper limit of 10 years after a negative test. This is also because HPV testing in older women yields a higher specificity.\(^{46}\) In the enhanced setting, if HPV screening 2, 5, and 10 years after the last positive result. If women have received no or irregular screening, they should undergo screening once at age 65 years, and if the result is negative, they should exit screening (Type: formal consensus based; Evidence quality: low; Strength of recommendation: weak).
If cytology triage results are abnormal (ie, quality: low; Strength of recommendation: weak). For VAT: Type: formal consensus based; Evidence quality: high; Strength of recommendation: strong; and genotyping: Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Follow-up after triage is the same as in maximal-resource settings. For management of precursor lesions, the Expert Panel recommends using LEEP as a first choice, but if LEEP is not available or is contraindicated and the patient is eligible for ablation (Table 2), then the clinician may use ablation. The other recommendations are the same as in the maximal setting.

Limited-Resource Setting
Cervical cancer screening with HPV DNA testing should be offered to women age 30 to 49 years every 10 years, corresponding to two to three times per lifetime (Type: evidence based [age range], Type: formal consensus based [interval]; Evidence quality: intermediate; Strength of recommendation: moderate).

If the results of the HPV DNA test are positive, clinicians should then perform triage with reflex cytology (quality assured) and/or HPV genotyping for HPV 16/18 (with or without HPV 45) or with visual assessment for treatment (VAT; for cytology and genotyping: Type: evidence based; Evidence quality: high; Strength of recommendation: strong; for VAT: Type: formal consensus based; Evidence quality: low; Strength of recommendation: weak).

If cytology triage results are abnormal (ie, ASC-US), women should be referred to quality-assured colposcopy (the first choice, if available and accessible), during which biopsies of any acetowhite (or suggestive of cancer) areas should be taken, even if the acetowhite lesion might appear insignificant. If colposcopy is not available, then perform VAT (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

If HPV genotyping or VAT triage results are positive, then women should be treated. If the results from both of these forms of triage are negative, then repeat HPV testing at the 12-month follow-up (Type: evidence based; Evidence quality: high; Strength of recommendation: strong). If test results are positive at the repeat 12-month follow-up, then women should be treated (Type: formal consensus based; Evidence quality: intermediate; Strength of recommendation: moderate).

For treatment, clinicians should offer ablation if the criteria are satisfied; if not and resources are available, then offer LEEP (if there is a high level of QA; Table 2; Type: evidence based; Evidence quality: high; Strength of recommendation: strong). After women receive treatment of precursor lesions, follow-up should consist of the same testing at 12 months (Type: formal consensus based; Evidence quality: intermediate; Strength of recommendation: moderate).

CEAs. The interval of 10 years (three times per lifetime) is supported by a CEA found in ASCO’s literature search for CEAs and was based on data from demonstration projects in South Asia, Central America, and East Africa. The objective of this study was analyzing cost-effectiveness of various tests (HPV DNA test, VIA, and cytology), age ranges, screening intervals, and numbers of screens per lifetime in limited-resource settings. This analysis supported the WHO guidelines for the age range of 30 to 49 years and found that HPV DNA testing three times per lifetime every 10 years starting at age 30 was a cost-effective strategy with attractive ICERs of 350 to 580 (international dollars) per life-year saved (LYS), varying by region. Cost of screening three times per lifetime with intervals of 5 years ranged from $180 to $1,600 international dollars per LYS (starting at age 30 years in India and at age 25 years in Uganda). 

Source guidelines and discussion. In limited-resource settings, which often correspond to rural areas in middle-income countries, most of the recommendations are based on the WHO guideline. The triage of positive screening results will depend on resources and the sample available from the screening. If there is sufficient sample from the primary test and genotyping is available or if genotyping is concurrent, that should be used, as recommended by the Huh et al guideline. If not and if cytology meets QA metrics, that may be used. If cytology does not meet the QA metrics, then VAT should be used, as recommended by WHO. If cytology results are positive, then women may receive quality-assured colposcopy, if available; otherwise, see and treat on the basis of the triage results. Although it was not within the scope of this guideline to develop de novo or formally review others’ recommendations on QA for colposcopy, groups that have addressed this include the National Health Service and the Society of Canadian Colposcopists. In addition, the 2011 International Federation for Cervical Pathology and Colposcopy Nomenclature is used worldwide.
If a woman has a history of abnormalities (eg, repetitively HPV-positive results) and recalling women for follow-up after abnormal results is a challenge, the woman might have an elevated risk for ≥ CIN2, and it might be cost-effective to offer treatment in limited or basic settings. (However, in enhanced and maximal settings, when recall is more feasible, further tests should be performed before treatment.)

The recommendation to follow-up other results if HPV genotyping is not available is a modification of CCO and WHO recommendations. The management of precursor lesions is based on the ASCCP\textsuperscript{26} and WHO guidelines\textsuperscript{29}; the latter supports performing LEEP. On the basis of each authority that provides screening CEA, women older than age 49 years with no previous screening may be offered screening, after the priority age group (30 to 49 years) is covered.

Basic-Resource Setting

If HPV DNA testing for cervical cancer screening is not available, then VIA should be offered with the goal of developing health systems and moving to population-based screening with HPV testing at the earliest opportunity. Screening should be offered to women age 30 to 49 years at least once per lifetime but not more than three times per lifetime (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong). If the results of available HPV testing are positive, clinicians should then perform VAT followed by treatment with cryotherapy and/or LEEP, depending on the size and location of the lesion (Type: formal consensus based; Evidence quality: low; Strength of recommendation: moderate). If primary screening is VIA and results are positive, then treatment should be offered with cryotherapy and/or LEEP, depending on the size and location of the lesion (Type: evidence based; Evidence quality: intermediate\textsuperscript{52}; Strength of recommendation: moderate).

After women receive treatment of precursor lesions, then follow up with the available test at 12 months. If the result is negative, then women should return to routine screening (Type: formal consensus based; Evidence quality: intermediate; Strength of recommendation: moderate).

CEAs. In addition to the study by Campos et al\textsuperscript{23} discussed in limited-setting recommendations, the study by Shi et al\textsuperscript{20} (found in ASCO literature search for CEAs) was a CEA that involved several substudies that compared HPV versus VIA versus VIA/visual inspection with Lugol’s iodine once or twice per lifetime or at routine intervals for primary testing in rural China. The outcomes included cost-effectiveness, incidence, mortality, and optimal age ranges. The investigators found that the lowest cost-effectiveness ratio (CER) for screening (compared with no intervention) was associated with VIA once per lifetime at age 35 years, and the second lowest was with VIA twice per lifetime (at age 35 to 45 years). The average lifetime reduction in cancer mortality was 8% for once per lifetime for VIA and 12% for HPV; twice per lifetime reductions were 16% and 24%, respectively. “Depending on the test technology used, and assuming a participation rate of approximately 70%, we found that once-lifetime screening at age 35 years would reduce age-standardised cervical cancer mortality in the population by 8-12% over the long term, with a CER of $557-959 per LYS. Regular screening at a feasible age-standardised participation rate of 62% in women aged 30-59 years would reduce cervical cancer mortality by 19-54%, with a CER of $665-2,269 per LYS.\textsuperscript{20} (The World Bank currently categorizes China as an upper-middle-income economy.\textsuperscript{53})

Source guidelines and discussion. These recommendations are based on the WHO guideline. In basic settings, where there is no mass screening and no culture of screening, VIA may be used, with the goal of moving to population-based screening with HPV testing at the earliest opportunity. There have been mixed results regarding VIA as primary screening. A cluster RCT on VIA involving 151,538 women in India was published after the WHO guidelines.\textsuperscript{54} Outcomes including cervical cancer mortality and incidence for 75,630 women receiving four rounds of VIA plus cancer education were compared with those of 76,178 women receiving cancer education alone. The authors have published 12 years of follow-up. Age-adjusted rates (AARs) for incidence of cervical cancer were 29 (95% CI, 24.5 to 33.4) for VIA plus education compared with 29.4 (95% CI, 27.2 to 31.7) for education alone (incident rate ratio, 0.8-1.2; \( P = .79 \)). AARs for cervical cancer mortality were 14.4 (95% CI, 12.7 to 16.2) for VIA plus education compared with 19.8 (95% CI, 17.8 to 21.8) for education alone, with an incident rate ratio of 0.69 (95% CI, 0.54 to 0.88; \( P = .003 \)). All-cause mortality AARs were 1,340.5 (95% CI, 1,321.2 to 1,359.6) for VIA plus education compared with 1,391.3 (95% CI, 1,372.1 to 1,410.4) for education alone, and the mortality rate ratio was 0.93 (95% CI, 0.79 to 1.1; \( P = .41 \)). (All figures were for 100,000 person-years of observation.)\textsuperscript{54} An earlier four-arm cluster RCT conducted in India compared HPV testing,
cytology, VIA, and standard care; it was published with 8 years of follow-up.\textsuperscript{55} In that study, the statistically significant outcomes were in the HPV testing arm, but not in the VIA arm. The hazard ratio for mortality was 0.52 (95% CI, 0.33 to 0.83) with HPV versus control. The hazard ratios for the incidence of stage II or higher cervical cancer were 0.47 (95% CI, 0.32 to 0.69) for HPV versus control and 1.04 (95% CI, 0.72 to 1.49) for VIA versus control.

Screening with VIA helps build infrastructure and brings women into medical care and screening (eg, in Bangladesh and Tamil Nadu, India).\textsuperscript{56,57} If screening is not started, the infrastructure will not develop for HPV testing. This is recommended while recognizing that follow-up opportunities may be limited. Regions should build toward having systems in place to diagnose and treat women with positive results and invasive cancer. For public health entities that initiate VIA for primary screening, it is crucial to invest significant effort to use validated training and validation procedures. These entities must have a plan for quality control of trained VIA evaluators’ performance.

After the establishment of such patterns, public health systems can introduce HPV testing. As these systems develop infrastructure for population-based screening, parallel development of systems for diagnosis and treatment of invasive cancer needs to occur. Concurrently with the development of screening programs, programs should develop the capacity to assess women with symptoms, including women outside of the target age range. In addition, the introduction of VIA screening may lead to identification of symptoms and women with symptoms seeking care. There may be high levels of screen-detected cancers on the first round of screening (many presumably in symptomatic women). Downstaging can be valuable too if treatment is available. The recommendations for age range, screening interval, triage, and special populations in the basic setting are modifications of the WHO recommendations.\textsuperscript{28} Follow-up of abnormal results and treatment of women with $\geq$ CIN2 follow the WHO recommendations on this condition.\textsuperscript{29}

Recommendations for Special Populations

Recommendation SP1a: Women who are HIV positive. Women who are HIV positive should begin screening with HPV testing, every 2 to 3 years, as soon as they receive an HIV diagnosis. The recommended frequency depends on the resource level; in general, it should be twice as many times in a lifetime as in the general population (Type: formal consensus based; Evidence quality: low; Strength of recommendation: weak).

The recommended frequencies, according to resource setting, are as follows:

- **Maximal:** Women should be screened for HPV approximately every 2 to 3 years.
- **Enhanced:** Women should be screened for HPV at intervals of 2 to 3 years, then, if negative, every 5 years (approximately eight screenings per lifetime).
- **Limited:** Women should be screened for HPV at intervals of every 2 to 3 years and twice as many times in a lifetime as in the general population (approximately four to six screenings per lifetime).
- **Basic:** If HPV testing is available, women with HIV should be screened for HPV as early as possible starting at age 25, every 3 years if the test results are negative initially; approximately twice per lifetime. If HPV testing is not available, use VIA at the same intervals (Type: evidence-based; Evidence quality: low; Strength of recommendation: weak).

The management of abnormal results of screening for women with HIV and positive results of triage is the same as in the general population (Type: formal consensus based; Evidence quality: low; Strength of recommendation: moderate).

Recommendation SP1b: Women who are immunosuppressed—all settings. Women who are immunosuppressed for any reason other than HIV should be offered the same screening as women who are HIV positive (Type: formal consensus based; Evidence quality: insufficient; Strength of recommendation: weak).

Discussion of SP1a and SP1b. There is insufficient evidence regarding screening women with HIV; only the WHO guideline made specific recommendations regarding these women. There are no data to inform screening for women who are immunosuppressed for other reasons. In general, these recommendations agree with the WHO guidelines, with the grateful acknowledgment of the panel.\textsuperscript{52} In addition, Forhan et al\textsuperscript{58} performed a systematic review on see-and-treat strategies for women with HIV in LMICs and found a lack of long-term outcome data (including morbidity and mortality and some HIV-specific outcomes). All the studies found in the systematic review by Forhan et al\textsuperscript{58} were observational.

Further, Vanni et al\textsuperscript{59} used a model-based approach to compare 27 strategies of primary HPV
testing or cytology with triage of cytology, HPV, or colposcopy, and each of these combinations at 6 months, 1 year, or 2 years, for women with HIV in Brazil, which is characterized as a middle-income country. The authors found that once-yearly HPV testing with cytology triage would be the most cost-effective strategy for women with HIV in Brazil with CER results of US$4,911 per LYS, with the threshold of Brazil’s per capita gross domestic product of US$8,625 per LYS. The World Bank currently categorizes Brazil as an upper-middle-income economy.

Recommendation SP2a: Women who are pregnant—all settings. Pregnant women should not receive screening.

Recommendation SP2b: Women who are postpartum—all settings. Women who are postpartum should be screened with VIA 6 weeks after delivery in basic settings. In other settings, HPV testing is recommended 6 months after delivery, unless there is uncertainty about completion of follow-up, in which case case screening at 6 weeks after delivery is advised (Type for both: formal consensus based; Evidence quality: insufficient; Strength of recommendation: weak).

Discussion of SP2a and SP2b. There is no evidence available to support evidence-based recommendations for women who are pregnant or postpartum; therefore, the recommendations are based on formal consensus. There is some indication that as a result of immune changes during pregnancy, some pregnant women may have increased HPV, which can subside after pregnancy. Performing HPV testing during this time of elevation may then produce inaccurate results. The test specificity increases with time. However, in some settings, loss to follow-up may be a concern, and because women may already be seeing clinicians for a postpartum and/or new baby visit at 6 weeks, the recommendation presents an opportunity to screen when the likelihood of a 6-month visit is low. Providers can discuss the potential risks, including opportunity costs, and benefits of screening with pregnant women to help reach individual decisions.

Recommendation SP3: Women who have had hysterectomies (with no history of ≥ CIN2). In all settings, screening may be discontinued in women who have received a total hysterectomy for benign causes with no history of cervical dysplasia or HPV. Women who have received a subtotal hysterectomy (with an intact cervix) should continue to receive routine screening (Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Discussion of SP3. The recommendation regarding women who have had hysterectomies was adapted from the 2011 CCO interim recommendations and the 2012 ACS/ASCCP/ASCP guidelines that state that no screening is necessary for women who have undergone hysterectomy with cervix removal and have had no history of ≥ CIN2 within the past 20 years. The ACS/ASCCP/ASCP recommendation on screening for vaginal cancer was based on observational data.

SPECIAL COMMENTARY

What Is the Role of Self-Collection (Only for HPV Molecular Testing)?

For improving coverage of screening, there is evidence emerging or under way on self-collection (also known as self-sampling). Self-collected (self-sampled) specimens may be used, with a validated collection device, transport conditions, and assay, as an alternative to provider-collected specimens for HPV testing. Triage and follow-up must be performed according to the setting and resources available. An ASCO literature search found three systematic reviews and/or meta-analyses on self-collection. A meta-analysis by Arbyn et al found that “the pooled sensitivity of HPV testing on self-samples was lower than HPV testing on a clinician-taken sample (ratio 0.88 [95% CI 0.85 to 0.91] for CIN2 or worse and 0.89 [0.83 to 0.96] for CIN3 or worse). In addition, specificity was lower in self-samples versus clinician-taken samples (ratio 0.96 [0.95 to 0.97] for CIN2 or worse and 0.96 [0.93 to 0.99] for CIN3 or worse).” There is a significant difference in the sensitivity of self-sampling versus cervical sampling when a signal amplification test is used, but that difference is minimal or null when a polymerase chain reaction–based test is used. A systematic review and meta-analysis by Racey et al found that relative compliance was higher with home-based self-collection HPV DNA testing kits than with standard clinic-based cytology. An earlier systematic review by Stewart et al found high acceptability by women performing self-collection.

The self-collection protocol, which includes the specimen collection (ie, device), handling (ie, transport buffer and storage conditions), and HPV test, needs to be validated in limited and basic settings if not previously validated. For example, a temperature higher than what is recommended or a different transport medium may affect the test performance.
As more evidence on self-collection is published, the Expert Panel will consider whether to make a formal recommendation.

What Screening Is Recommended for Women Who Have Received HPV Vaccination?

Public health providers should consider changes in cervical cancer screening in the HPV vaccination era in the absence of the two most carcinogenic HPV genotypes. As a consequence of the absence of HPV 16/18, positive screening tests will be less predictive of CIN3 and cervical cancer (\( \geq \) CIN3) because the point prevalence of \( \geq \) CIN3 is expected to be reduced by \( \geq 50\% \), whereas the test positivity will be reduced by \( \approx 30\% \).\(^{33,63,64}\) Moreover, HPV 16– and HPV 18–related cervical cancers occur at an earlier age than those related to other HPV genotypes;\(^{65}\) therefore, the risk of cancer is also lowered. Less predictive screening means a poorer benefit-to-harm ratio. Although more data are needed, under the assumption that women were vaccinated before becoming sexually active, in the enhanced and maximal settings, women may receive routine screening with HPV testing at ages 30, 45, and 60 years. However, age and frequency cannot be fully addressed until there are more data.

Screening can be changed in several ways to help restore good benefit-to-harm ratios in bivalent or quadrivalent HPV-vaccinated populations. First, screening can be started at an older age than is currently implemented because the population risk of cervical cancer will be lower in HPV-vaccinated (HPV 16 and HPV 18 negative) populations and cervical cancer caused by other HPV genotypes happens at a median age approximately 5 years older than does cervical cancer caused by HPV 16 and HPV 18. For example, many screening programs screen unvaccinated women under the age of 25 years, despite the lack of evidence of benefit in this age group,\(^{66}\) and vaccinated women in this age group would be even less likely to benefit given their lower cancer risk. Second, using the principle of equal management for equal risk,\(^{67}\) longer intervals between screens and/or follow-up in management could be considered. This would allow more benign infections and related abnormalities to clear without detection and intervention while shifting the focus to persisting HPV infections that carry a significant risk of progression.\(^{68,69}\) Finally, new, more specific biomarkers could be used to triage screen-positive women to help differentiate between benign hrHPV infections or related cytologic abnormalities and clinically important hrHPV infections that have caused, or will cause, \( \geq \) CIN3. Although much more data are needed before new approaches can be implemented into routine screening practices, the most promising of these biomarkers include p16\(\text{Ki-67}\) immunocytochemistry,\(^{70}\) E6 oncoprotein detection,\(^{71}\) and HPV viral genome methylation.\(^{72,73}\) (See New Screening Technologies for background and discussion on biomarkers.)

Although it will be at least a decade before we will consider the predicted impact of the newest HPV vaccines, in HPV-naive populations vaccinated with the nonavalent HPV vaccine, the question will be to screen at all. Most \( \geq \) CIN3 will be prevented, especially if there is cross-protection against hrHPV not targeted by nonavalent HPV vaccine. The few remaining CIN3 diagnoses caused by borderline hrHPV or low-risk HPV genotypes may rarely, if ever, become invasive cancer. These HPV genotypes can still cause significant numbers of minor cytologic\(^{74,75}\) and histologic\(^{76}\) abnormalities that have little clinical importance but would be picked up by screening. Thus, the harms to the women and costs would be disproportionately high compared with the benefits to women. Speculatively, a single screening of mid-adult-aged women approximately 35 or 40 years of age may be valuable if it leads to the detection of early-stage cervical cancer caused by hrHPV types not covered by the nonavalent HPV vaccine or caused by borderline hrHPV, and perhaps other female reproductive tract cancers,\(^{77}\) if the lead-time detection of the latter provides significant health benefit (eg, reduced mortality).

New Screening Technologies

Several new technologies are being investigated for all resource setting levels. They need to be tested and approved before use in any setting. These include a number of potentially promising new biomarkers that might achieve better performance as a triage for women with hrHPV-positive results than cytology and/or HPV genotyping. The most advanced of these next-generation biomarkers with respect to validation and readiness for introduction into routine practice is p16\(\text{IN}^{\text{dkK}}\) immunocytochemistry (p16 ICC). In a number of studies, p16 ICC has demonstrated high sensitivity and specificity that is similar to or better than cytology testing for \( \geq \) CIN2 and \( \geq \) CIN3 among women with hrHPV-positive results.\(^{70,78,79}\) In addition, Ki-67, a cell proliferation marker, has been included with p16 ICC (p16/Ki-67 ICC) as a dual stain to create a morphology-independent test.\(^{78}\) There is also a manual, lateral flow test for the detection of E6 protein that was developed for lower resource settings. The research use-only
version of the test targeted HPV 16, HPV 18, and HPV 45 E6 protein, whereas the current commercialized version targets HPV 16 and HPV 18. HPV E6 protein detection has been shown to be more specific than DNA detection for CIN3 and cervical cancer, even when accounting for restriction to the detection of the highest risk HPV genotypes. Additional study is needed to confirm this test’s performance.

There are a considerable number of additional biomarkers that are being developed. These include, but are not limited to, viral and host methylation, 3q amplification, and viral integration. All of these new biomarkers will need further study and validation before use in any clinical setting, regardless of resource level.

COST AND POLICY IMPLICATIONS

The secondary prevention of cervical cancer is a cost-effective strategy to reduce the incidence and mortality of cervical cancer. CEAs discussed in this guideline support the introduction of HPV DNA tests in maximal-, enhanced-, and limited-resource settings and the introduction of VIA in basic-resource settings. However, there are specific implementation issues regarding providing screening and treatment in limited and basic settings in primary care, outside of research studies.

The age group of 30 to 49 years (target age range recommended in limited- and basic-resources settings) represents approximately 20% to 25% of the entire population of women in a given country. LMICs typically have only basic health systems, lack resources and facilities, and have limited or no capacity to manage cancers. These formidable barriers to starting a screening program for this target group can lead to inertia. One strategy to overcome these barriers is to consider further restriction of the target age for screening. Targeting screening to women in their 30s (eg, 30 to 39, 30 to 34, or 35 to 39 years) reduces the number of women needing screening, thereby reducing burden on the health care system and costs, and decreases the number of screen-detected cancers, which typically peak in women in their 40s and 50s. Even targeting a single-year age group, for example, 30 or 31 years, would enable the development of programs to start and would help prevent cancer. When more resources and capacities become available, the program can be expanded for catch-up screening in older populations.

Additional strategies to further implementation of mass screening include buy-in from policymakers, which affects the provision of resources, including physical infrastructure, prioritizing cancer prevention, sponsorship of screening, and quality control. It is important to address this, at a minimum, by assessing the needs and preferences, follow-up systems, monitoring, evaluation, and partnering with institutions, regions, and countries with treatment facilities. A publication entitled “Infrastructure Requirements for Human Papillomavirus Vaccination and Cervical Cancer Screening in Sub-Saharan Africa” describes specific infrastructure elements needed for screening and cryotherapy programs and can help program managers plan for obtaining these elements.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and women in general populations and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely, including through many forms of ASCO communications and the ASCO Web site.

LIMITATIONS OF RESEARCH

There were limitations in the evidence regarding the best ages for starting and exiting from screening, screening women with HIV and other types of immunosuppression, comparative risks and benefits of treatment, and follow-up of women with precursor lesions. Future research is suggested in these areas.

FUTURE DIRECTIONS

In addition to addressing research limitations, future research is needed in other areas (eg, self-collection, biomarkers, needs and preferences of women, low-cost technology, and impact of vaccination on screening). Addressing policy/health system barriers may include the following:

- Education of medical and public health communities to change practices and incorporate new technologies
- Participation and sponsorship from policymakers
- Partnerships with institutions, regions, or countries with treatment facilities
- Coordinated volume purchasing and procurement of HPV testing
Improvement of health information systems to have better follow-up and treatment of women with positive screening results

- Quality control
- Monitoring and evaluation

ADDITIONAL RESOURCES

Additional information including a Data Supplement with additional tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets and clinical tools, and resources can be found at www.asco.org/rs-cervical-cancer-secondary-prev-guideline and www.asco.org/guidelineswiki. Patient information is available there and at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

ASCO believes that cancer and cancer prevention clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

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REFERENCES


## Table A1. Panel Members

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<th>Member</th>
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<tr>
<td>Jose Jeronimo, MD, Co-Chair, Steering Committee member</td>
<td>PATH, Seattle, WA</td>
<td>Gynecologic Oncology, Cancer Control</td>
</tr>
<tr>
<td>Surendra Shastri, MBBS, MD, DPh, DHA, Co-Chair, Steering Committee member</td>
<td>Tata Memorial Centre, Mumbai, India</td>
<td>Preventive Oncology/Primary Care</td>
</tr>
<tr>
<td>Philip Castle, PhD, MPH, Steering Committee member</td>
<td>Albert Einstein College of Medicine; Global Coalition against Cervical Cancer, Arlington, VA</td>
<td>Epidemiology/Biophysics</td>
</tr>
<tr>
<td>Lynette Denny, MD, PhD</td>
<td>University of Cape Town, Capetown, South Africa</td>
<td>Gynecologic Oncology</td>
</tr>
<tr>
<td>Vandana Gupta</td>
<td>V Care, Mumbai, India</td>
<td>Patient Representative</td>
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<tr>
<td>Jane J. Kim, PhD</td>
<td>Harvard T.H. Chan School of Public Health, Boston, MA</td>
<td>Health Economics</td>
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<tr>
<td>Eduardo Lazcano, MD, PhD</td>
<td>Research Center on Public Health National Institute of Public Health, Mexico</td>
<td>Public Health</td>
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<tr>
<td>Silvana Luciani, MHSc</td>
<td>PanAmerican Health Organization, Washington, DC</td>
<td>Cancer Control</td>
</tr>
<tr>
<td>Daniel Murokora, MB, ChB</td>
<td>Uganda Women’s Health Initiative, Kampala, Uganda</td>
<td>Medical Oncology</td>
</tr>
<tr>
<td>Twalib Ngoma, MD</td>
<td>International Network for Cancer Treatment and Research, Dar Es Salaam, Tanzania</td>
<td>Radiotherapy and Nuclear Medicine</td>
</tr>
<tr>
<td>Youlin Qiao, MD</td>
<td>Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China</td>
<td>Cancer Prevention and Control</td>
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<tr>
<td>Michael Quinn, MD, MGO</td>
<td>University of Melbourne, Melbourne, Australia</td>
<td>Gynecologic Oncology</td>
</tr>
<tr>
<td>Rengaswamy Sankaranarayanan, MD</td>
<td>International Agency for the Research of Cancer, Lyon, France</td>
<td>Radiotherapy and Oncology; Cancer Epidemiology and Control</td>
</tr>
<tr>
<td>Peter Sasieni, PhD</td>
<td>Queen Mary, University of London, Wolfson Institute, London, United Kingdom</td>
<td>Biostatistics/Epidemiology</td>
</tr>
<tr>
<td>Kathleen M. Schmeler, MD</td>
<td>The University of Texas, MD Anderson Cancer Center, Houston, TX</td>
<td>Gynecologic Oncology</td>
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Note. American Society of Clinical Oncology staff: Sarah Temin, MSPH.
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Abbreviations: ACOG, American College of Obstetricians and Gynecologists; ACS, American Cancer Society; ASC, American Society of Cytopathology; ASCCP, American Society for Colposcopy and Cervical Pathology; ASCP, American Society for Clinical Pathology; CAP, College of American Pathologists; SGO, Society of Gynecologic Oncology.
Project ECHO: A Telementorering Program for Cervical Cancer Prevention and Treatment in Low-Resource Settings

Cervical cancer incidence and mortality rates are significantly higher in low- and middle-income countries compared with the United States and other developed countries. This disparity is caused by decreased access to screening, often coupled with low numbers of trained providers offering cancer prevention and treatment services. However, similar disparities are also found in underserved areas of the United States, such as the Texas-Mexico border, where cervical cancer mortality rates are 30% higher than in the rest of Texas. To address these issues, we have adopted the Project ECHO (Extension for Community Healthcare Outcomes) program, a low-cost telementoring model previously proven to be successful in increasing local capacity, improving patient management skills, and ultimately improving patient outcomes in rural and underserved areas. We use the Project ECHO model to educate local providers in the management of cervical dysplasia in a low-resource region of Texas and have adapted it to inform strategies for the management of advanced cervical and breast cancer in Latin America and sub-Saharan Africa. This innovative approach, using ECHO, is part of a larger strategy to enhance clinical skills and develop collaborative projects between academic centers and partners in low-resource regions.

INTRODUCTION

Cancer is one of the leading causes of death worldwide. In 2012, approximately 14 million new cases and 8.2 million cancer-related deaths were reported. Cancer and other noncommunicable diseases are responsible for >60% of deaths globally. In low- and middle-income countries (LMICs), cancer is a primary cause of early death, and its prevalence has been increasing steadily, partly because of population aging and improved control of infectious diseases.

Cervical cancer is a notable example of cancer disparities in LMICs. Worldwide, cervical cancer is the fifth most common cancer among women. However, in the United States, cervical cancer is now relatively uncommon; it is the 11th most common cancer among women. The development of the Papanicolaou (Pap) test and the introduction of organized screening programs have led to a 70% decrease in cervical cancer incidence and mortality rates over the past 60 years in the United States and other high-income countries.

In contrast, cervical cancer remains the second most common cancer among women in LMICs, and it is the most common cancer in many regions of sub-Saharan Africa. For example, in Mozambique, cervical cancer is the most common cancer in women, followed by breast cancer. Of note, higher rates of cervical cancer are also seen in medically underserved areas of the United States because of a lack of regular screening and limited access to care. Once such areas is the Rio Grande Valley (RGV) of south Texas, located along the Texas-Mexico border. The population in this area is largely Hispanic and is medically underserved. The cervical cancer incidence and mortality rates in this region are 30% higher than in the rest of Texas.

There are many reasons for higher cervical cancer rates in LMICs and underserved regions of the United States. These populations are less likely to receive cervical cancer screening because of economic, social, educational, and geographical barriers. In addition, there is often a shortage of locally available trained providers to perform screening tests and to manage patients with abnormal findings according to evidence-based guidelines, including performing colposcopy, cervical biopsies, and loop electrosurgical excision procedures. Furthermore, many women with abnormal screening tests do not receive the recommended diagnostic and treatment procedures because they are unable to travel to central health care facilities for the multiple necessary follow-up visits because of the long distances and high costs associated with travel. Thus, increased participation in screening, together with navigation services and an extension of diagnostic and treatment services, is needed to...
decrease cervical cancer rates in underserved areas worldwide.

**SPECIFIC CHALLENGES RELATED TO TRAINING AND EDUCATION IN LMICS AND LOW-RESOURCE REGIONS IN THE UNITED STATES**

The number of trained physicians and nurses in LMICs is extremely low in comparison with high-income countries. For example, there are 2.6 physicians in Mozambique per 100,000 population compared with 247 in the United States and 222 in the United Kingdom for the same population. Furthermore, few of the physicians in LMICs have specialty training and are capable of treating the high volume of patients presenting with cancer.9 Shortages of clinicians, including specialists, are also found in the RGV area of Texas, a medically underserved region. In the RGV, there are currently no local public hospitals, and there are 40% fewer physicians and 50% fewer nurse practitioners per 100,000 people compared with the Texas average.10 Project ECHO (Extension for Community Healthcare Outcomes), a telementoring program, can help increase clinical capacity in such low-resource settings.

**PROJECT ECHO TELEMENTORING**

Project ECHO was developed in 2003 by Sanjeev Arora, MD, a hepatologist at the University of New Mexico (UNM), to improve both provider capacity and access to specialty care for rural and underserved populations.11,12 ECHO is a low-cost, high-impact initiative linking multidisciplinary specialist teams with community primary care clinicians through regularly scheduled teleECHO clinics, in which the participants use videoconferencing to comanage patient cases, and specialists share their expertise via mentoring, guidance, feedback, and didactic education. This approach has enabled clinicians in medically underserved areas to develop the skills, confidence, and knowledge to treat patients with common, complex diseases in their own communities, thereby reducing travel costs, wait times, and avoidable complications. Project ECHO is different from telemedicine, in which the specialist assumes the care of the patient, but instead, involves telementoring, in which the community clinician retains responsibility for managing the patient, operating with increasing independence as his/her skills and self-efficacy grow. Clinicians in underserved areas learn from the university specialists and from each other, and specialists learn from the community providers. This is a many-to-many approach, as opposed to the approach of traditional telemedicine.

The first teleECHO clinic at UNM was developed for the management of patients with hepatitis C virus (HCV) in rural New Mexico.13 Providers from 16 rural community clinics and five prisons throughout New Mexico participated in weekly HCV teleECHO clinics with specialists from UNM, presenting their cases, including patients’ medical histories, laboratory results, treatment plans, and individual challenges, and asked questions and received guidance about best practices. Specialists from the fields of hepatology, infectious diseases, psychiatry, and pharmacology at UNM provided advice and clinical mentoring during these teleECHO clinics. Working together, the community providers and specialists managed the patients’ care according to evidence-based guidelines. The effectiveness of the HCV ECHO clinic was evaluated in a prospective cohort study of 407 patients with chronic HCV that was published in *New England Journal of Medicine* in 2011.11 This study compared the outcomes of patients treated by specialists at UNM with those of patients treated by primary care providers at the 21 rural ECHO clinics. There were no significant differences in sustained viral response between the UNM cohort (57.5%) and the ECHO cohort (58.2%). Furthermore, serious adverse events were higher in the UNM cohort (13.7%) than in the ECHO cohort (6.9%). Specifically, Project ECHO improved patient satisfaction, physician self-efficacy, and patient outcomes while concomitantly reducing regional disparities in evidence-based HCV management across the state of New Mexico.

Project ECHO has since expanded to cover almost 50 other specialty areas across the United States and globally.14,15 TeleECHO clinics are currently conducted at 82 hub institutions in 13 countries for the management of conditions such as cancer, addictions, rheumatology, HIV/AIDS, dementia, palliative care, autism, diabetes, and cardiovascular disease worldwide.

**PROJECT ECHO AT THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER, UNITED STATES**

Our group recently adopted Project ECHO for cancer prevention and management. The Cervical Cancer Prevention Project ECHO clinics are held via a free videoconferencing platform for 1 hour, every other week, at a time convenient for the providers (before their clinics start). Continuing medical and nursing education credits are awarded, free of charge, after each session, and providers receive direct input on case management. The first 45 minutes involve case discussions. Case details
This program is under development and some of the locations might change in the future; this program is currently under early discussions with sister institutions in North America.

**PROJECT ECHO FOR THE PREVENTION AND TREATMENT OF CERVICAL CANCER IN THE RGV**

The University of Texas MD Anderson Cancer Center’s first Project ECHO program is run in collaboration with the University of Texas Medical Branch (UTMB), the University of Texas Health Science Center School of Public Health Brownsville Regional Campus, and Su Clinica Familial, a federally qualified health center in the RGV area of south Texas (Table 1). In this region, cervical cancer incidence and mortality is 30% higher than in the rest of the state, and there is a significant shortage of providers and specialists. The US Census Bureau estimated the population in this region to be 1,336,323 in 2014. Approximately 90% of the population is Hispanic (mostly Mexican American), and approximately 35% of the population lives below the federal poverty line. Seventy percent do not have health insurance, and among those who do, two thirds have Medicare or Medicaid.

The Project ECHO program started in April 2014 as part of a larger strategy with the aims of increasing professional capacity in the RGV community and increasing public participation in regular cervical cancer screening. To increase cervical cancer screening in this region, community health workers use an evidence-based approach to educate women about the importance of screening and human papillomavirus vaccination in combination with patient navigation services. In parallel, Project ECHO is improving health care provider skills in managing abnormal cervical screening tests using existing evidence-based guidelines.

Hands-on training complements this Project ECHO initiative. Five local providers have been trained to perform colposcopy through the American Society for Colposcopy and Cervical Pathology course and mentoring program, which requires the participant to perform colposcopic procedures and cervical biopsies under the direct supervision of a mentor. This is accomplished by faculty from MD Anderson and UTMB serving as the mentors and traveling (without patient-identifying information) are sent to the specialists by the providers before each ECHO clinic and are presented to the group during the videoconference. In general, an interactive and lively discussion follows the case presentations. Case discussions are followed by a 15-minute didactic presentation by a participating faculty member or a guest lecturer. A few minutes are reserved at the end of the session for additional questions or comments from the participants. The ECHO programs at MD Anderson started as an initiative for the RGV and have since been expanded globally to other low-resource areas (Fig 1).
regularly to the RGV area for hands-on training and supervision. Participants from the RGV travel to MD Anderson and partner hospitals for additional training. In addition to the five providers trained in colposcopy, a provider has been trained to perform loop electrosurgical excision procedures, which allows more patients in the RGV to receive treatment locally without the need for referral to a distant facility.

The RGV Cervical Cancer Prevention ECHO program has since expanded and currently includes clinicians from Mexico, El Salvador, Colombia, and Brazil who are interested in cervical cancer prevention. The multidisciplinary specialist team from MD Anderson and UTMB provide input and guidance for patient management and program operations. In the first 2 years of Project ECHO implementation, 45 videoconference sessions have been held, with an average of 16 providers per session, including gynecologists, family physicians, nurse practitioners, physician assistants, and midwives. A preliminary survey of provider satisfaction after 1 year of the program suggests that the majority of providers find the clinics useful in patient management and in improving their skills and knowledge.

PROJECT ECHO LATIN AMERICA

In 2015, a Project ECHO program for cervical cancer prevention and management was created for providers practicing in Latin America. This program was initiated by providers from Uruguay who were participating in the ECHO Program for the RGV and wished to expand the program to their colleagues in Latin America and to hold the videoconferences in Spanish. The sessions are comoderated by gynecologic oncologists and gynecologists from MD Anderson, UTMB, and the Universidad de La República in Uruguay. To date, seven sessions have been held, with an average of 18 participants from various institutions in Mexico, El Salvador, Guatemala, Colombia, Bolivia, Paraguay, Ecuador, Peru, Uruguay, Chile, and Brazil (Table 1). Because the landscape of cancer screening and treatment is so diverse in Latin America, this forum offers the opportunity to share cervical cancer prevention and treatment experience, with the aim of closing the gap of knowledge and decreasing disparities.

PROJECT ECHO AFRICA

We have expanded the Project ECHO program by partnering with clinicians in Zambia and Mozambique, specifically for the management of cervical and breast cancer. Project ECHO Zambia is conducted in collaboration with physicians and nurses from the Cancer Diseases Hospital in Lusaka. These videoconferences are held monthly, with the focus alternating between breast cancer and cervical cancer. To date, 12 sessions have been held, with an average of eight participants per session including gynecologists, radiation

Table 1. Project ECHO Programs at The University of Texas MD Anderson Cancer Center

<table>
<thead>
<tr>
<th>ECHO Program</th>
<th>Focus</th>
<th>Collaborators</th>
<th>Participating Countries</th>
<th>Frequency</th>
<th>Language</th>
<th>ECHO Sessions to Date</th>
<th>Average Number of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rio Grande Valley</td>
<td>Cervical dysplasia</td>
<td>UTMB; Su Clinica Familiar and The University of Texas School of Public Health Brownsville Regional Campus, Rio Grande Valley</td>
<td>United States, Mexico, Brazil, El Salvador, Guatemala</td>
<td>Every 2 weeks</td>
<td>English</td>
<td>45</td>
<td>16</td>
</tr>
<tr>
<td>Zambia</td>
<td>Invasive breast and cervical cancer</td>
<td>Cancer Diseases Hospital, Lusaka</td>
<td>United States, Zambia</td>
<td>Monthly</td>
<td>English</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Mozambique</td>
<td>Invasive breast and cervical cancer</td>
<td>Hospital Central de Maputo, Mozambique; Barretos Cancer Hospital, A.C. Camargo and Hospital Israelita Albert Einstein, Brazil</td>
<td>United States, Brazil, Mozambique</td>
<td>Monthly</td>
<td>Portuguese</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Latin America</td>
<td>Cervical dysplasia and invasive cervical cancer</td>
<td>Universidad de la Republica de Uruguay</td>
<td>United States, Uruguay, Bolivia, Colombia, El Salvador, Peru, Ecuador, Honduras, Guatemala, Mexico, Paraguay</td>
<td>Monthly</td>
<td>Spanish</td>
<td>7</td>
<td>16</td>
</tr>
</tbody>
</table>

Abbreviations: ECHO, Extension for Community Healthcare Outcomes; UTMB, University of Texas Medical Branch.
The Project ECHO model was created for the treatment of a common infectious disease, with clear metrics for treatment success identifiable in a short period of time. Although cervical dysplasia is common in the United States, cervical cancer is relatively rare. In addition, the time of progression from dysplasia to cancer may be > 10 years, so individual patient outcomes are not an effective way to monitor program success. Cervical cancer is a progressive disease requiring different types of providers as the disease progresses from dysplasia to cancer. Complicating this is the fact that there are different approaches to care within regions and across borders that may vary according to differences in health policies, standards of care, and resources. Providers screening for cervical cancer are frequently not the same providers treating dysplasia and invasive disease. Furthermore, there is often limited communication between gynecologic oncologists treating cervical cancer and providers performing cervical cancer screening. In LMICs, these communication challenges also exist, complicated by the lack of accurate record keeping, the difficulty in tracking patients, and the lack of specialty providers, such as gynecologic oncologists. These conditions create an opportunity in particular for the Project ECHO program in Latin America, because this ECHO program looks to provide a comprehensive approach to the natural history of cervical cancer (discussions alternate between cervical cancer prevention and cervical cancer treatment). Providers engaged in screening and early detection strategies interact with oncologists treating patients with invasive cancer during these videoconferences.

The MD Anderson ECHO programs, in particular those engaged with international partners in LMICs, must also consider the local context and local resources in care delivery. Attaining the standard of care in the United States is not feasible in many regions, and, given limited resources, creative solutions for providing basic services provide a basis for many discussions. In addition to resource limitations, cultural differences and difficulty initiating change can create challenges and often require unique, region-specific strategies for care delivery. Regular videoconferences help build trust and encourage the development of partnerships through the exchange of information and knowledge.

The evaluation of the programs is ongoing and includes three components: process metrics, provider satisfaction, and levels of collaborations. The process metrics include the number of participants, the number of ECHO sessions held, and the number of individual cases discussed. Provider satisfaction and self-efficacy are measured at baseline and will continue to be measured with follow-up surveys once a year. Furthermore, collaborative efforts will be measured through the number of workshops delivered successfully; the number of joint research programs; the number of providers participating in colposcopy, surgery, and other workshops; and the number of observerships and trainee exchanges completed. In addition, a parallel effort in the RGV...
is evaluating the impact of Project ECHO and related programs by measuring changes in the number of women undergoing cervical cancer screening and receiving appropriate management of abnormal results, as well as in the number of women diagnosed with high-grade cervical dysplasia and invasive cancer.

**NEXT STEPS**

In the short term, the program is engaging additional providers working in medically underserved areas such as other Texas-Mexico border areas and other LMICs. Existing programs are also expanding to include initiatives in other cancer types as well as palliative care. Furthermore, we are developing additional hands-on training programs, workshops, and observerships. Our long-term goal is to continue to provide training, mentoring, and support for providers in medically underserved areas to substantially reduce the incidence of cervical cancer and other malignancies and provide optimal care for patients with these diseases.

**AUTHOR CONTRIBUTIONS**

**Conception and design:** Melissa S. Lopez, Ellen S. Baker, Ana M. Rodriguez, José Humberto Tavares, Gustavo Zucca-Matthes, Donato Callegaro-Filho, Fernanda Nozar, Veronica Fiol, Mauricio Maza, Sanjeev Arora, Ernest T. Hawk, Kathleen M. Schmeler

**Administrative support:** Melissa S. Lopez, Ellen S. Baker, Andrea M. Milbourne, Mila Pontremoli-Salcedo, Veronica Fiol, Sanjeev Arora, Ernest T. Hawk, Kathleen M. Schmeler

**Provision of study materials or patients:** Rose M. Gowen, Ana M. Rodriguez, Cesaltina Lorenzoni, Catherine Mwaba, Susan Citonje Msadabwe, Donato Callegaro-Filho, Danielle Ramos-Martín, Icaro Thiago de Carvalho, Robson Coelho, Renato Moretti-Marques, Thiago Chulam, Mila Pontremoli-Salcedo, Fernanda Nozar, Veronica Fiol, Mauricio Maza, Kathleen M. Schmeler

**Collection and assembly of data:** Rose M. Gowen, Cesaltina Lorenzoni, Catherine Mwaba, Susan Citonje Msadabwe, José Humberto Tavares, Gustavo Zucca-Matthes, Donato Callegaro-Filho, Mila Pontremoli-Salcedo, Ernest T. Hawk, Kathleen M. Schmeler

**Data analysis and interpretation:** Andrea M. Milbourne, Ana M. Rodriguez, Cesaltina Lorenzoni, Catherine Mwaba, Susan Citonje Msadabwe, José Humberto Tavares, Georgia Fontes-Cintra, Gustavo Zucca-Matthes, Donato Callegaro-Filho, Danielle Ramos-Martín, Icaro Thiago de Carvalho, Robson Coelho, Renato Moretti-Marques, Thiago Chulam, Mila Pontremoli-Salcedo, Fernanda Nozar, Veronica Fiol, Mauricio Maza, Sanjeev Arora, Ernest T. Hawk, Kathleen M. Schmeler

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Accountable for all aspects of the work:** All authors

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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**Melissa S. Lopez**

No relationship to disclose

**Ellen S. Baker**

No relationship to disclose

**Stock or Other Ownership:** Merck

**Andrea M. Milbourne**

No relationship to disclose

**Rose M. Gowen**

No relationship to disclose

**Ana M. Rodriguez**

No relationship to disclose

**Cesaltina Lorenzoni**

No relationship to disclose

**Susan Citonje Msadabwe**

Travel, Accommodations, Expenses: AstraZeneca

**José Humberto Tavares**

No relationship to disclose

**Georgia Fontes-Cintra**

No relationship to disclose

**Gustavo Zucca-Matthes**

No relationship to disclose

**Donato Callegaro-Filho**

No relationship to disclose

**Danielle Ramos-Martín**

No relationship to disclose

**Icaro Thiago de Carvalho**

No relationship to disclose

**Robson Coelho**

No relationship to disclose

**Renato Moretti-Marques**

No relationship to disclose

**Thiago Chulam**

Travel, Accommodations, Expenses: A.C. Camargo Cancer Center

**Mila Pontremoli-Salcedo**

No relationship to disclose

**Fernanda Nozar**

No relationship to disclose

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Multidisciplinary Gynecologic Oncology Clinic in Botswana: A Model for Multidisciplinary Oncology Care in Low- and Middle-Income Settings

Purpose Cervical cancer is a major cause of mortality in low- and middle-income countries (LMICs) and the most common cancer diagnosed in women in Botswana. Most women present with locally advanced disease, requiring chemotherapy and radiation. Care co-ordination requires input from a multidisciplinary team (MDT) to deliver appropriate, timely treatment. However, there are limited published examples of MDT implementation in LMICs.

Methods In May 2015, a weekly MDT clinic for gynecologic cancer care was initiated at Botswana’s national referral facility. The MDT clinic served as a forum for discussion and coordination of patients with gynecologic cancer and consisted of a gynecologist, pathologist, medical oncologist, radiation oncologist, palliative care specialist, and nurse coordinator.

Results Between May 2015 and December 2015, 135 patients were seen in the MDT clinic. The mean age of the patients was 49 years. Most (60%) of the patients were HIV positive. The most common diagnosis was cervical cancer (60%), followed by high-grade cervical intraepithelial neoplastic lesions (12%) and vulvar cancer (11%). Only data up to September 2015 were assessed for treatment delays. It was found that only 38% of patients needed more than one visit for care coordination before treatment initiation. Among patients with cervical cancer, the median delay from date of biopsy to start of radiation treatment was 39 days (interquartile range, 34 to 57 days) for patients treated after MDT initiation, compared with 108 days (interquartile range, 71 to 147 days) for patients treated before MDT initiation (P < .001).

Conclusion Implementation of MDT clinics in LMICs is feasible and can help reduce delays in treatment initiation, as demonstrated by a gynecologic MDT clinic in Botswana. Streamlining care through MDT clinics can enhance care coordination and improve clinical outcomes. This model can apply to cancer care in other LMICs.

INTRODUCTION

Cervical cancer is the fourth most common cancer affecting women worldwide, with an estimated 528,000 new cases and 266,000 deaths annually. Approximately 85% of these new cases and 87% of deaths occur in low- and middle-income countries (LMICs). Because of limited screening programs and high HIV prevalence, cervical cancer is the leading cause of cancer death in Botswana.

More than 75% of patients with cervical cancer in Botswana have locally advanced disease. In Botswana, current treatment includes radiotherapy and cisplatin-based chemotherapy. Radiotherapy, however, is not available in the public sector; hence, patients are referred to the private sector for radiation. On the basis of our pilot data, the median time from diagnosis to treatment is 108 days. To decrease cervical cancer morbidity and mortality, it is imperative to identify and address factors contributing to delays.

Cancer management requires action from a range of expert providers over a prolonged time. Difficulties in communication and coordination among these various providers can cause cancer care to become fragmented, ultimately contributing to treatment delays and worse outcomes, which are a potential cause of delay in cervical cancer care in Botswana. Studies in developed countries in which surgeons, pathologists, oncologists, radiologists, social workers or psychologists, and nurses are involved in discussing each case suggest that multidisciplinary teams (MDTs) can decrease time to diagnosis, time to treatment, and...
duplication of investigations, as well as improve accuracy of diagnosis.\textsuperscript{8} Thus, the establishment of an MDT is warranted.

Actionable knowledge about scaling MDTs into LMICs remains sparse. Results from an international survey showed that breast cancer MDT clinics across the world used different models and lacked standard guidelines.\textsuperscript{9} In several developing countries, cancer centers do not have formal MDTs.\textsuperscript{10} Another survey in Arab countries revealed that only 49\% of respondents reported having MDTs.\textsuperscript{11} This could be because establishing MDT clinics in LMICs is difficult because of competing health-care demands, limited health-care personnel, and poor infrastructure.\textsuperscript{12,13} Although there are established oncology MDT clinics in LMICs in Africa, such as in Uganda and Egypt, there have been no published studies on the direct benefits of these MDT clinics.\textsuperscript{14,15}

The purpose of this paper is to describe the implementation and early outcomes of a gynecologic MDT clinic in Botswana, which, to our knowledge, is the first gynecologic MDT clinic in an LMIC. We also describe the impact of the MDT clinic on reducing treatment delay.

**METHODS**

Organization Before Weekly Meeting

Through a collaborative effort across providers, we established a weekly gynecologic MDT clinic at Botswana’s national referral facility in Gaborone. A nurse coordinator was assigned to manage patient flow. All new referrals with basic information, including stage, date of biopsy, results of biopsy specimen assessment, and HIV status, were sent to the nurse coordinator, who then procures patient records and ensures that biopsy results are available. All patients to be discussed were contacted by the coordinator the day before the clinic meeting.

Workflow During Weekly Meeting

At the beginning of each clinic meeting, a team composed of a radiation oncologist, clinical oncologist, gynecologist, pathologist, nurse coordinator, and palliative care specialist discuss all patients referred to the MDT clinic. Together, an oncologist and gynecologist examine patients and determine an appropriate care plan. If the patient requires radiation, paperwork to document sponsorship of treatment by the government of Botswana is completed and submitted to the referral office. Investigations for staging or treatment planning are ordered if they have not been done previously. If patients are HIV positive or untested, they are referred to an HIV clinic for antiretroviral treatment evaluation or retesting for HIV. Patients are then counseled on the treatment plan by an oncologist, gynecologist, and palliative care doctor, and given a follow-up date in 2 weeks to make sure all the investigations are completed and all submitted documents are processed.

**Table 1.** Patient, Clinical, and Treatment Characteristics of Patients Seen in a Multidisciplinary Gynecologic Oncology Clinic in Botswana, May 2015 Through December 2015

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td>135</td>
</tr>
<tr>
<td>Age, years, mean ± SD</td>
<td>49 ± 14.35</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>82 (60.74)</td>
</tr>
<tr>
<td>Negative</td>
<td>42 (31.11)</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (8.15)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Cervical SCC</td>
<td>81 (60.00)</td>
</tr>
<tr>
<td>Stage IA</td>
<td>13 (16.05)</td>
</tr>
<tr>
<td>Stage IB</td>
<td>8 (9.88)</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>3 (3.70)</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>11 (13.58)</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>1 (1.23)</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>14 (17.28)</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>2 (2.47)</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>1 (1.23)</td>
</tr>
<tr>
<td>None</td>
<td>2 (2.47)</td>
</tr>
<tr>
<td>Unknown</td>
<td>23 (28.40)</td>
</tr>
<tr>
<td>CIN3</td>
<td>16 (11.85)</td>
</tr>
<tr>
<td>Vulvar SCC</td>
<td>14 (10.37)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>11 (8.15)</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>3 (2.22)</td>
</tr>
<tr>
<td>Cervical adenocarcinoma</td>
<td>2 (1.48)</td>
</tr>
<tr>
<td>Retropertoneal Kaposi sarcoma</td>
<td>1 (0.74)</td>
</tr>
<tr>
<td>Uterine carcinosarcoma</td>
<td>1 (0.74)</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>1 (0.74)</td>
</tr>
<tr>
<td>Cervical carcinosarcoma</td>
<td>1 (0.74)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment prescribed</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>104 (48.60)</td>
</tr>
<tr>
<td>CRT/RT</td>
<td>57 (26.64)</td>
</tr>
<tr>
<td>Surgery</td>
<td>24 (11.21)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>12 (5.61)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (7.94)</td>
</tr>
</tbody>
</table>

Abbreviations: CIN, cervical intraepithelial neoplasia; CRT/RT, chemoradiation/radiation; SCC, squamous cell carcinoma.
We evaluated the patient characteristics and radiation treatment delays in patients seen in this clinic. The Wilcoxon rank-sum test was used to compare the delay in treatment before and after MDT clinic initiation. Only data up to September 2015 were assessed for treatment delays, because the radiation department in Botswana closed in September 2015 for an upgrade and patients were referred to South Africa.

**RESULTS**

A gynecologic MDT clinic was initiated at Princess Marina Hospital in May 2015. Between May and December 2015, 135 patients were seen in this clinic, with an average of 28 patients per month. Most patients (n = 82; 60%) were HIV positive, 31% (n = 42) were HIV negative, and the HIV status of 11 patients was unknown. The most common diagnosis of patients who came to the MDT clinic was cervical cancer (60%), followed by high-grade preinvasion, or cervical intraepithelial neoplasia 3, lesions (12%) and vulvar cancer (11%). Forty-two percent of patients (n = 57) had locally advanced cancer and needed chemoradiation. Further details of patients seen in the clinic are listed in Table 1. Sixty-two percent of patients (n = 83) needed only one visit for care coordination. Treatment delays were evaluated for radiation treatment as well as surgery. The median delay from date of biopsy to start of radiation treatment was 39 days (interquartile range [IQR], 34 to 57 days) after MDT initiation, compared with 108 days (IQR, 71 to 147 days; P < .001) before MDT initiation. The median delay from clinic visit to the start of radiation treatment was 24 days (IQR, 19 to 31 days) and median delay from clinic visit to surgery was 31 days (IQR, 13 to 43 days) after MDT initiation (Table 2).

**DISCUSSION**

The complexity of cancer care makes it vulnerable to delay and suboptimal outcomes. By enhancing communication and streamlining care, MDTs are important in reducing treatment delays and improving patient outcomes. The results from the establishment of a gynecologic MDT clinic in Botswana are promising. The time from diagnosis to the start of radiation treatment was reduced by greater than 50% following initiation of the MDT clinic. Furthermore, only 38.5% of patients needed more than one clinic visit, suggesting that even one visit to the MDT clinic was sufficient to facilitate patient navigation through the system.

Similar MDT models are also being piloted for head and neck, palliative care, and breast cancer in Botswana. A follow-up clinic is being piloted where all patients treated with gynecologic cancer are seen after treatment or followed up until signs of toxicities or recurrence appear. All the patients seen in the MDT clinic will be linked to the follow-up clinic and will receive regular reminders for a visit or a telephone call for follow-up.

In summary, establishment of an MDT clinic in LMIC settings is feasible. It can help with care coordination and reducing delays, and can be used more broadly as a model of cancer care for all cancers in Botswana and other LMICs.

**Table 2.** Clinic Visits for Gynecologic Oncology Multidisciplinary Clinic in Botswana, May Through December 2015

<table>
<thead>
<tr>
<th>Clinic Visits</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>135</td>
</tr>
<tr>
<td>Mean no. of patients per month</td>
<td>28</td>
</tr>
<tr>
<td>Clinic visits per patient, No.</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>83 (61.48)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>52 (38.52)</td>
</tr>
<tr>
<td>Month of clinic visit</td>
<td></td>
</tr>
<tr>
<td>May</td>
<td>16 (7.37)</td>
</tr>
<tr>
<td>June</td>
<td>25 (11.52)</td>
</tr>
<tr>
<td>July</td>
<td>30 (13.82)</td>
</tr>
<tr>
<td>August</td>
<td>27 (12.44)</td>
</tr>
<tr>
<td>September</td>
<td>26 (11.98)</td>
</tr>
<tr>
<td>October</td>
<td>29 (13.36)</td>
</tr>
<tr>
<td>November</td>
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**AUTHOR CONTRIBUTIONS**

Manuscript writing: All authors  
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**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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Surbhi Grover  
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Affiliations

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The Quality in Oncology Practice Initiative (QOPI) is ASCO’s quality assurance initiative launched in 2006. It provides oncology practices with a tool for self-evaluation of the care they deliver and benchmarks for comparison. Furthermore, QOPI provides certification to those who submit their work for external audit. After certifying close to 300 practices in the United States, QOPI has launched an international effort. This year’s ASCO annual meeting marked a significant moment for our practice, as we were the first outside the United States to attain QOPI certification.

Certification was the result of a long road to quality improvement that started a number of years ago for us. We learned several important lessons from this process, among which that patient safety comes first. To ensure patient safety, we learned that all health care personnel should be involved in quality efforts; thus, nursing staff training became of utmost importance. Furthermore, we were reminded to always address the psychosocial in addition to the medical needs of the patient.

As the dust settles, one tends to evaluate the effort for its worth, and in the framework of expanding QOPI beyond the United States, important questions have arisen. Quality and value are ethical terms based on accepted concepts of what is good or bad, acceptable, and expected. However, as much as we live in an era of globalization, for better or for worse we are far from a globalized view of ethical concepts. One culture’s high-held ethical premise (eg, full explanation of prognosis to the patient) may be unacceptable in another. Obvious measures, such as fertility preservation, may be unacceptable or irrelevant in another society or religion. The epitome is probably advance directives, which are still not legal even in some European countries. In our case, the question of referral to hospice was always answered in the negative because hospice does not exist in Greece! One wonders whether this is only due to poor management by the state or to the tendency of Greek families to take over the terminal care of patients.

Different health care systems approach quality improvement in different ways, and a private initiative is more or less relevant in countries where health care is for the most part centrally managed. Then comes the greater other part of the world, that is, low- and middle-income countries (LMICs) where appropriate antiemetic or analgesic therapy is irrelevant because advanced antiemetics or, even worse, analgesics are plainly not available or are well outside the financial ability of the majority of the population. Therefore, in this context, one wonders how realistic and, more importantly, how relevant, the expansion of QOPI outside the United States is.

To answer this question, one needs to go back to the basics: The whys and hows lie in the fundamental values that brought 37,000 oncologists from all over the world to the ASCO annual meeting this year, many from LMICs where some of the latest discoveries simply are not relevant. Surely, science is an important unifying goal, but I suspect that for the most part, we were all there because we want to provide better care to our patients, and better is inherently an ethical concept, which by definition incorporates quality.

Therefore, I propose that qualitative amelioration is a universally accepted goal. This then automatically establishes a role for efforts that ensure the achievement of this goal. The road to this goal involves yet another universally accepted concept: You cannot improve what is not first measured. Furthermore, you do not want to measure the quality of oncology care with a tool used for a motor vehicle company.

So far, so good. A quality in oncology practice initiative is, by definition, useful to all persons involved in oncologic care and, above all, to all persons in need of oncologic care! In taking the next step, the key issue is to evaluate whether the quality points (measures and standards) put forth by QOPI should become global; that is, we should all agree that they are inherently universal in value and, therefore, that the world of oncology should be streamlined on the basis of these standards, that local quality standards should exist everywhere and local efforts should seek to meet those, or, finally, that a hybrid should be established. The
latter approach is probably the most realistic and the one that maintains respect for the diversity of culture, ethical values, health care systems, and economies worldwide.

QOPI has some core measures that are seminal and constitutional in nature. For example, I believe it is universally accepted that the patient’s histology report should be in the chart. That is, of course, if there is a report (and if there is a chart to begin with). In some countries, having either may be a challenge but should nonetheless be a goal. A tiered approach could exist where in some countries, the measure reads: “If the tumor has been biopsied or resected, the pathology report is in the chart; or, if estrogen receptors have been tested, the results are in the chart; or, if estrogen receptor status has been established to be positive, hormonal therapy has been given.” Another universally accepted standard is that appropriate identification of the patient receiving a drug is necessary. No one would advocate that it is acceptable to administer chemotherapy to anyone who happens to be around!

In summary, I propose that certain standards are basic and universally accepted and that oncology practitioners worldwide should strive to meet them. In fact, they should be what new oncology clinics in LMICs are built upon. Among such standards are a biopsy-proven diagnosis whenever possible, the use of patient identifiers, patient record keeping, and safe chemotherapy handling. On the other hand, other measures may need adaptation to culturally appropriate ethical values or to other social and economic parameters.

Also relevant to this discussion is the concept of value. Value is a reflection of both what is meaningful to and what is expected by the patient and by society; thus, it is inherently tied to ethical, cultural, and economic parameters. Therefore, through outcomes research, some parameters should be established to aid not only in quality assurance but also, and more importantly, in the establishment of the organizing principles for cancer clinics worldwide. Such research may also be used in higher-income settings to reduce costs and overtreatment.

Therefore, as QOPI unfolds its international wings, it will take a hybrid approach to make this an immensely valuable tool, useful to oncologists throughout the world. ASCO should keep QOPI’s basic structure and values but work with the international community to adapt the measures, to some extent, to match the health care systems, cultures, etc., of other parts of the world.

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Evangelia D. Razis
Honoraria: Roche, Genentech, Novartis, MSD, Pfizer, AstraZeneca, Bristol-Myers Squibb
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Affiliations
Evangelia D. Razis, Hygeia Hospital, Marousi, Greece
Atypical T1 Hyperintense Neurocysticercosis Masquerading As Cystic Brain Metastases

INTRODUCTION

Neurocysticercosis (NCC) is a clinical condition characterized by involvement of the CNS by an encysted larval form of the parasite *Taenia solium*. It is a common cause of seizures and neurologic morbidity in developing countries.1,2 Brain metastasis is a common complication of cancer, and cystic brain lesions often pose a diagnostic challenge in this clinical scenario.3 The imaging appearance of NCC on magnetic resonance imaging (MRI) depends on the stage of the disease. To our knowledge, cystic lesions in NCC appearing hyperintense on T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) images have not been described in the literature. We report one such case, with multiple intracranial cystic lesions showing hyperintense signals on T1-weighted images.

CASE REPORT

A 63-year-old woman with breast cancer and lung, bone, nodal, and skin metastases presented with a history of headache and dizziness. She was referred for contrast-enhanced computed tomography (CT) scanning to rule out brain metastases. CT imaging (Fig 1) revealed multiple hypodense lesions in the bilateral cerebral and cerebellar hemispheres, with attenuation values of approximately 17 to 18 Hounsfield units. These lesions showed no significant perilesional edema or postcontrast enhancement. Most of these lesions, however, showed eccentric calcifications. On the basis of the imaging findings, a provisional diagnosis of NCC appearing hyperintense on T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) images have not been described in the literature. We report one such case, with multiple intracranial cystic lesions showing hyperintense signals on T1-weighted images.

DISCUSSION

Presence of multiple cystic lesions in the brain carries a wide range of differential diagnosis (Table 1), and knowledge of imaging patterns is important to accurately diagnose these lesions and differentiate them from their close mimics.2,3 The diagnosis depends on imaging findings (CT and MRI), CSF studies, and clinical correlation. The imaging diagnosis in such lesions depends on the imaging pattern and clinical-epidemiologic background. NCC is a common systemic parasitic infection affecting the nervous system, muscles, and other soft tissues. Clinical presentation ranges from trivial symptoms, such as headache, vomiting, and fever, to seizures, focal neurologic deficit, and stiff neck. Because there is no specific clinical sign to suggest a diagnosis of NCC, imaging by CT scan or MRI is the mainstay of the diagnostic workup.1 Brain metastasis is a common complication of cancer, and differentiating these lesions from NCC may be challenging in the presence of an atypical imaging pattern.1,2

The imaging appearance of NCC on MRI depends on the stage of the disease. The four recognized stages of NCC are vesicular, colloidal vesicular, FLAIR sequences. None of them showed diffusion restriction, perilesional edema, or a significant enhancing cystic solid component. A few of the lesions showed subtle, thin, peripheral rim enhancement. Susceptibility-weighted imaging (SWI) revealed eccentric focal blooming in most of these cystic lesions, corresponding to the calcification seen on the CT scan. No evidence of any intracranial metastases was noted. The features suggested NCC, but an unusual finding was the hyperintense signal in the cystic component of a few lesions seen on T1-weighted images (asterisk in Fig 2) and focal eccentric T1-weighted hyperintense foci (arrow in Fig 2A) in a few lesions. A final diagnosis of NCC was made, and the patient was treated with albendazole therapy.
granular nodular, and nodular calcified. The vesicular stage on CT/MRI appears as a well-defined cyst with a thin perceptible wall and no perilesional edema or postcontrast enhancement. The cyst follows fluid signal on both the CT scan (isoattenuating to CSF) and MRI (hypointense to isointense relative to CSF on T1-weighted images, hyperintense on T2-weighted images, and suppressed on FLAIR images). An eccentrically located discrete scolex within the cyst characterizes the stage. The parasite larva is viable but escapes the host immune response in this stage. Thereafter, the larva degenerates, with features of hyaline degeneration. The cyst shrinks in size, and fluid becomes turbid, with proteinaceous content inciting the inflammatory response from the host. This progresses into the colloidal vesicular stage, characterized by cyst fluid contents that appear slightly hyperattenuating on CT compared with CSF and follows a fluid intensity pattern on MRI. This stage is characterized by the appearance of ring enhancement and perilesional edema. The granular nodular stage shows retraction and mineralization of the lesion. On imaging, partial regression of the edema and postcontrast peripheral enhancement are shown. The nodular calcified stage is characterized by complete mineralization of the lesion. The cyst becomes calcified, with no
edema or postcontrast enhancement. The lesion is typically hypointense on T1-weighted and T2-weighted sequences and calcified on CT scan.2,4,5 Because there are no specific clinical signs to suggest the diagnosis of NCC, imaging by CT scan or MRI is the mainstay of diagnostic work-up. Incidental findings of multiple calcifications in brain parenchyma were the main imaging findings in the initial studies.4 Comparisons between the diagnostic ability of CT and MRI are well established. MRI has been shown to be superior to CT imaging in the detection of parenchymal as well as ventricular NCC.2,4 CT scanning, however, better delineates the calcifications in the later stages.2,4 In atypical cases, laboratory testing of the serum using enzyme-linked immunosorbent blot and the CSF using enzyme-linked immunosorbent assay or enzyme-linked immunoelectrotransfer blot-2 aids the diagnosis.4,5

In our case, the fluid component of a few lesions showed hypointense signal on T1-weighted imaging, and a few lesions showed eccentric hyperintense signal on T1-weighted imaging. The cause of T1-weighted hyperintensity in NCC has not been well described in the literature. Small eccentric T1-weighted hyperintense areas may occur as a result of the paramagnetic effect of the soft calcification in the scolex of the larva, which on gradient recalled echo/SWI appears as a hypointense signal and corresponds to hyperdense calcified areas on CT.6 The hyperintensity of the cystic fluid component of the lesion can be secondary to degeneration of the encysted larval form. The cyst fluid becomes turbid with an increased amount of proteinaceous material, which explains the hyperintense signal on T1-weighted sequence and can be considered an early sign of degeneration of cysticercus larva and its transformation into the colloidal vesicular stage. In our case, the final diagnosis of NCC was made, and the patient was treated with albendazole therapy.

Our case highlights the importance of always considering neuroinfection in the differential diagnosis of patients with known extracranial malignancy in endemic regions. In conclusion, in developing countries where enzyme-linked immunosorbent assay and immunoblot essays for NCC are not routinely available, knowledge of this atypical imaging pattern has great clinical implications for a timely diagnosis and appropriate management.

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Fig 3. (A) T1-weighted, (B) T2-weighted, (C) fluid-attenuated inversion recovery, and (D) postcontrast T1-weighted magnetic resonance images showing multiple cystic lesions in the cerebral and cerebellar hemispheres. The cyst followed fluid signal on magnetic resonance imaging (hypointense to isointense relative to CSF on T1-weighted, hyperintense on T2-weighted, and suppressed on fluid-attenuated inversion recovery images). A few lesions showed eccentric hyperintense focus on T1-weighted imaging (arrow) that on susceptibility-weighted images revealed eccentric focal blooming corresponding to calcification seen on CT imaging; no hemorrhage was seen within. None of the lesions showed diffusion restriction or perilesional edema. Thin ring enhancement was seen in a few of the lesions.

Table 1. Common Differential Diagnosis for Multiple Cystic Lesions in the Brain

| Normal variant: enlarged Virchow-Robin spaces, multifocal ischemic infarct |
| Infections: tuberculomas; neurocysticercosis, hydatid cysts, and other parasitic infections |
| Neoplastic: metastases |

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Refractory Choriocarcinoma: Complete Response With Oral Etoposide

CASE REPORT

A 33-year-old, married woman came to the hospital in 2015 with bleeding from the vagina and shortness of breath of 3 months’ duration. Her obstetric history was as follows: the first pregnancy ended in a miscarriage, the second was a stillbirth, and the third was a molar pregnancy. She delivered a healthy girl after her fourth pregnancy 4 years ago. At presentation, her beta human chorionic gonadotropin (hCG) level was 450,000 mIU/mL, an ultrasound of the abdomen showed a 7 cm × 6 cm × 5 cm cystic mass in the endometrial cavity, a chest radiograph and a computed tomography scan of the chest showed multiple lung metastases, and magnetic resonance imaging of the brain showed hemorrhagic metastasis.

The patient was diagnosed with gestational trophoblastic tumor (GTT) and stage IV choriocarcinoma, with a WHO risk score of 20. A regimen of etoposide and cisplatin with etoposide, methotrexate, and dactinomycin (EMA-EP) was initiated, after which her hCG level declined in a logarithmic linear fashion, and the lung metastases resolved. However, after the seventh cycle of EMA-EP, her hCG level started rising. She was subsequently treated with combination chemotherapy comprising paclitaxel, ifosfamide, and cisplatin. Although the hCG level declined to a normal level after the second cycle, the patient developed life-threatening toxicity with grade IV neutropenic sepsis with liver and renal dysfunction. She refused further intravenous chemotherapy and was monitored without treatment. A month later, her hCG level was abnormal and a radiograph of her chest showed metastases.

The patient declined further intensive treatment, so she was prescribed oral etoposide 50 mg/day for 7 days every 3 to 4 weeks. After six cycles, she was in biochemical remission with a normal computed tomography scan of the chest and brain. She was treated with two more cycles of etoposide and she is currently well without any evidence of disease.

DISCUSSION

High-risk GTT is usually treated with combination chemotherapy. However, approximately 20% of patients have a recurrence of disease after initial treatment. These patients are treated with second-line chemotherapy consisting of various combinations of drugs (eg, EMA-EP; vinblastine sulfate, ifosfamide, and cisplatin; paclitaxel, ifosfamide, and cisplatin; ifosfamide, carboplatin, and etoposide). The agents that have shown response in refractory GTT include ifosfamide, gemcitabine, and capecitabine. Ifosfamide alone or in combination (eg, combined etoposide, ifosfamide, and cisplatin) are active in patients with refractory disease. Gemcitabine plus cisplatin has shown activity in a patient who progressed after combination chemotherapy and EP-EMA. Ifosfamide alone can produce complete and long-lasting remission in refractory GTT. If there is biochemical remission, then it could be consolidated with high-dose chemotherapy supported with peripheral blood stem cells.

To the best of our knowledge, this is the first case of refractory GTT showing complete remission with oral etoposide without any significant toxicity. Etoposide, a topoisomerase II inhibitor, is a drug specific to cell-cycle phase and is active when given orally to maintain a cytotoxic trough level. It was not administered continuously in this patient because of previous toxicity; however, it could be considered to represent metronomic treatment. Metronomic chemotherapy has not been previously used in refractory choriocarcinoma. Systematic analysis has shown that metronomic chemotherapy is effective and safe in a broad range of tumors. The mechanism of action of metronomic chemotherapy is probably due to the effect on stromal components within a tumor. It had been thought that metronomic chemotherapy targeted angiogenesis, but recent data have shown that metronomic chemotherapy targets activated endothelial cells and decreases the chance of developing acquired drug resistance.
In conclusion, oral etoposide is an active agent in the treatment of refractory choriocarcinoma. Further phase II studies are indicated.

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Manikandan Dhanushkodi
No relationship to disclose

Trivadi Ganesan
No relationship to disclose

Tenali Gnana Sagar
No relationship to disclose

Affiliations

Manikandan Dhanushkodi, Trivadi Ganesan, Tenali Gnana Sagar, Cancer Institute (WIA), Chennai, India.

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Breast Course for Nurses: Educating Health Care Workers to Perform Clinical Breast Screening

TO THE EDITOR:

In many places in Africa, the first contact with a health professional for women with breast complaints is a nurse in a primary clinic. Over the past decades, there has been little formal breast training for nurses because the emphasis has been on the prevention and management of infectious diseases. However, as the incidence of infectious diseases falls, the WHO predicts that mortality due to noncommunicable diseases in the developing world will increase by 17% in the next 10 years. This will have a major impact on an already overburdened health system. Similarly, Goss et al have predicted that the prevalence of cancer in developing countries could increase by 90% by 2030. In many high-income countries, mammographic screening programs are offered. However, some countries, such as Switzerland, are reviewing their programs.

Mammographic screening programs are not appropriate or feasible for the majority of low-income countries. In many African countries, there is minimal access to mammography equipment, and it is expensive. Although there are few accurate statistics for South Africa, an estimated 54% of women with breast cancer present with locally advanced disease. In a study from Baragwanath Hospital in Johannesburg, South Africa, it was found that women who lived further away from the breast clinic were diagnosed at a later stage. Health care services in South Africa are a mixture of those seen in low- and high-income countries. A different model of breast screening is necessary to improve the general well-being of the majority of women who rely on state health services.

Clinical breast examination has been studied as a modality of screening for cancer with variable results. In Canada, where clinical breast examination was compared with mammographic examination, the mortality from breast cancer after 20 years was similar in both groups, although more cancers were diagnosed in the mammographically screened population. In Sudan, nurses and volunteers were trained to perform clinical breast examinations on all women ≥ 18 years of age in a screened population. The incidence and stage of breast cancer were compared with that in an unscreened population. Results showed that clinical screening resulted in women being diagnosed with earlier-stage breast cancer.

To address the need for competent nurses in South Africa who are able to provide clinical breast screening, the Breast Course for Nurses (BCN) was developed. The course content of the BCN is based on the Breast Care course book, which is part of the Bettercare series. The Bettercare series of course books is written for nurses working in primary clinics and is designed to promote self-learning. The topics covered in each book are divided into small, easy-to-understand sections. The language used is tailored to nurses whose first language is not English. The Breast Cancer course book is divided into eight chapters. Three chapters are devoted to assessment of the breast and changes found in the normal breast, three chapters cover the principles of breast cancer care, one chapter covers investigations, and one chapter covers palliative care. The book was written in collaboration with professionals in breast cancer management in South Africa.

The BCN combines a distance education component using the Breast Care course book with a residential course. The residential course places the theory learned from the course book into practice. It is divided into three modules. Each module is progressively more specialized. Lay volunteers, community care workers, and registered nurses complete module 1, and doctors and the oncology sisters complete module 2. (Module 3 covers...
the material in module 1 in an abbreviated form.) The aim is to enable healthcare workers to differentiate between women who need to be referred for additional evaluation and women who can be safely managed locally.

One of the aims of the course is to make care for women with breast problems more accessible. The course teaches clear guidelines about when a woman with a breast lump needs to be referred. For example, the recommendation is that any women ≤ 25 years of age with no significant family history and with a new breast mass < 5 cm can be followed up clinically in 4 months, reducing the burden on the breast clinic. Should the mass increase in size, she should be referred for investigation. However, for any woman > 25 years of age with a new mass, investigation is mandatory.

The WHO conducted a survey on the availability of palliative care globally. They found no evidence of any form of palliative care in 22 African countries. Each course invites local health care providers to teach the principles of palliative care with the four drugs most commonly available (acetaminophen, morphine, amitriptyline, and ibuprofen).

Lymphedema is poorly managed in much of Southern Africa, with few facilities available. One of the founders of the BCN is a trained lymphedema therapist. Lymphedema is not recognized as a disease in most African countries and is thought to be a normal occurrence for women with advanced breast cancer or after breast cancer surgery. Although South Africa is fortunate to have over 70 registered lymphedema therapists, Zimbabwe currently has only two, and there is no documented evidence of any lymphedema therapists in any other African countries.

Lymphedema management can be expensive. In urban South Africa, patients with lymphedema may be referred to a therapist outside the cities, because few facilities exist. The BCN aims to educate nurses about lymphedema, how to recognize it, and how to manage and prevent it through simple exercises and breathing techniques.

The emphasis of the BCN course is on learning rather than teaching. Most of the faculty in the residential course are local health care providers. Therefore, although the core content of the course remains the same wherever the course is taught, the information becomes applicable for the available resources. It can also be adapted, depending on the type of healthcare workers being trained.

Since 2012, the BCN has been taught in South Africa on numerous occasions (Cape Town, Johannesberg, Durban, and Port Elizabeth), as well as in Malawi (Lilongwe), Zimbabwe (Harare and Bulawayo), and Namibia (Windhoek and Ongwediva). To date, over 600 health care providers have successfully completed the course.

One of the advantages of the BCN in its current format is its flexibility, allowing adaptation to local conditions. All participants complete a multiple-choice test, which is based on the Breast Care course book, before attending the residential course. At the moment, all participants receive a certificate of completion if they complete the multiple-choice test and attend the course. We are continuing to discuss the possibility of an end-of-course examination. Application has been made to the OCSA Academy of Excellence for registration for the BCN.

The learning methodology used in the Breast Care course book is the same methodology widely used and extensively evaluated in the Perinatal Education Program over the past two decades in South Africa. Nurses fill in an assessment form at the beginning of the course and are asked to complete the assessment again 6 months later. We are gradually accumulating data from participants. A study is being performed to determine whether women with breast cancer are being diagnosed at an earlier stage.

The BCN has many challenges but has been developed by health care practitioners in South Africa for the training of health care workers throughout southern Africa. The course is offered to health departments on request. Because local faculty are actively involved, there has not been much resistance to the content offered.

The stage of diagnosis of women with breast cancer is dependent on many factors. It is hoped that by educating nurses in primary clinics, women with breast cancer will be referred more appropriately and in a more timely manner.

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Jenny Edge
Travel, Accommodations, Expenses: Novartis
Lieske Wegelin
Travel, Accommodations, Expenses: Novartis

Affiliations
Jenny Edge and Lieske Wegelin, Christiaan Barnard Memorial Hospital; and Dave Woods, Red Cross Children’s Hospital, Cape Town, South Africa

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