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Treating Nephroblastoma in Rwanda: Using International Society of Pediatric Oncology Guidelines in a Novel Oncologic Care Model

Purpose Success in treating nephroblastoma in high-income countries has been transferred to some resource-constrained settings; multicenter studies report disease-free survival of greater than 70%. However, few reports present care models with rural-based components, care tasks shifted to internists and pediatricians, and data collection structured for monitoring and evaluation. Here, we report clinical outcomes and protocol compliance for patients with nephroblastoma evaluated at Butaro Cancer Center of Excellence in Rwanda.

Patients and Methods This retrospective study reports the care of 53 patients evaluated between July 1, 2012, and June 30, 2014. Patients receiving less than half of their chemotherapy at Butaro Cancer Center of Excellence were excluded.

Results Of the 53 patients included, 9.4% had stage I, 13.2% had stage II, 24.5% had stage III, 26.4% had stage IV, and 5.7% had stage V disease; the remaining 20.8% had unknown stage disease from inadequate work-up or unavailable surgical report. The incidence of neutropenia increased with treatment progression, and the greatest proportion of delays occurred during the surgical referral phase. At the end of the study period, 32.1% of patients (n = 17) remained alive after treatment; 24.5% (n = 13) remained alive while continuing treatment, including one patient with recurrent disease; 30.2% (n = 16) died; and 13.2% (n = 7) were lost to follow-up.

Conclusion Our findings confirm that nephroblastoma can be effectively treated in resource-constrained settings. Using an approach in which chemotherapy is delivered at a rural-based center by non-oncologists and data are used for routine evaluation, care can be delivered in safe, novel ways. Protocol modifications to mitigate chemotherapy toxicities and strong communication between the multidisciplinary team members will likely minimize delays and further improve outcomes in similar settings.

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continued
Screening by Clinical Breast Examination in Western Kenya: Who Comes?

**Purpose** More than 80% of women with breast cancer in Kenya present to medical care with established late-stage disease. We sought to understand why women might not participate in breast cancer screening when it is offered by comparing the views of a cohort of those who attended a screening special event with those of community controls who did not attend.

**Methods** All residents living close to three health centers in western Kenya were invited to participate in screening. Participants (attendees) underwent clinical breast examination by trained physician oncologists. In addition, women who consented were interviewed by using a modified Breast Cancer Awareness Module questionnaire. Nonattendees were interviewed in their homes the following day.

**Results** A total of 1,511 attendees (1,238 women and 273 men) and 467 nonattendee women participated in the study. Compared with nonattendees, the women attendees were older, more often employed, knew that breast cancer presented as a lump, and were more likely to have previously felt a lump in a breast. In addition, they were more likely to report previously participating in screening activities, were more likely to have performed breast self-examination, and were less concerned about wasting a doctor’s time. Almost all those surveyed (attendees and nonattendees) expressed interest in future breast cancer screening opportunities.

**Conclusion** The women who volunteer for breast cancer screening in western Kenya are more aware of breast cancer than those who do not volunteer. Screening recruitment should seek to close these knowledge gaps to increase participation.

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Outcomes of Saudi Arabian Patients With Nasopharyngeal Cancer Treated With Primarily Neoadjuvant Chemotherapy Followed by Concurrent Chemoradiotherapy

**Purpose** Nasopharyngeal cancer (NPC) is the most common head and neck cancer in Saudi Arabia. This study reports the locoregional disease control and survival outcomes in patients with NPC treated in King Abdulaziz University Hospital.

**Methods** Patients treated for NPC between June 2007 and October 2014 were retrospectively reviewed. Demographic information, clinicopathologic variables, and chemotherapy data were collected and analyzed. Cumulative survival and disease control rates were calculated by Kaplan-Meier product-limit actuarial method.

**Results** Thirty-nine patients with NPC were reviewed. Thirty-five (90%) patients received definitive radiotherapy (RT) and four (10%) had palliative RT. Mean prescribed dose for definitive RT was 68 Gy (range, 60 to 70.2 Gy), delivered with mean doses per fraction of 1.9 Gy (range, 1.8 to 2.1 Gy). After a median follow-up of 15 months (range, 1 to 84 months), 22 (63%) patients who underwent definitive RT were disease free and 13 (37%) were still with disease. During this period, seven (18%) patients died of the disease; five (13%) of them received definitive RT. After 2 years’ follow-up, the actuarial estimate rates were: 85.7% for local control, 91.4% for nodal control, and 85.7% for distant control.

**Conclusion** Our study showed a disease with clinical behavior similar to what has been observed in East and Southeast Asia. Further it explored the neoadjuvant chemotherapy approach in treating NPC with results that are comparable to literature. However, little is known about the molecular pathogenesis of this disease in this region, and further research integrating clinical and molecular biomarkers is required.

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Treatment of Chronic Myeloid Leukemia in Rural Rwanda: Promising Early Outcomes

**Purpose** The burden of cancer is rising in low- and middle-income countries, yet cancer treatment requires resources that are often not available in these settings. Although management of chronic myeloid leukemia (CML) has been described in low- and middle-income countries, few programs involve patients treated in rural settings. We describe characteristics and early outcomes of patients treated for CML at rural district hospitals in Rwanda.

**Methods** We conducted a retrospective review of patients with confirmed BCR-ABL–positive CML who were enrolled between July 1, 2009 and June 30, 2014. Types of data included patient demographics, diagnostic work up, treatment, clinical examination, laboratory testing, and death.

**Results** Forty-three patients were included, with a maximum follow-up of 58 months. Of 31 patients who were imatinib-naïve at enrollment, 54.8% were men and the median age at diagnosis was 36.9 years (interquartile range: 29-42 years). Approximately two-thirds of patients (67.7%) were on the national public insurance scheme. The imatinib dose was reduced for 16 patients and discontinued for five. Thirty-two of the 43 patients continued to have normal blood counts at last follow-up. Four patients have died and four are lost to follow-up.

**Conclusion** Our experience indicates that CML can be effectively managed in a resource-constrained rural setting, despite limited availability of on-site diagnostic resources or specialty oncology personnel. The importance of model public-private partnerships as a strategy to bring high-cost, life-saving treatment to people who do not have the ability to pay is also highlighted.

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Pulmonary Nodules in Patients With Nonpulmonary Cancer: Not Always Metastases

Introduction The differential diagnosis of pulmonary nodules (PNs) includes metastases, lung cancers, infectious diseases, and scar tissue, among others. Because data regarding whether and when to perform a PN biopsy in patients with cancer are scarce, clinicians tend to assume that PNs are metastatic disease based solely on imaging. The current study evaluated the findings of PN biopsies in a population of patients with cancer and sought to determine the variables that correlated with higher odds of metastatic disease.

Patients and Methods We conducted a retrospective, single-institution study that included consecutive patients with nonpulmonary solid malignancies who underwent PN biopsy from January 2011 to December 2013. Imaging and clinical variables were analyzed by logistic regression to determine the correlation between such variables and the odds of metastatic disease. Patients with previously known metastatic disease or primary hematologic malignancies were excluded.

Results Two hundred twenty-eight patients were included in the study. Metastatic disease was found in 146 patients (64%), 60 patients (26.3%) were diagnosed with a second primary lung tumor, and 22 patients (9.6%) had no cancer on biopsy. On multivariate analysis, the presence of multiple PNs (> 5 mm) and cavitation/necrosis were the only variables associated with higher odds ($P < .05$) of metastatic disease. We registered six (2.6%) procedure complications demanding active interventions, and no procedure-related death occurred.

Conclusion Multiple PNs (> 5 mm) and cavitation were the two characteristics associated with the highest chances of metastatic disease. Our findings demonstrate that PNs should not be assumed to be metastases without performing a biopsy. This assumption may lead to high rates of misdiagnosis. Tissue sampling is fundamental for accurately diagnosing patients with cancer.
Cheaper Options in the Prevention of Chemotherapy-Induced Nausea and Vomiting

Chemotherapy-induced nausea and vomiting (CINV) is a common challenge in oncology practice for which there are expensive guideline-based treatment options. Although supportive care in cancer adds significantly to the overall cost, the discussion of unaffordability of anticancer treatment frequently only revolves around the targeted drugs and immunotherapies. In this review, we highlight the available cost-saving strategies and recent updates in preventing CINV in patients with cancer. This is the first work, to our knowledge, to review specifically the less expensive alternatives in CINV prevention, which is particularly important for those working in resource-limited settings. Whereas patients in these settings often cannot afford expensive antiemetics, we now have the science to offer cheaper, more affordable options without necessarily compromising efficacy.
Me, Too

Every year at the annual ASCO meeting, the economic unfeasibility of anticancer therapies becomes a hot topic of discussion. The skyrocketing cost of newer therapies, especially the targeted drugs and immunotherapeutic agents, has taken cancer treatment beyond the reach of the majority. At the ASCO Annual Meeting in 2015, a speech at the plenary session by Dr Leonard Saltz on the cost of anticancer therapies provoked a big discussion, both in the oncology community and the media.³

Some points raised by Dr Saltz are particularly noteworthy. That the median monthly price for new anticancer drugs has risen from $4,716 in 2000 to 2004 to $9,900 in 2010 to 2014 is staggering. The fact that there are no regulations on pricing of new anticancer drugs is both absurd and sad. That a pharmaceutical company is free to price its drug at whatever price it deems appropriate, on the basis of what the market will bear,² and that the US Government, via Medicare, is obligated to purchase the drug at that price and is barred by law from negotiating price, is illogical, baffling, and inhumane. The affordability of cancer treatment cannot be treated similarly to that of commodities such as cars or paintings.³⁴

Dr Saltz commented on a study presented earlier in that same plenary session, which showed that the combination of nivolumab and ipilimumab resulted in a median progression-free survival of nearly 1 year in patients with metastatic melanoma,⁵ but at a cost of nearly $295,000 per year per patient just for those two drugs. In 2012, of the 13 new drugs approved for cancer, 12 were priced at more than $100,000 per year.⁶ Yes, progress comes at a price, but there is a limit to what we, as a society, can afford.

As spokespersons for the pharmaceutical industry often point out, the research required to develop new drugs requires investment and risk, with many agents ultimately not making it to market. However, the industries’ estimates of drug development costs are often highly inflated and rarely, if ever, supported by an open sharing of corroborating data.²³ The disconnect between development costs and drug price is exemplified by the price of imatinib, which started at $30,000 per year in 2001 but increased to $92,000 per year in 2012, despite there being no additional development costs during that time. Further, the price did not drop but rather rose when newer competing agents, such as dasatinib and ponatinib, came on the market. In addition, as new indications for imatinib were added, making the potential market larger, the price continued to increase, further demonstrating the disconnect between drug pricing and development and production costs.³⁷⁸

Recently, there was a Comments and Controversies article published in Journal of Clinical Oncology regarding the inequalities in approval of the same drug across different countries.⁹ The authors expressed their concern that bevacizumab, though approved in the United States and Europe for epithelial ovarian cancer, is not approved in Canada or the United Kingdom. However, the issue I want to highlight is that not only bevacizumab but nearly all anticancer drugs, both old and new, are out of reach for people living in low- and low-middle-income countries (LMICs). I represent Nepal, a small country sandwiched between India and China, which was poor even before the recent devastating earthquake. While oncologists at the ASCO meeting were debating the value and affordability of new targeted drugs and immunotherapies, patients in my country were deciding whether to sell their house for the treatment of their mother’s ovarian cancer with paclitaxel and carboplatin, or to accept best supportive care as first-line treatment. There would be no point in talking about bevacizumab; it would be out of the realm of consideration. The affordability of generic paclitaxel and carboplatin is what would be in question.

In 2014, a Lancet Oncology Commission highlighted the status of cancer epidemiology, treatment, and research in the developing countries of India, China, and Russia.¹⁰ These countries constitute one-third of the world’s population and one-half of the total cancer burden, with a mortality rate nearly twice that of the United States or the United Kingdom.¹⁰ But these countries are sidelined when it comes to accessibility of cancer therapies. When countries as large as India and China receive insufficient attention, it is not at all a surprise that a small country sandwiched between them is completely forgotten. GLOBOCAN estimates that more than 65% of cancer deaths occur in low-income countries (LICs),¹¹ although only 5% of global
cancer-care resources are directed toward these countries.12

Nepal shares many similarities with India, including religions, culture, values, and languages, as well as the lack of a national health insurance scheme. This 100% pay-from-the-pocket model severely cripples oncologists from providing even the most basic services to patients, most of whom live well below the poverty line. The government of Nepal has allocated an allowance of 50,000 rupees (approximately US$500) for each cancer patient, which is not enough to purchase even one vial of trastuzumab.13 Countries like Nepal and India need a different model of national insurance, in concordance with the local economic capacity and feasibility.13 However, even if an insurance system were to come into place, the government of Nepal, and even that of India, could never bear the current high costs of newer anticancer therapies.

Despite such difficult circumstances, Nepal had been slowly trying to raise its oncology standards with the popularization of outpatient chemotherapy, as well as beginning bone marrow transplant services in 2012.13a However, the aftermath of the earthquake is sure to divert the attention of the government to rebuilding and to the most basic health care. Concerns are already arising regarding vector-borne communicable diseases and maternal-child care in the postearthquake era.14,15 No article, however, has yet raised the question of cancer care in postearthquake Nepal. This lack of attention, as well as other high-priority issues after the earthquake, will further limit the oncology services in this small nation, already crippled by lack of resources, difficult geography, and a severe lack of education. It should be remembered that we are discussing providing cancer-care access to populations who truly believe that the earthquakes are due to our mountains getting angry.16

How to incorporate the newer agents in the United States or European health systems should not be the only priority; how to make these agents affordable even in LLMICs like Nepal should also be a matter of discussion. There is no denying that the accessibility of expensive cancer drugs to all is still a problem in countries like the United States17; however, the oncology community cannot and should not move forward ignoring half of the patients with cancer in the world. How or why should anyone be excited about these advances if nearly half of those who need them are not going to receive them because of cost?

Lack of educated manpower has been identified as an important challenge for cancer control in developing nations.16 However, I am at a loss as to what the education of oncologists in Nepal should constitute. Being well versed in the major cancer treatment guidelines is more of a pain than solace in such a resource-limited setting. While the developed world is worried about the economic viability of incorporating sipuleucel-T, we oncologists in the South Asian Association for Regional Cooperation region are worried about the economic feasibility of incorporating generic doxetaxel into the management of prostate cancer. Pertuzumab and trastuzumab emtansine are not the concerns in our world, where people are not able to afford even trastuzumab. For the patients and oncologists of Nepal, the finding that palbociclib is effective in breast cancer10 is similar to the discovery of black holes: quite exciting from a scientific point of view, pointless from practical point of view. Under such circumstances, practice of evidence-based medicine seems a far-fetched dream. If oncologists in Canada feel sad about not being able to prescribe bevacizumab,3 consider how it must feel to be unable to prescribe nearly 100% of targeted and immune therapies because of unaffordability! The era of targeted therapies has not yet dawned in half of the world. I, although in Japan now, get excited about every new drug discovery in cancers. But when I am back home in Nepal, such news brings despair because that is one more drug that I could use, if only we could afford it.

So how can we enable poor patients from LLMICs to benefit from progress in cancer treatment? One way is to bring awareness and attention to the problem. The recent earthquake serves as a good metaphor for cancer control in LLMICs. The media did an excellent job of covering the natural catastrophe, which brought the national and international authorities and aid agencies together to deal with this disaster. Lack of access to anticancer treatment is also a catastrophe but on an international scale involving more people.4 Oncologists must bring this issue forward and encourage the media and responsible authorities to take notice. Other approaches need to focus on the costs of cancer care and what can be done to mitigate them. The high costs of cancer care in the developed world serve as the starting point from where prices in the undeveloped world are established.

Tabernero18 recently highlighted that there are too many “me too” drugs being developed in oncology. Developing many drugs belonging to the same category with little or no difference adds
to development costs but adds little benefit. Although we can hope that such agents will stimulate competition and drive down prices, we have yet to see evidence of this.

Another opportunity that has yet to be explored and could have important positive global economic impact is early-phase clinical trials conducted in countries like Nepal and India, as we have previously proposed. Because the cost of supportive management is low compared with that in other nations, and the health system in these countries is English-language based, conducting phase I and II trials in these nations is much cheaper. This helps reduce the cost of cancer-related chemotherapy in patients with leukemia.

We recently reported that a cheaper version of amphotericin B emulsified in lipids could be used as a substitute for expensive liposomal amphotericin for antifungal prophylaxis during induction chemotherapy in patients with leukemia in Nepal. Research done in countries like Nepal, exploring the cost-effective approaches to treatment, can be easily translated to the West. The recommendations made by the International Agency for Research on Cancer regarding the futility of ultrasonography, mammography with tomosynthesis and magnetic resonance imaging in breast cancer screening also present an important cost-saving finding, given that breast cancer is the leading cause of death in LICs. LLMICs provide a unique opportunity for cancer research because certain cancers (e.g., virus-associated cancers) have a higher incidence in these regions. An active collaboration between researchers from developed countries and LLMICs like Nepal also provide a unique opportunity to conduct clinical trials on cheaper options of supportive care, such as olanzapine for chemotherapy-induced nausea and vomiting, that are unlikely to be industry sponsored and conducted in the developed world. Olanzapine is a commonly used antipsychotic easily and cheaply available even in countries like Nepal and has already shown promising results in trials of chemotherapy-induced nausea and vomiting.

Oncologists themselves cannot completely solve these problems. Nevertheless, oncologists can indeed play a pivotal role if they are organized and united. Although oncologists cannot change rules and make policies, we are not entirely powerless. Just as an example, the price of ziv-aflibercept was reduced by half within 1 week of publication of an editorial in The New York Times that highlighted the ridiculous expensive-ness of ziv-aflibercept compared with bevacizumab despite similar benefits in colorectal cancer. Similar to the control of profiteering by the government of Nepal after the earthquake, oncologists should join hands to protest the inflated pricing of drugs by the companies, because cancer is also a natural disaster and excessive pricing of drugs is profiteering to that end.

We must also promote research not just on new drug development but also on the cost efficacy of available drugs; for example, the economic analysis of adding ixabepilone to capecitabine or the economic analysis of CALGB/SWOG B0405. In fact, the journals should require all the phase III positive trials to report economic analyses as a part of their publication, similar to reporting of adverse effects. Financial burden should also be acknowledged as an important adverse event, not
just for the patient but the whole family, country, and humanity.

Some common cost-saving measures oncologists all over the world can individually accomplish include avoiding tumor-marker surveillance, which has no benefit in most cancers, stopping the use of chemotherapy for patients with a performance status of greater than 2, and curbing the rampant use of granulocyte-colony stimulating factors despite the lack of evidence of meaningful benefit.32 Another area in which we oncologists can change is our own behaviors. It has been demonstrated that more generously reimbursed physicians tend to prescribe more expensive regimens.33 ASCO has slowly but surely been expanding its network of responsibility across the globe. Along with the frequent International Clinical Trial Workshops they hold in developing countries (there was one in Nepal in 2014), ASCO has also now launched a new journal to particularly address the developing world, Journal of Global Oncology. Furthermore, I am hopeful that ASCO’s first ever clinical trial, Targeted Agent and Profiling Utilization Registry (TAPUR) study, will be a blessing to many poor patients who would otherwise never have access to these drugs. ASCO has also recently published a framework to assess the value of cancer treatment options.34 This is a helpful strategy to make treatment decisions in both developed and developing countries, although further work is needed to make it more easily and swiftly usable in busy clinics. Such academic organizations also have a role to motivate the industry to fund research in LLMICs and pressure the companies on their corporate social responsibilities.35 It is no wonder that a recent survey among oncologists showed that oncologists from high-income countries were more involved in industry-sponsored research than those from LICs, and oncologists from LICs cited lack of funding as the most important obstacle.36 The Breast Health Global Initiative is another example of how oncologists can work together to make some difference.37,38 After the Breast Health Global Initiative, the National Comprehensive Cancer Network panel has also recently announced the launch of its guidelines on the basis of economic feasibility; the cervical cancer guidelines are already in place.39 Similarly, the International Federation of Gynecology and Obstetrics staging system for gynecologic cancers does not involve expensive imaging and yet can help inform important decisions.40

In conclusion, the underdeveloped world cannot be ignored in our planning of the global combat against cancer. The fundamental step is acknowledging the problem. I have found a number of editorials and perspective pieces in highly reputed journals on the issue of economic feasibility of anticancer treatment, but all of them focused on developed countries alone, ignoring more than half of the global cancer burden, which occurs in LLMICs.3,4,6,29,32,41-46 Acknowledgment of the global problem is the first step. As a representative of the oncologists and our patients from the underdeveloped world, I am saying “Me, too.”

DOI: 10.1200/JGO.2015.000588
Published online on jgo.ascopubs.org on January 20, 2016.
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Treating Nephroblastoma in Rwanda: Using International Society of Pediatric Oncology Guidelines in a Novel Oncologic Care Model

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INTRODUCTION

Nephroblastoma (Wilms tumor [WT]) is the most common pediatric kidney cancer. With standardized surgical techniques and chemotherapy, survival is greater than 85% in high-income countries. In contrast, survival rates in African settings are generally less than 45%, although one recent collaborative effort achieved an event-free survival rate of 77%. This outcome disparity reflects lack of access to high-quality, multidisciplinary oncologic care, with many cancer facilities often situated in urban centers and within the private sector.

The Butaro Cancer Center of Excellence (BCCOE) in Rwanda is a public-sector facility located in the rural Northern province, providing cancer care in partnership with international nongovernmental organizations and academic cancer institutes. In this model, clinical care is shifted to general physicians, pediatricians, and internists who receive mentorship from oncology specialists through scheduled conference calls, on-site visits, and e-mail communication. Patients with WT are treated using a nationally approved protocol based on International Society of Pediatric Oncology (SIOP) guidelines and adapted to regionally available resources. Training, supplies (including chemotherapy), social supports for patients, and other resources are supported by the Rwandan Ministry of Health, foundation grants, and individual donations. In this retrospective cohort review, we...
report outcomes and protocol compliance for WT managed at BCCOE and evaluate delays and deaths at each stage of treatment.

PATIENTS AND METHODS

Setting

BCCOE was established in 2012 through a partnership among the Rwandan Ministry of Health, the nonprofit organization Partners in Health/Inshuti Mu Buzima, and the Dana-Farber Brigham and Women’s Cancer Center (DFBWCC). The 160-bed district hospital, a 3-hour drive from the capital Kigali, provides basic imaging (x-ray and ultrasound), laboratory tests, pathology specimen processing, chemotherapy, and social services. Advanced imaging and surgery over the study period were performed at national referral hospitals in Kigali, and pathology reports were provided by pathologists at Brigham and Women’s Hospital, Rwandan referral hospitals, or BCCOE visiting pathologists. Given the lack of radiotherapy available in Rwanda, patients are referred to Mulago Hospital in Uganda on a case-by-case basis and at no cost to the patients. Care is administered regardless of ability to pay.

The care team consisted of Rwandan-trained physicians and nurses without prior specialty training. Additional staff and longitudinal training were provided by Partners in Health/Inshuti Mu Buzima, rotating DFBWCC nurses based at Butaro, and visiting oncologists. This team directed patient care and chemotherapy administration according to the nationally approved protocol (see below). On-site clinicians were supervised by structured weekly phone calls with pediatric oncologists from the DFBWCC with more frequent communication as necessary.

Patients

This study was approved by ethics review boards in Rwanda (Rwanda National Ethics Committee, Kigali, Rwanda) and the United States (Partners Healthcare, Boston, MA). A retrospective review was performed on 56 consecutive patients with available medical records who were evaluated or treated for nephroblastoma between July 1, 2012, and June 30, 2014, at BCCOE. Data were collected from July 1, 2012, through September 30, 2014. At the time of analysis, three patients were excluded from analysis; two of these patients had more than 50% of their chemotherapy delivered at another facility, and one patient was pathologically diagnosed as having renal clear cell carcinoma. Of the 53 patients remaining, 49 patients initially presented for diagnostic evaluation, and four patients were referred to BCCOE after a nephrectomy. Patients continuing therapy at the end of the study were considered alive and disease free.

Management and Treatment

Staging, pathology, and treatment were based on the SIOP 2001 guidelines. Pathology results were classified into low (completely necrotic, cystic partially differentiated), intermediate (regressive, epithelial, stromal, mixed, and focal anaplastic nephroblastoma), and high risk (blastemal, diffuse anaplastic). Treatment was adapted to Rwanda’s health infrastructure and endorsed through expert review at an international conference in Kigali in March 2012 (Data Supplement).

Patients suspected of having nephroblastoma underwent laboratory evaluations (CBCs and renal and liver function tests) and imaging. In compliance with SIOP 2001 recommendations, imaging included abdominal ultrasound, chest x-ray, and computed tomography (CT) scan of the abdomen and pelvis if the ultrasound imaging was suspicious. Pretreatment biopsy was performed only if diagnostic uncertainty existed.

Preoperative chemotherapy depended on tumor stage (a two-cycle regimen of vincristine and actinomycin for localized stage I to III disease and a three-cycle regimen with added doxorubicin for metastatic stage IV and V disease). Preoperative treatment was modified for patients with localized tumors unresponsive to initial therapy; one patient received two additional cycles of chemotherapy, and three patients received an additional three cycles of the metastatic regimen. Surgery was performed at national referral hospitals. Postoperative chemotherapy followed the SIOP higher risk regimen given inconsistent availability of pathology and surgical reports. Radiotherapy is currently not available in Rwanda and thus not part of the national protocol. Basic supportive care including RBC transfusions and intravenous antibiotics was available with intermittent access to platelet transfusions.

Data Collection and Analysis

Clinical encounters were documented in paper charts and transferred into the OpenMRS (Indianapolis, IN) electronic medical record system. Data were collected by a data collector using a structured chart abstraction form and were analyzed using STATA version 12 (STATA, College Station, TX).

Nonmetastatic, localized disease included stages I to III, and metastatic disease included stages IV
and V; this distinction guided the preoperative chemotherapy regimen. Deaths were considered disease related (before treatment began or after relapse) or treatment related (once chemotherapy had been initiated). Loss to follow-up (LTFU) was defined as not returning after surgery or missing the most recent appointment. For assessment of delays, if a patient had a chemotherapy regimen delay, defined as lasting greater than 2 weeks more than the expected duration, all single-event delays were then recorded. Delays during transfer for surgery were defined as greater than 21 days, as recommended by SIOP.15

RESULTS

Patient Demographics

For the 53 patients included in the study (Table 1), the median age was 3.6 years (interquartile range [IQR], 1.9 to 4.9 years), and 58.5% of patients (n = 31) were girls. The majority of patients came from Rwanda (52 patients, 98.1%) with all five provinces represented, and the remaining patient was from the neighboring country of Burundi (1.9%). Median body mass index at presentation was 15.2 kg/m² (IQR, 14.1 to 16.7 kg/m²).

Disease Characteristics

Of the 53 patients, 42 were completely staged (Table 1); five patients (9.4%) had stage I, seven (13.2%) had stage II, 13 (24.5%) had stage III, 14 (26.4%) had stage IV, and three (5.7%) had stage V disease. The remaining patients were not staged as a result of incomplete imaging or missing surgical report (11 patients, 20.8%). Thirty-seven patients completed surgery; three patients (8.1%) had low-risk pathology, 13 (35.1%) had intermediate-risk pathology, and five (13.5%) had high-risk pathology. The remainder had missing or incomplete pathology reports (16 patients, 43.2%).

Disease Work-Up and Treatment Course

Forty-nine patients presented for evaluation. Four patients died before beginning treatment; an additional four patients presented after nephrectomy (Fig 1). Median time from patient-reported symptoms to presentation at BCCOE (Table 1) was 16.0 weeks (IQR, 8 to 28 weeks). Patients most often presented with abdominal distention or mass (52 patients, 98.1%), weight loss (20 patients, 37.7%), fever (14 patients, 26.4%), and hematuria (10 patients, 18.9%; Table 1). Forty-seven patients (88.7%) received both chest and abdominal imaging, and six patients (11.3%) had only documented abdominal imaging (ultrasound, CT scan, or magnetic resonance imaging). One patient received a presurgical biopsy. Once evaluated at BCCOE, patients began treatment within a median of 1 day (IQR, 1 to 2 days).

Forty-five patients began preoperative chemotherapy; 39 of these patients completed therapy, and six died during this phase. Patients with nonmetastatic disease completed chemotherapy over a median of 21 days (IQR, 20.5 to 25 days; expected duration of 21 days), and patients with metastatic disease completed treatment over a median of 38 days (IQR, 35 to 48 days; expected duration of 35 days).

After preoperative chemotherapy, the 39 patients were transferred for surgery at national referral centers; 33 of these patients completed surgery. Three patients died during transfer, one died during surgery, one was LTFU, and one was awaiting surgery at the end of the study period. Of 33 patients for whom surgical transfer dates were documented, 60.6% of patients (n = 20) were beyond the 21-day time frame recommended by SIOP.

Including the four patients transferred to BCCOE after surgical resection, 19 of 37 patients completed the 10-cycle high-risk postoperative chemotherapy over a median of 200 days (IQR, 195 to 233 days; expected duration of 182 days); two of these patients were later LTFU. The remaining 18 patients were continuing treatment (n = 11), died after relapse that was clinically noted and verified by imaging (n = 2), were alive with relapse (n = 1), or were LTFU (n = 4). Finally, two patients (one stage III patient and one stage IV patient) received radiotherapy, both of whom remain alive without disease.

Outcomes

At the end of the study period (Table 2), 30 patients (56.6%) were alive and all but one remained disease free, 16 patients (30.2%) died, and seven patients (13.2%) were LTFU. Of the 17 patients who completed treatment and are in active follow-up, 10 patients were alive at 6 months after completion of their treatment, and five patients were at 1 year. In the case that outcomes are stratified by stage (Data Supplement), it seems that patients with early-stage disease do better, but a fair portion of patients with late-stage WT also do well (Data Supplement); longer term follow-up will be needed to elucidate any relation.

Of the 16 patient deaths, six were classified as disease related (four patients died before initiation of treatment, and two died as a result of relapse on therapy) and 10 were considered treatment...
related. Of these 10 patients, three had documented evidence of malnutrition, and for the remainder, the cause of death was not clear.

Delays and Toxicity

Medical delays in therapy (Data Supplement) most commonly were a result of neutropenia, febrile neutropenia, infections, and other laboratory abnormalities (six delays during preoperative chemotherapy and 28 delays during postoperative chemotherapy). Focusing on hematologic toxicity, the incidence of severe grade 4 neutropenia increased with duration of treatment (zero patients at intake to 19 during postoperative chemotherapy). Inadequate patient resources contributed to socioeconomic-driven delays for seven patients who experienced a total of 16 unique delays in care; one delay occurred during preoperative chemotherapy, and 15 occurred during postoperative chemotherapy. Reasons included ill family members and financial or logistical barriers to transportation.

Last, delays arose secondary to limitations of the health care system. Treatment for two patients was delayed after inability to obtain vincristine for preoperative chemotherapy, and delays occurred for three patients as a result of dactinomycin shortages during postoperative chemotherapy. Although radiotherapy is not currently part of the national protocol, 30 patients with confirmed stage III to V disease would have qualified for radiotherapy according to SIOP guidelines, whereas only two patients actually received radiation.

DISCUSSION

At the BCCOE from July 2012 to June 2014, nephroblastoma represented more than 20% of the pediatric cancers seen and was the most common childhood malignancy. The incidence is similar to that reported from Zambia and other centers in Africa. This is in contrast to the United States, where WT accounts for only 5% of childhood cancers. Whether this represents a true difference based on underlying biologic factors or reflects referral and presentation biases is currently unknown. As a result of the slow growth and few symptoms early in the course of WT, these patients may be over-represented because they survive long enough to present for medical evaluation.

More than half of patients presented with advanced disease similar to that seen in other resource-constrained settings. In contrast, in the United States, only 35% of patients present with stage III or greater disease. However,
staging was imperfect in our study, and the distribution could have been skewed toward either understaging (lack of access to full imaging work-up and incomplete surgical reporting) or over staging (benign lesions being mistaken for metastases or large tumors mistaken for bilateral tumors on ultrasound). Age and sex distribution were comparable to that seen in similar settings and the United States.5,6,21

Our reported outcomes and toxicities for patients with nephroblastoma were encouraging. Although much higher than reported in high-income countries, less than 20% of patients experienced mortality from therapy-related causes, suggesting the current protocol was tolerable for the majority of patients. Treatment-related deaths occurred early in the treatment course during the preoperative chemotherapy and surgery phase. Furthermore, deaths particularly early in treatment were often difficult to distinguish from deaths as a result of disease, given limitations in postmortem documentation. The LTFU rate was 13.2%, which is less than the 20% reported in a Moroccan cohort.22 This is perhaps a result of subsidized chemotherapy and social supports at BCCOE5,6; however, we currently do not have sufficient data to evaluate contributing factors. Relapse rates may also be probed in the future with additional data.

Although many children successfully completed therapy, there remain challenges in the BCCOE model. The cancer center is situated at a district hospital without an intensive care unit, pediatric surgical services, or ability to conduct advanced radiology (CT and magnetic resonance imaging). As a result, treatment relied on close collaborations and coordination with national referral centers. These changes in care venue contributed to delays seen during surgical transfer. Finally, the lack of oncology specialists based at Butaro Hospital affects care delivery. However, the rates of treatment-related death and LTFU support the use of this model as an interim step toward building national oncology capacity.

Within the BCCOE model, delays arose from medical causes, lack of patient resources, and health system issues; this classification of delays guides subsequent improvements in patient care.
Medical delays, including those caused by neutropenia and fever/infection, were the most common and expected in oncologic populations. More stringent use of dose reductions in underweight and malnourished patients, as recommended by SIOP Pediatric Oncology in Developing Countries Committee, and ongoing education are essential. Medical delays caused by infections could also be addressed through developing capacity to perform blood cultures and broadening antibiotic options. Malnutrition has been documented among patients with nephroblastoma in similar settings and likely contributes to medical delays. In our population, mid-upper arm circumference was not standardly recorded, although body mass index at presentation was similar to that in a cohort in Malawi. Increased toxicity during preoperative chemotherapy in malnourished patients with nephroblastoma has been previously addressed with nutritional supplementation. Protocol modifications, including several rounds of dose-reduced chemotherapy, may also allow patients to medically stabilize before starting full-intensity chemotherapy. At BCCOE, dose reductions for malnutrition were initially not consistently applied. Currently, evaluation by a nutritionist, nutritional support, and dose reductions have begun to be routinely incorporated into care.

In addition to medical causes, lack of patient resources led to care delays in this resource-constrained setting. Location serves as one barrier; some patients travel up to 12 hours for weekly chemotherapy. Social support for transportation will be essential in achieving treatment continuity. In general, emphasis on social services has been cited as critical for treatment of WT in resource-constrained settings. The Rwandan national insurance plan (Muteulle) and BCCOE’s financial support ranging from transport to chemotherapy coverage likely explain the low rate of LTFU at BCCOE compared with similar settings. Continued emphasis on overcoming barriers to care, such as finances, transportation, and cultural influences not addressed in this work, may further decrease LTFU rates.

The final class of delays stems from the health systems infrastructure. Strengthening communication among health facilities is one improvement initiative. Although existing collaborations among Rwandan referral facilities were central to outcomes, further streamlining care could decrease delays during surgical transfer, which is currently the greatest contributor to delays. Communication again serves a role in timely pathology and surgical reporting. To address missing surgical reports, a standardized intraoperative form was developed in early 2014 to template information required for disease staging and surgical complications. Similar interventions for pathology in addition to cross-institutional tumor boards could further facilitate this communication. Ideally, future increases in multidisciplinary cancer centers in Rwanda will mitigate these delays by centralizing and increasing access to services.

Medication shortages are also a reality that impact patient care in unpredictable ways. Variations in the demands for chemotherapy, which were subsidized and procured by nongovernmental partners, are challenging to predict, particularly as patient volume increases. Over time, we hope to design a computer-based system to model projected needs. This, in addition to improved communications with the clinical team, will improve the accuracy of drug procurement.

Access to radiotherapy is the final health systems issue discussed and has been a barrier to

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>30</td>
<td>56.6</td>
</tr>
<tr>
<td>Disease free, treatment completed</td>
<td>17</td>
<td>32.1</td>
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<tr>
<td>Disease free, treatment continuing</td>
<td>12</td>
<td>22.6</td>
</tr>
<tr>
<td>Relapsed</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>Deceased</td>
<td>16</td>
<td>30.2</td>
</tr>
<tr>
<td>Disease related</td>
<td>6</td>
<td>11.3</td>
</tr>
<tr>
<td>Treatment related*†</td>
<td>10</td>
<td>18.9</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>7</td>
<td>13.2</td>
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<tr>
<td>During treatment</td>
<td>5</td>
<td>9.4</td>
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<tr>
<td>After completion of treatment</td>
<td>2</td>
<td>3.8</td>
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<tr>
<td>Relapse</td>
<td>3</td>
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<tr>
<td>Deceased</td>
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<tr>
<td>Alive</td>
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<tr>
<td>Survival</td>
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<tr>
<td>Completed treatment and in follow-up</td>
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<td></td>
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<tr>
<td>Survival, ‡ days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>299</td>
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<tr>
<td>Range</td>
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<tr>
<td>Alive at 6 months</td>
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</tr>
<tr>
<td>Alive at 12 months</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

*Considered treatment-related if death occurred any time after patient initiated treatment.
†Of treatment-related deaths, six deaths were within two cycles of preoperative chemotherapy, and patients were often deconditioned.
‡From completion of postoperative chemotherapy until study end date of September 30, 2014.
treatment with curative intent for many cancers seen at BCCOE.\textsuperscript{13,27} On the basis of confirmed clinical staging, an estimated 30 patients in the past 2 years qualified for radiotherapy, which currently costs around US$2,800 per patient. Given its curative and palliative benefits for all cancers, radiotherapy has become a national priority for the Rwandan Ministry of Health.\textsuperscript{13}

Beyond achieving clinical outcomes comparable to similar settings, the BCCOE model demonstrates the value of using an implementation science framework. All data collected and analyzed were derived from routine clinical data systems implemented to monitor and improve quality of care. Intentional use of robust data collection tools embedded within delivery systems allows for consistent evaluation without depending on episodic, resource-intensive research efforts. Implementation science is a critical tool in the implementation and improvement of care in settings such as rural Rwanda.

In summary, BCCOE has taken a unique approach to making specialty care accessible in a rural resource-limited setting. Although ultimate outcomes for these patients will require longer follow-up, we show that nephroblastoma can be safely and effectively treated in this setting using this approach. Communication across multidisciplinary teams and multiple facilities was critical, particularly given the rural location of the cancer center. Finally, nephroblastoma protocols may need further adaptations to best serve specific populations. For example, modifications of pre-operative chemotherapy in the setting of malnutrition could decrease therapy-related toxicity. Preliminary outcomes suggest nephroblastoma treatment even in resource-constrained settings ought to be a priority given tolerable treatment toxicity and favorable outcomes. Careful documentation of care coupled with a focus on monitoring and evaluation have created the foundation for future improvements. Looking forward, the chemotherapeutic agents used to treat WT have few long-term sequelae, so the majority of children cured of this cancer should be able to resume a normal life and development. Thus, the treatment of WT can serve as a paradigm, demonstrating that a cancer diagnosis is not universally fatal in low-resource settings and children can be successfully treated in the earliest stages of creating a cancer delivery program.

DOI: 10.1200/JGO.2015.000067
Published online on jgo.ascopubs.org on January 27, 2016.

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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 jco.ascopubs.org/site/ifc.

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ACKNOWLEDGMENT
We thank the following for their dedication to clinical care: Butaro Hospital leadership and staff, the oncology ward nurses, the pathology department, Inshuti Mu Buzima staff, and everyone who strives to improve the lives of our patients and their families. In particular, the authors thank Dr. Molly Moore, Dr. Lena Matthews, Dr. Paul Park, Dr. Egide Mpanumusingo, Roshan Sethi, Natalie Pritchett, and Hari Iyer for their support of this work. We thank the Rwandan Ministry of Health, Partners in Health/Inshuti Mu Buzima, Dana-Farber Brigham and Women’s Cancer Center, the Clinton Health Access Initiative, and the Jeff Gordon Children’s Foundation for their support of the Butaro Cancer Center of Excellence.

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Supported by the Rwandan Ministry of Health, Partners in Health/Inshuti Mu Buzima, the Dana-Farber Brigham and Women’s Cancer Center, and Harvard Medical School.

Presented in part as a poster presentation at the 46th Congress of the International Society of Pediatric Oncology Conference, Toronto, Ontario, Canada, October 22-25, 2014.

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Screening by Clinical Breast Examination in Western Kenya: Who Comes?

**Purpose** More than 80% of women with breast cancer in Kenya present to medical care with established late-stage disease. We sought to understand why women might not participate in breast cancer screening when it is offered by comparing the views of a cohort of those who attended a screening special event with those of community controls who did not attend.

**Methods** All residents living close to three health centers in western Kenya were invited to participate in screening. Participants (attendees) underwent clinical breast examination by trained physician oncologists. In addition, women who consented were interviewed by using a modified Breast Cancer Awareness Module questionnaire. Nonattendees were interviewed in their homes the following day.

**Results** A total of 1,511 attendees (1,238 women and 273 men) and 467 nonattendee women participated in the study. Compared with nonattendees, the women attendees were older, more often employed, knew that breast cancer presented as a lump, and were more likely to have previously felt a lump in a breast. In addition, they were more likely to report previously participating in screening activities, were more likely to have performed breast self-examination, and were less concerned about wasting a doctor’s time. Almost all those surveyed (attendees and nonattendees) expressed interest in future breast cancer screening opportunities.

**Conclusion** The women who volunteer for breast cancer screening in western Kenya are more aware of breast cancer than those who do not volunteer. Screening recruitment should seek to close these knowledge gaps to increase participation.

INTRODUCTION

Breast cancer is the most common cancer in Kenya, accounting for approximately 23% of all cancers in the country.\(^1\) Kenya is not alone in having such a breast cancer burden. Worldwide, almost 50% of breast cancer cases and 58% of deaths occur in low- and middle-income countries (LMICs).\(^2\) Breast cancer affects younger women and is more clinically aggressive in women from sub-Saharan Africa than among women from North America.\(^3\) Screening for breast cancer is important because this disease has a preclinical phase during which the condition is localized and asymptomatic, a stage in which this cancer may have a greater chance of being cured and may have longer survival.\(^4\) Perhaps because there are low levels of breast cancer awareness and there is limited access to health care, more than 80% of women in western Kenya present late, at a stage associated with poor outcomes.\(^5,6\)

Screening for Breast Cancer

Mammographic screening of women for breast cancer is widely used in countries in which screening facilities are available.\(^7,8\) By contrast, because of the lack of access to mammography screening in the public sector, Kenya National Guidelines for cancer management recommend breast self-examination (BSE) and clinical breast examination (CBE) for early cancer detection.\(^9\)

Efficacy of CBE as a Screening Strategy

Clinical trials of breast cancer screening have reported sensitivity and specificity for CBE screening of 51.7% and 94.3%, respectively.\(^10-12\) Preliminary results of a cluster-randomized controlled trial in India that used CBE suggested that this approach may uncover significantly more early-stage cancers in the screened population (18.8 per 100,000 women) than emerged in a control group (8.1 per 100,000 women).\(^10\)

Screening for Breast Cancer in Resource-Constrained Settings

In most LMICs, screening events use CBE and are usually donor-funded special opportunities. In some of these events, most of the abnormalities identified by the clinicians are already symptomatic.
The participants in such events may come there to confirm what they already know or to seek further care for an existing disease, not the ideal situation for screening and early detection efforts. This might be one explanation of why screening activities in LMICs find cancers in advanced stages more often than do similar activities in the developed world. Hoping that we might find ways to encourage women to participate in screening at an earlier stage in their disease natural history, we searched the literature for relevant studies but found no research describing predictors of women’s participation in breast cancer screening in Kenya. For this reason, we conducted a prospective cohort study to ascertain what distinguished women who chose to participate in CBE screening from those who did not participate in our setting. We believed that this kind of information might subsequently be used to design public education efforts that would motivate nonattendees to become attendees.

METHODS

Study Site

The Academic Model Providing Access to Health-care (AMPATH) is a collaboration among Moi University School of Medicine, Moi Teaching and Referral Hospital (MTRH), Kenya’s Ministry of Health, and North American academic institutions led by Indiana University School of Medicine. Initially, AMPATH focused on HIV care, but it has now broadened its services to include primary health care and chronic disease management, including prevention and care for cancer through the AMPATH Oncology Institute (AOI). Since 2006, annual screening has been performed during the month of October (Breast Cancer Awareness Month). The Walther Project, in which this study is nested, was initiated in 2011 under the auspices of AOI with a grant from Walther Cancer Foundation of Indianapolis, IN, in support of research on cancer prevention in Kenya.

During October and November 2012, the Walther Project organized breast health education and screening activities in three communities within the AMPATH catchment area (Fig 1). The study communities were chosen on the basis of unpublished data from the Eldoret Cancer Registry in an attempt to represent counties with high, medium, and low burdens of breast cancer. Uasin Gishu, Nandi, and Mount Elgon account for 45%, 5%, and 0.2% of the cases in the registry, respectively. These three counties are ethnically diverse and are representative of the overall population of western Kenya.

One-day screening special events were conducted at public health facilities serving the three counties. In the week before screening, communities were mobilized to participate by local leaders who invited everyone in the nearby area to attend breast cancer screening events. On the advice of health center leaders, both men and women in the target communities were invited to attend to secure male support for the screening activity. We acted on this advice because Kenya is predominantly a paternal society in which women usually seek permission from men before attending events like screening, vaccination, and family planning. The screening events included education and CBE provided by trained physician oncologists. At the screening event, any participants with breast lumps detected by CBE underwent fine-needle aspiration immediately. Those with cytology reported as suspicious for malignancy underwent core needle biopsies 1 week later followed by appropriate treatment at MTRH.

Study Design

The study was a cross-sectional survey conducted in two parts. Part one (survey of screening participants) involved administering a questionnaire to all consenting women at CBE events. For this survey, we used the validated breast module of the Breast Cancer Awareness Module (BCAM) survey. Prior work had been done to modify its language to improve the face validity and understandability in Kenya.

The second part (survey of community women who did not volunteer) involved home-based interviews of women who had not presented themselves for screening and who were identified by a systematic random sampling of residents within a 5-km radius along all roads leading to the health center. This survey of community residents used the same BCAM survey and was conducted the day after the screening event. Ethical approval was obtained from the Moi University Institutional Research and Ethics Committee as well as the Indiana University Institutional Review Board.

Study Procedures

The questionnaire was administered in one of two languages (English or Kiswahili) by trained research personnel. Written consent was obtained from participants. Questionnaire items included the six domains of BCAM: sociodemographic characteristics, socioeconomic characteristics, experience with previous breast examinations, prior training in how to examine for a breast lump, knowledge of availability of screening programs,
and perceived barriers to CBE if a woman noted changes in her breast. An open-ended question on reasons for not attending the current screening event was asked only of those who had heard about the screening event but had not attended. Another open-ended question with structured prompts inquired about preferences for learning about future screening events.

**Data Analysis**

Data analysis was performed by using STATA SE 13 (STATA, College Station, TX). Categorical variables were summarized as frequencies and the corresponding percentages, whereas continuous variables were summarized as medians and the corresponding interquartile ranges (IQRs). Gaussian assumptions were assessed empirically by using the Shapiro-Wilk test for normality. Association between categorical variables was assessed by using Pearson’s \( \chi^2 \) test, whereas association between a continuous variable and a binary variable was assessed by using Wilcoxon two-sample test (Mann-Whitney \( U \) test). A logistic regression model was used to assess the joint effect of the covariates on the outcome. The covariates that were associated with the outcome at the bivariate level were included in the multivariable level. Variables that had been established to be associated with and/or were known a priori to be associated with each other were not included together in the logistic model to avoid multicollinearity. Only the independent variable that was thought to be the most important and statistically significant in bivariate analyses was included. For the logistic model results, we report the odds ratios (ORs) and the corresponding 95% CIs. Age as used in the logistic regression model was scaled down by 10 years to be able to compare two persons who were 10 years apart. Only significant results were presented in the tables; the remaining data are available from the corresponding author upon request.

**RESULTS**

A total of 1,511 volunteers (1,238 women and 273 men) attended CBE screening. After CBE, 594 women (48% of total screening attendees) consented and were interviewed by using the modified BCAM questionnaire. A total of 467 women who did not attend were interviewed in their homes. Men were not interviewed. The overall median age (Table 1) was 34 years (IQR, 26 to 44 years). More than three quarters of participants (809 [76%]) were married, and the rest were single, separated, divorced, or widowed. The median number of biologic children that participants had was three (IQR, two to five children), whereas the median number of siblings was seven (IQR, five to nine siblings). Half the participants had either no education or elementary education. Fifty-six percent (595) of the participants were unemployed.

As shown in Table 1, attendees were older, more often married, had more children, more often
employed, and were more often menopausal. Attendees were more likely to validate signs and symptoms typical of late-stage breast cancer (change in position, enlargement, discharges, bleeding from nipple; breast lump; change in skin color; increase in size of lump; and lump in the armpit). Attendees also were more likely to report checking their breast for lumps (self-examination), having

<table>
<thead>
<tr>
<th>Variable</th>
<th>Community Nonattendees (n = 467)*</th>
<th>Screening Attendees (n = 594)*</th>
<th>Overall (N = 1,061; 100%)*</th>
<th>Attendee Versus Nonattendee OR (95% CI)</th>
<th>$\chi^2$ or Wilcoxon Two-Sample Test P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (range)</td>
<td>32 (25-41)</td>
<td>35 (28-45)</td>
<td>34 (26-44)</td>
<td>1.18 (1.08 to 1.30)</td>
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<td>30 (20-60)</td>
<td>30 (20-45)</td>
<td>1.60 (1.27 to 2.01)</td>
<td>.001</td>
</tr>
<tr>
<td>No. of children (range)</td>
<td>3 (1-5)</td>
<td>3 (2-6)</td>
<td>3 (2-5)</td>
<td>1.05 (1.01 to 1.10)</td>
<td>.003</td>
</tr>
<tr>
<td>Married</td>
<td>337 (72)</td>
<td>472 (79)</td>
<td>809 (76)</td>
<td>1.49 (1.12 to 1.98)</td>
<td>.060</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>71 (15)</td>
<td>130 (22)</td>
<td>201 (19)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Self-employed</td>
<td>147 (32)</td>
<td>114 (19)</td>
<td>261 (25)</td>
<td>0.42 (0.29 to 0.62)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Unemployed</td>
<td>248 (53)</td>
<td>347 (59)</td>
<td>595 (56)</td>
<td>0.76 (0.55 to 1.07)</td>
<td></td>
</tr>
<tr>
<td>Still having menses</td>
<td>350 (75)</td>
<td>414 (70)</td>
<td>764 (72)</td>
<td>0.76 (0.57 to 0.99)</td>
<td>.045</td>
</tr>
<tr>
<td>Signs of breast cancer acknowledged by attendees</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in position of nipple</td>
<td>268 (58)</td>
<td>377 (63)</td>
<td>645 (61)</td>
<td>1.28 (1.00 to 1.65)</td>
<td>.049</td>
</tr>
<tr>
<td>Nipple discharge a sign of breast cancer</td>
<td>359 (77)</td>
<td>491 (83)</td>
<td>850 (80)</td>
<td>1.42 (1.05 to 1.92)</td>
<td>.023</td>
</tr>
<tr>
<td>Bleeding from the nipple</td>
<td>357 (77)</td>
<td>499 (84)</td>
<td>856 (81)</td>
<td>1.59 (1.17 to 2.16)</td>
<td>.003</td>
</tr>
<tr>
<td>Lump in the breast</td>
<td>397 (85)</td>
<td>553 (93)</td>
<td>950 (90)</td>
<td>2.31 (1.54 to 3.48)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Change in breast color</td>
<td>332 (71)</td>
<td>465 (78)</td>
<td>797 (75)</td>
<td>1.44 (1.09 to 1.91)</td>
<td>.010</td>
</tr>
<tr>
<td>Lump under the armpit</td>
<td>291 (63)</td>
<td>424 (72)</td>
<td>715 (68)</td>
<td>1.50 (1.16 to 1.94)</td>
<td>.002</td>
</tr>
<tr>
<td>Change in the size of the breast</td>
<td>315 (68)</td>
<td>462 (78)</td>
<td>777 (73)</td>
<td>1.68 (1.28 to 2.21)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Change in the size of the nipple</td>
<td>296 (64)</td>
<td>420 (71)</td>
<td>716 (68)</td>
<td>1.38 (1.06 to 1.79)</td>
<td>.015</td>
</tr>
<tr>
<td>Changes in the shape of breast</td>
<td>322 (69)</td>
<td>460 (77)</td>
<td>782 (74)</td>
<td>1.52 (1.16 to 2.01)</td>
<td>.003</td>
</tr>
</tbody>
</table>

Practices and beliefs acknowledged by attendees

<table>
<thead>
<tr>
<th></th>
<th>Community Nonattendees (n = 467)*</th>
<th>Screening Attendees (n = 594)*</th>
<th>Overall (N = 1,061; 100%)*</th>
<th>Attendee Versus Nonattendee OR (95% CI)</th>
<th>$\chi^2$ or Wilcoxon Two-Sample Test P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check for breast lumps</td>
<td>187 (40)</td>
<td>332 (56)</td>
<td>519 (49)</td>
<td>1.88 (1.47 to 2.40)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Trained to check for lumps</td>
<td>89 (19)</td>
<td>207 (35)</td>
<td>296 (28)</td>
<td>2.25 (1.69 to 3.00)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Ever felt a lump</td>
<td>31 (7)</td>
<td>94 (16)</td>
<td>125 (12)</td>
<td>2.65 (1.73 to 4.06)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Worried about wasting the doctor’s time</td>
<td>19 (4)</td>
<td>11 (2)</td>
<td>30 (3)</td>
<td>0.44 (0.21 to 0.94)</td>
<td>.031</td>
</tr>
<tr>
<td>Believes that the doctor would not understand her language</td>
<td>34 (7)</td>
<td>22 (4)</td>
<td>56 (5)</td>
<td>0.49 (0.28 to 0.85)</td>
<td>.010</td>
</tr>
<tr>
<td>Believes that the doctor would not understand her culture</td>
<td>36 (8)</td>
<td>27 (5)</td>
<td>63 (6)</td>
<td>0.57 (0.34 to 0.95)</td>
<td>.030</td>
</tr>
</tbody>
</table>

Believes that a 70-year-old is more likely to get breast cancer compared to a 30- or 50-year-old

<table>
<thead>
<tr>
<th></th>
<th>Community Nonattendees (n = 467)*</th>
<th>Screening Attendees (n = 594)*</th>
<th>Overall (N = 1,061; 100%)*</th>
<th>Attendee Versus Nonattendee OR (95% CI)</th>
<th>$\chi^2$ or Wilcoxon Two-Sample Test P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>42 (9)</td>
<td>80 (14)</td>
<td>122 (12)</td>
<td>1.59 (1.07 to 2.35)</td>
<td>.021</td>
</tr>
</tbody>
</table>

Abbreviation: OR, odds ratio.
*No. (%) or median (interquartile range).
been trained in self-examination, and having ever felt a lump in their breasts. Attendees were also less likely than nonattendees to worry about wasting a doctor’s time, that the doctor might not understand their language or culture, and more often knew that older women were most likely to get breast cancer.

Table 2 shows the variables independently associated with uptake of breast cancer screening. Attendees were older, took a longer time to travel to the health facility, more often employed, believed that a lump in the breast is a sign of breast cancer, self-examined for lumps in the breast, had been previously trained to check for lumps, had ever felt a lump in the breast, were less worried about whether a doctor would not understand their language, and knew that older women are more likely to get breast cancer.

Because BSE showed a substantial association with attendance at CBE screening (an 88% increased chance of checking for lumps among those who visited the clinic for breast cancer screening compared with those who did not visit the clinic for breast cancer screening; odds ratio, 1.88; 95% CI, 1.47 to 2.40) within our pooled data set, we also explored factors associated with reported BSE. In bivariate analyses, many independent variables demonstrated significant associations with BSE (results available from the corresponding author upon request). The variables that were statistically significant in the bivariate analysis level were included in the multivariate level. The results of the final model are shown in Table 3. The adjusted effects showed that participants who reported BSE were younger, more often employed, had better education, reported family history of breast cancer, and believed that cancer presented as a mass in the breast. There was a strong association with reports of prior training for BSE, ever having felt a lump in her breast, and having had prior screening.

Clinical Yield of CBE Special Events

As noted previously and in Table 4, a total of 1,511 volunteers underwent CBE. A total of 59 breast abnormalities were detected, including lumps and ulcers (eight in men and 51 in women). Only one man of five with lumps consented to fine-needle aspiration (reported as negative for malignancy). Three other men had ulcerating disease presumed to be breast cancer. Thirty-seven women accepted fine-needle aspiration, and 15 were biopsied. Three men and four women had breast cancer confirmed by histology. All the men and two women with breast cancer had ulcerating lumps, believed their disease was advanced, and declined further care. One woman had stage III disease and underwent treatment at MTRH and Kenyatta National Hospital. The other woman was lost to follow-up.

Interest in Future CBE Special Events

All the health center participants and 98% of community participants interviewed reported interest in participating in annual screening if such programs were available. For that reason, and because the Walther Project group wanted to know how best to announce future activities, we added a question to the BCAM survey that inquired about preferred mechanisms for alerting the communities (Table 5). Fifty-four percent (574) chose the local radio station as the best means of communication to help convey breast cancer information. The rest chose national radio (41%) and mailed information (5%).

DISCUSSION

Mammographic screening of women for breast cancer followed by early diagnosis and intervention has been shown to decrease mortality from breast cancer in resource-rich countries. Unfortunately, mammography is generally not available in LMICs because of a lack of both human and physical resources. In its absence, CBE every 3 years for women younger than age 40 years and annually for women older than age 40 years has been used. CBE may be effective for detection in LMIC settings because the mean tumor size at presentation among women in these countries is palpable. A study in Sudan suggested that CBE using local volunteers can increase detection of breast cancer in asymptomatic women. Other studies conducted in India and Malaysia have suggested that CBE can significantly downstage breast cancer in screened populations. Follow-up of longer-term outcomes is ongoing to assess mortality benefit. In addition, CBE increases breast cancer awareness and early response to symptoms, a combination of effects that may have decreased mortality from breast cancer in the East Anglia study.

In our circumstances, we adopted CBE as the best available option for screening. We focused on social mobilization for mass CBE screening as our primary approach, but another option might be integrating CBE into provision of primary health services at clinic appointments for other indications. At AMPATH Oncology Institute, both approaches are used and have been found to be complementary. Challenging logistic arrangements, substantial cost, and restricted access to special events for women on particular
days make mass screening a less-than-ideal approach to reach our populations. Our target study population, for example, was 45,187 women older than age 45 years residing in the catchment areas of the three rural health facilities per the last National Census in 1999. Although all were invited, only 1,238 women attended our special events. To increase participation in screening, a sustained awareness program and availability of screening services is required. Such a program can be integrated into primary care visits with other age- and sex-appropriate health risk screening services, such as those for hypertension and cervical cancer as practiced in the National Breast and Cervical Cancer Early Detection Program in America.²⁴

Alternative approaches to create awareness of breast health and screening options are also needed. We noted that more than half of those surveyed preferred to be alerted about screening activities through messages broadcast by local radio stations. Health staff partnering with local radio stations to create public service announcements or participating in talk shows about breast health might promote and improve responsiveness to breast cancer screening opportunities.

### Table 2 – Adjusted Logistic Regression Model Assessing the Factors Associated With Attending Breast Cancer Screening in the Health Center

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sample Size</th>
<th>Screening Attendees Versus Community Nonattendees</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted OR (95% CI)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1,058</td>
<td>1.18 (1.08 to 1.30)</td>
</tr>
<tr>
<td>Travel time to health care (minutes)</td>
<td>1,057</td>
<td>1.60 (1.27 to 2.01)</td>
</tr>
<tr>
<td>Employment status</td>
<td>1,057</td>
<td>Ref</td>
</tr>
<tr>
<td>Employed</td>
<td></td>
<td>0.42 (0.29 to 0.62)</td>
</tr>
<tr>
<td>Self-employed</td>
<td></td>
<td>0.76 (0.56 to 1.07)</td>
</tr>
<tr>
<td>Lump in the breast a sign of breast cancer</td>
<td>Yes versus no</td>
<td>2.31 (1.54 to 3.48)</td>
</tr>
<tr>
<td>Check for lumps</td>
<td>Yes versus no</td>
<td>1.88 (1.47 to 2.40)</td>
</tr>
<tr>
<td>Trained to check for lumps</td>
<td>Yes versus no</td>
<td>2.25 (1.69 to 3.00)</td>
</tr>
<tr>
<td>Ever felt a lump</td>
<td>Yes versus no</td>
<td>2.65 (1.73 to 4.06)</td>
</tr>
<tr>
<td>Believes the doctor would not understand her language</td>
<td>Yes versus no</td>
<td>0.49 (0.28 to 0.85)</td>
</tr>
<tr>
<td>Believes a 70-year-old is more likely to get breast cancer compared to a 30- or 50-year-old</td>
<td>1,053</td>
<td>1.59 (1.07 to 2.35)</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; Ref, reference.

### Table 3 – Adjusted Logistic Regression Model Assessing the Factors Associated With Breast Self-Examination (Check for Lumps)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sample Size</th>
<th>Check for Lumps (Yes Versus No)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Unadjusted OR (95% CI)</td>
</tr>
<tr>
<td>Age (10 years scaled)</td>
<td>1,058</td>
<td>0.87 (0.80 to 0.95)</td>
</tr>
<tr>
<td>Employment status</td>
<td>1,054</td>
<td>Ref</td>
</tr>
<tr>
<td>Employed</td>
<td></td>
<td>0.46 (0.31 to 0.67)</td>
</tr>
<tr>
<td>Self-employed</td>
<td></td>
<td>0.42 (0.30 to 0.58)</td>
</tr>
<tr>
<td>Education level of tertiary, college, or university versus none or elementary school</td>
<td>1,058</td>
<td>1.77 (1.39 to 2.26)</td>
</tr>
<tr>
<td>Family history of breast cancer</td>
<td>Yes versus no</td>
<td>2.36 (1.29 to 4.33)</td>
</tr>
<tr>
<td>Lump in the breast a sign of breast cancer</td>
<td>Yes versus no</td>
<td>2.67 (1.73 to 4.12)</td>
</tr>
<tr>
<td>Trained to check for lumps</td>
<td>Yes versus no</td>
<td>3.74 (2.80 to 5.00)</td>
</tr>
<tr>
<td>Ever felt a lump</td>
<td>Yes versus no</td>
<td>4.35 (2.79 to 6.79)</td>
</tr>
<tr>
<td>Ever undergone breast cancer screening</td>
<td>Yes versus no</td>
<td>3.56 (2.26 to 5.60)</td>
</tr>
</tbody>
</table>

Abbreviation: OR, odds ratio.
Was CBE Screening in Our Health Center-Based Approach Productive?

We examined 1,511 people (men and women) and diagnosed seven breast cancers, a yield of one breast cancer detected for every 215 people screened. This yield is lower than the one breast cancer for every 42 women screened by Luyeye Mvila et al.13 in the Democratic Republic of Congo but higher than one for every 606 screened by Abuidris et al.20 in Sudan. The higher yield in the study by Luyeye Mvila et al could be the result of the combined use of CBE and mammography, whereas Abuidris et al used CBE alone. There also seemed to be an educational product from the exposure of women to CBE. After being examined, women who attended CBE screening were 2.25 times more likely to report that they had been trained to do breast self-examination. The US Preventive Services Task Force recommends against teaching women BSE because of lack of mortality benefit and increased unnecessary biopsies,7 but we found that women who reported doing BSE were more likely to volunteer for CBE (56%) than those who did not (40%). From our data, there seems to be a relationship between BSE, training for BSE, and volunteering to be screened. Although we did not directly test for this effect, it is possible that exposure to CBE was interpreted by women as training on BSE. Because of this association, we at AOI are inclined to advocate for teaching BSE to women as in the National Guidelines for Cancer Management in Kenya.9

Application of the Study Findings

The study has identified some of the factors associated with women who volunteer for breast cancer screening. These include being trained to feel for lumps, believing that a doctor would understand their language, and not being worried about wasting the doctor’s time. All these factors should be considered when designing breast cancer screening invitation messages. We have also developed a brief educational process that has been used to teach women more about breast cancer and CBE screening.25

The strengths of this study included the use (after modification for language and culture) of the BCAM survey, an internationally validated tool for measuring breast cancer awareness in various domains. The study participants were ethnically diverse and represented several Western Kenyan ethnic communities. The weaknesses of the study included a less-than-ideal participation rate in our health center-based survey and lack of mammography to confirm that women were reassured that they actually had normal breasts. Finally, we acknowledge that this study of screening may, like studies in other LMICs, be describing the characteristics and beliefs of women who had symptoms that led them to participate in the CBE special event in the first instance. In that sense, our special events may not have been true screening of asymptomatic individuals in a strict sense. Nonetheless, because the effort in our setting is to detect the presence of breast cancer at an earlier and less anatomically advanced stage, the activities we report may fairly be said to represent screening in the context of resource-scarce Kenya at this point in history.

Ninety-nine percent of all the women who participated in this study were willing to take part in

Table 4 – Screening Yield

<table>
<thead>
<tr>
<th>Attendee</th>
<th>Benign Mass</th>
<th>Malignant Mass</th>
<th>Normal CBE</th>
<th>Total No. of Persons Examined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>5</td>
<td>3</td>
<td>265</td>
<td>273</td>
</tr>
<tr>
<td>Women</td>
<td>47</td>
<td>7</td>
<td>1,184</td>
<td>1,238</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>10</td>
<td>1,449</td>
<td>1,511</td>
</tr>
</tbody>
</table>

Abbreviation: CBE, clinical breast examination.

Table 5 – Preferred Means of Communication

<table>
<thead>
<tr>
<th>Preferred Means of Communication</th>
<th>Respondents (n = 1,061)</th>
<th>Responses (n = 3,033)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Local radio station</td>
<td>574 (54)</td>
<td>574 (19)</td>
</tr>
<tr>
<td>National radio station</td>
<td>440 (41)</td>
<td>440 (15)</td>
</tr>
<tr>
<td>Billboards</td>
<td>119 (11)</td>
<td>119 (4)</td>
</tr>
<tr>
<td>Text messages</td>
<td>231 (22)</td>
<td>231 (8)</td>
</tr>
<tr>
<td>Newspapers</td>
<td>164 (15)</td>
<td>164 (5)</td>
</tr>
<tr>
<td>Church pastor</td>
<td>382 (36)</td>
<td>382 (13)</td>
</tr>
<tr>
<td>Women’s group meetings</td>
<td>245 (23)</td>
<td>245 (8)</td>
</tr>
<tr>
<td>Leaflets or brochures</td>
<td>132 (12)</td>
<td>132 (4)</td>
</tr>
<tr>
<td>Public gatherings/word of mouth</td>
<td>315 (30)</td>
<td>315 (10)</td>
</tr>
<tr>
<td>Posters</td>
<td>235 (22)</td>
<td>235 (8)</td>
</tr>
<tr>
<td>Mailed information</td>
<td>53 (5)</td>
<td>53 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>143 (13)</td>
<td>143 (5)</td>
</tr>
</tbody>
</table>
future screening events. There is an opportunity to significantly increase breast cancer awareness in our communities by continuing to offer CBE during special events, integrating this service into primary care for those unable to participate in mass screening, disseminating breast health information to our communities, and actively educating and training those who present themselves for screening.

DOI: 10.1200/JGO.2015.000687
Published online on jgo.ascopubs.org on January 27, 2016.

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Data analysis and interpretation: Naftali Wisindi Busakhala, Job Wapangana Kisuya, Alfred Keter, Ann Mwangi, Grieven Otieno, Gabriel Kigen, Patrick Loehrer Sr, Thomus Inui
Manuscript writing: All authors
Final approval of manuscript: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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ACKNOWLEDGMENT

We thank the Walther Cancer Foundation of Indianapolis for funding this work. We also thank Moi Teaching and Referral Hospital, Moi University, Indiana University, Academic Model Providing Access to Healthcare, and communities across western Kenya who participated in the study.

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REFERENCES

Outcomes of Saudi Arabian Patients With Nasopharyngeal Cancer Treated With Primarily Neoadjuvant Chemotherapy Followed by Concurrent Chemoradiotherapy

**Purpose** Nasopharyngeal cancer (NPC) is the most common head and neck cancer in Saudi Arabia. This study reports the locoregional disease control and survival outcomes in patients with NPC treated in King Abdulaziz University Hospital.

**Methods** Patients treated for NPC between June 2007 and October 2014 were retrospectively reviewed. Demographic information, clinicopathologic variables, and chemotherapy data were collected and analyzed. Cumulative survival and disease control rates were calculated by Kaplan-Meier product-limit actuarial method.

**Results** Thirty-nine patients with NPC were reviewed. Thirty-five (90%) patients received definitive radiotherapy (RT) and four (10%) had palliative RT. Mean prescribed dose for definitive RT was 68 Gy (range, 60 to 70.2 Gy), delivered with mean doses per fraction of 1.9 Gy (range, 1.8 to 2.1 Gy). After a median follow-up of 15 months (range, 1 to 84 months), 22 (63%) patients who underwent definitive RT were disease free and 13 (37%) were still with disease. During this period, seven (18%) patients died of the disease; five (13%) of them received definitive RT. After 2 years’ follow-up, the actuarial estimate rates were: 85.7% for local control, 91.4% for nodal control, and 85.7% for distant control.

**Conclusion** Our study showed a disease with clinical behavior similar to what has been observed in East and Southeast Asia. Further it explored the neoadjuvant chemotherapy approach in treating NPC with results that are comparable to literature. However, little is known about the molecular pathogenesis of this disease in this region, and further research integrating clinical and molecular biomarkers is required.

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**INTRODUCTION**

Nasopharyngeal cancer (NPC) is a disease with a variable universal distribution geographically and racially. It is considered a rare human malignancy in white races in North America and Europe, with an incidence of one per 100,000 population per year, whereas it reaches a peak incidence rate of around 20 per 100,000 person-years in China and South Korea. Evidence suggests that NPC is a unique disease in terms of its risk factors and biologic association with the Epstein-Barr Virus (EBV) and its sensitivity to chemotherapy and radiotherapy (RT).

In Saudi Arabia, NPC ranks first (35%) among all head and neck cancers and 17th (2.9%) among all cancers, with male predominance (2:1). Regardless of race and geography, the most common form of nasopharyngeal cancers arises from the epithelial cells lining the nasopharynx, which constitute 75% to 95% of all the cases diagnosed. Nonkeratinizing type (WHO III) is the most common type in Saudi Arabia, predominantly in the younger age population, mimicking China and South Korea in the histopathologic type and distribution. Despite the importance of this topic in our region, there remains a paucity of evidence on the characteristics and outcome of this disease in the Middle East. Debate continues about whether the features of this disease are comparable to those of Western or Asian studies.

The purpose of this study is to explore our experience in NPC management in King Abdulaziz University Hospital from 2008 to 2014. The
observed outcomes were overall survival (OS) and locoregional control (LRC), defined from the end of treatment until death for any reason or local recurrence time, respectively.

**METHODS**

We retrospectively reviewed adult patients diagnosed with NPC and treated at King Abdulaziz University Hospital in Jeddah, Saudi Arabia between May 2007 and December 2014. Pediatric patients were excluded from the study. Staging of the disease was stated according to the Cancer Staging Manual by the American Joint Committee on Cancer, sixth edition.\(^\text{12}\)

All the patients had a confirmed pathologic diagnosis in our center. Computed tomography (CT) and/or magnetic resonance imaging (MRI), depending on the treating physician, were used to assess radiologic staging for the primary disease and to rule out or in metastasis. Follow-up CT scans and/or MRI were performed a month after the completion of three cycles of neoadjuvant chemotherapy (NACT) and a month after the completion of concurrent chemoradiotherapy (CCRT) for response assessment. Patients were seen before each NACT cycle and at least three times while receiving CCRT. Responders were followed up with CT scans and/or MRI as per consensus guidelines, thereafter.

**Chemotherapy**

In our center we used the neoadjuvant or induction chemotherapy (IC) protocol, consisting of taxane, platinum, and fluorouracil for three consecutive cycles separated by 3 weeks, followed by cisplatin as radio-sensitizer, given concurrently, either 100 mg/m\(^2\) every 3 weeks or 30 mg/m\(^2\) weekly.

**Radiotherapy**

The Radiation Therapy Oncology Group atlas was followed for target volume contouring.\(^\text{13}\) Gross primary and nodal tumors were contoured as gross tumor volume (GTV) on the basis of clinical findings and CT/MRI imaging that was performed before the neoadjuvant chemotherapy. Clinical target volume consisted of computer-generated 1-cm isotropic expansion around each gross tumor volume, respecting anatomic barriers, and included all nodal groups with a greater than 10% to 15% risk of containing subclinical disease (all the neck nodes bilaterally).\(^\text{14}\) Planning target volume was constructed by an automated 0.3- to 0.5-cm expansion of the clinical target volume surfaces, to account for setup error and daily uncertainty. Patients were positioned for simulation using customized thermoplastic mask. CT scans with intravenous contrast were used for treatment planning. Both intensity-modulated RT and three-dimensional conformal RT were used for treatment technique. Dose limits for the critical tissue structures and plan evaluation were followed as defined by the Radiation Therapy Oncology Group 0225.\(^\text{15}\)

**Statistical Analysis**

Patients’ demographic and clinical characteristics, such as age at the time of diagnosis, sex, stage, and treatment data, were collected and analyzed (Table 1).

Local control of the disease was determined from the day of treatment completion to the last documented clinic visit without recurrence. The same starting point was used for OS and disease-free survival (DFS).

For patients receiving definitive treatment, the correlation between disease control and patient

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>38</td>
</tr>
<tr>
<td>Range</td>
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</tr>
<tr>
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<td></td>
</tr>
<tr>
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<tr>
<td>Male</td>
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<tr>
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<tr>
<td>Undifferentiated carcinoma</td>
<td>30 (77)</td>
</tr>
<tr>
<td>Others</td>
<td>1 (2)</td>
</tr>
<tr>
<td>T classification</td>
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<td>16 (41)</td>
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<tr>
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<td>10 (26)</td>
</tr>
<tr>
<td>Chemotherapy (CCRT ± NACT)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (77)</td>
</tr>
<tr>
<td>No</td>
<td>9 (23)</td>
</tr>
</tbody>
</table>

Abbreviations: CCRT, concurrent chemoradiotherapy; NACT, neoadjuvant chemotherapy.
characteristics and between disease control and treatment data (RT dose, time from diagnosis to treatment initiation) was assessed by logistic regression, using IBM SPSS statistic software version 20. A \( P < .05 \) was considered significant.

Cumulative survival and disease control rates were calculated by Kaplan-Meier product-limit actuarial method. Data censoring occurred in February 2015.

RESULTS

Thirty-nine patients with NPC were reviewed. Thirty-five (90%) patients received definitive treatment, and only four (10%) received palliative treatment. Among the patients who received definitive treatments, 31 patients (86%) were treated with chemotherapy and radiation subdivided by the chemotherapy setting as follows: 15 patients received NACT followed by CCRT, 14 patients received only CCRT, and two patients had NACT followed by RT alone.

Mean prescribed dose for definitive treatments was 68 Gy (range, 60 to 70.2 Gy), delivered with mean doses per fraction of 1.9 Gy (range, 1.8 to 2.1 Gy). The median time between diagnosis and RT initiation was 4 months (range, 0 to 7 months).

Disease Control and Survival

After a median follow-up of 15 months (range, 1 to 84 months), 22 (63%) patients who underwent definitive RT with or without chemotherapy were free of disease, and 13 (37%) were with disease. During this period, seven (18%) patients died of the disease; out of these, five (13%) received definitive RT (Table 2).

The 2-year actuarial rates of local control, regional nodal control, and distant control were: 85.7%, 91.4%, and 85.7%, respectively (Fig 1).

A statistically significant correlation was demonstrated between local control and radiation dose (\( R^2 = 0.12; P = .041 \)) but not for regional (\( P = .486 \)) and distant control (\( P = .151 \)). The use of chemotherapy was significantly associated with distant (\( P = .023 \)) and regional (\( P = .043 \)) control but not with local control (\( P = .097 \)).

The median time from diagnosis to treatment initiation for disease-free patients was 2 months (range, 0 to 6 months), and for those who relapsed it was 4 months (range, 1 to 7 months). The time between diagnosis and treatment initiation showed a statistically significant relation with local control (\( R^2 = 0.16; P = .039 \)) but not with regional (\( P = .075 \)) and distant control (\( P = .369 \)).

Pattern of Failure

From a total of 35 patients receiving definitive RT, 13 (37%) developed disease recurrence during follow-up: six (17%) had local recurrence, three (8%) had regional recurrence, two (5%) had both local and regional recurrences, and six (17%) had distant relapse.

No statistically significant correlation was found between patients’ demographic and clinical characteristics and disease control. Patients with stage T1 to T2 disease had lower rates of local failure than those with stage T3 to T4 (20% vs 23%; \( P = .207 \)) but were not statistically significant. Freedom from distant metastasis was only significantly affected by patient age (\( P = .016 \)).

The 2-year OS and DFS actuarial rates were 85.7% and 68.6%, respectively (Fig 2). The use of chemotherapy did not show statistical significant influence on either OS (\( P = .286 \)) or DFS (\( P = .211 \)).

Table 2 – Clinical Outcome of Patients Receiving Definitive Radiotherapy (n = 35)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Free of Disease (n = 22)</th>
<th>With Disease (n = 13)</th>
</tr>
</thead>
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<td></td>
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<tr>
<td>Median</td>
<td>41</td>
<td>26</td>
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<td>Range</td>
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<tr>
<td>Male</td>
<td>14 (64)</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Pathology</td>
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<tr>
<td>Squamous cell carcinoma</td>
<td>5 (23)</td>
<td>2 (15)</td>
</tr>
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<td>Undifferentiated carcinoma</td>
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<tr>
<td>N0</td>
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<tr>
<td>N1</td>
<td>8 (36)</td>
<td>3 (23)</td>
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<td>19 (54)</td>
<td>12 (34)</td>
</tr>
<tr>
<td>No</td>
<td>3 (9)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

NOTE. Data presented as No. (%) unless otherwise noted.
DISCUSSION

This study reports the outcomes of patients with cancer of the nasopharynx who were treated in King Abdulaziz University Hospital, Jeddah, Saudi Arabia between the years 2007 and 2014. Patients in our center were treated with definitive RT with or without chemotherapy. Although adjuvant chemotherapy is considered the standard of care after the treatment with CCRT, the administration of adjuvant chemotherapy in our center was limited because of poor patient compliance. Alternatively, we used NACT with taxane, platinum, and fluorouracil followed by CCRT, which in our experience offered the patients a rapid clinical improvement and allowed a more conservative RT planning that spares critical structures such as chiasm, optic nerves, and brain stem. Selecting patients for NACT was based on the treating medical and radiation oncologists’ preference, but overall patients with nodal disease received NACT regardless of the tumor extent.

The actuarial rates of locoregional control (80%) and OS (85.7%) were comparable to those reported in the literature, and these results further support the neoadjuvant treatment method for NPC. The addition of chemotherapy did not influence the rates of local control but decreased distant recurrence. However, the improved distant control rates with the addition of chemotherapy did not translate into OS or DSF difference. In a phase III trial from China, CCRT proved its advantage on local and distant control, whereas the benefit of adding adjuvant and neoadjuvant chemotherapy to the CCRT is still not well established. The majority of patients in both trials had undifferentiated NPC, which is similar to what is reported in our cohort.

We observed a trend toward improved overall survival with chemotherapy, but statistical significance was not attained. This could be attributed to several confounding factors, which include the small number of patients, the short follow-up period, and the underutilization of chemotherapy during the early years of this study. This is in addition to the insufficient understanding of the natural history of this cancer in this region of the world. We acknowledge that our study represents a single institute experience with limited generalizability, but it certainly adds to the evidence that supports the neoadjuvant approach for treating NPC in countries where disparities in cancer treatments are a recognizable issue.

The molecular basis of undifferentiated NPC is still an active area of ongoing investigation. Recently, a local study was done to investigate the molecular evidence of this disease in which biopsies were obtained from 25 patients in Saudi Arabia with NPC and were examined for the presence of EBV DNA and for the frequency of p53 mutations. Results showed that despite a high association of EBV infection in the Saudi patients with NPC, the frequency of p53 mutations was low, which makes the results consistent with the worldwide observation of infrequent p53 mutations in NPC. Despite the promising results in such a chemotherapy- and radiotherapy-sensitive disease that is routinely treated with high-dose radiation, questions remain as to why there are still local control failures. A recent study with similar NPC pathology from China showed that the local failure remains the most common site of failure despite local control failures. Further studies, which take these variables into account, will need to be undertaken to answer this question to help recognize and select more effective treatment modalities.
A future study is in process involving retrieving pathologic material that will be used for specific virologic and genetic molecular biomarkers to investigate their contribution to the initiation and progression of NPC in this region.

In Saudi Arabia, NPC is the most common head and neck malignancy. Undifferentiated, nonkeratinizing squamous cell carcinoma subtype accounts for the majority of cases. The current study showed a disease with clinical behavior similar to what has been observed in East and Southeast Asia. Our study further supports the neoadjuvant chemotherapy methodology in treating NPC with results that are comparable to the literature. However, little is known about the molecular pathogenesis of this disease in this region, and further research integrating clinical and molecular biomarkers is required.

DOI: 10.1200/JGO.2015.001743
Published online on jgo.ascopubs.org on February 3, 2016.

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Manuscript writing: All authors
Final approval of manuscript: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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REFERENCES
Purpose The burden of cancer is rising in low- and middle-income countries, yet cancer treatment requires resources that are often not available in these settings. Although management of chronic myeloid leukemia (CML) has been described in low- and middle-income countries, few programs involve patients treated in rural settings. We describe characteristics and early outcomes of patients treated for CML at rural district hospitals in Rwanda.

Methods We conducted a retrospective review of patients with confirmed BCR-ABL–positive CML who were enrolled between July 1, 2009 and June 30, 2014. Types of data included patient demographics, diagnostic work up, treatment, clinical examination, laboratory testing, and death.

Results Forty-three patients were included, with a maximum follow-up of 58 months. Of 31 patients who were imatinib-naïve at enrollment, 54.8% were men and the median age at diagnosis was 36.9 years (interquartile range: 29-42 years). Approximately two-thirds of patients (67.7%) were on the national public insurance scheme. The imatinib dose was reduced for 16 patients and discontinued for five. Thirty-two of the 43 patients continued to have normal blood counts at last follow-up. Four patients have died and four are lost to follow-up.

Conclusion Our experience indicates that CML can be effectively managed in a resource-constrained rural setting, despite limited availability of on-site diagnostic resources or specialty oncology personnel. The importance of model public-private partnerships as a strategy to bring high-cost, life-saving treatment to people who do not have the ability to pay is also highlighted.
been made available for free to patients in resource-constrained settings through the Gleevec International Patient Assistance Program (GIPAP). 6,7 All patients are required to have confirmation of the BCR-ABL translocation in their leukemia cells. GIPAP assesses treatment programs for their ability to appropriately treat and monitor patients to ensure safe and effective drug administration. In 2007, there were 18,004 patients with CML worldwide who were being treated with the assistance of GIPAP. However, only 6% (1,021) of those patients lived in Africa. 6

With GIPAP’s support, a handful of programs have reported successful treatment of CML in resource-constrained settings. 5,8–17 However, most of these programs are based in private and/or urban academic facilities; there are few examples of programs for patients treated in rural settings.

Since 2008, patients with CML have been diagnosed and treated in two rural Ministry of Health district hospitals in Rwanda. This was achieved through the support of GIPAP, the nongovernmental organization Partners In Health, and oncology experts from Dana-Farber/Brigham and Women’s Cancer Center (DF/BWCC, Boston, MA). In this study, we describe the management and outcomes of patients with CML receiving therapy in this public-private program.

METHODS

Study Setting

The program was implemented at two public district hospitals in rural Rwanda, operated by the Ministry of Health in close collaboration with Partners In Health. Rwinkwavu Hospital, a 140-bed facility serving a catchment area of 207,757 people in eastern Rwanda, became the country’s first GIPAP-registered facility in 2008. Butaro Hospital is a 152-bed facility serving 321,000 people in the Northern Province of Rwanda. The Butaro Cancer Center of Excellence, which opened in 2012, serves as a national referral center for cancer care and receives patients from several neighboring countries. 18,19 Both hospitals anchor integrated care delivery systems comprising a district-wide network of health centers and several thousand community health workers (CHWs).

Patient Management

Patient care at both facilities was directed by trained generalist physicians and nurses, in consultation with oncology specialists at DF/BWCC. Patients suspected of having CML underwent evaluation including detailed medical history and examination, CBC with differential, peripheral blood smear review, bone marrow aspirate, and BCR-ABL testing. Diagnostic bone marrow biopsy was not performed in the majority of earlier cases because of resource limitations, but over time has become incorporated into standard care. BCR-ABL testing was not routinely available within the country; specimens were sent to DF/BWCC for pro bono molecular diagnosis. A few patients, particularly those from neighboring countries, were diagnosed through pathology performed outside of Rwanda. Multiple diagnostic methods were used over time. Of the 35 patients with adequate documentation on type of diagnosis available at the time of manuscript submission, 33 were diagnosed via polymerase chain reaction and two by fluorescent in situ hybridization.

On initial presentation, patients were admitted to the district hospital for cytoreductive therapy with hydroxyurea and supportive management including allopurinol, intravenous fluids, and monitoring of electrolytes and renal function. Once clinically stable with a leukocyte count below 50,000 cells/µL, patients were discharged and referred for outpatient follow-up at a nurse-led integrated noncommunicable diseases clinic at the district hospital. 20,21 Once BCR-ABL–positive status was confirmed, patients were started on imatinib 400 mg per day. Imatinib was ordered through GIPAP on a quarterly basis, at which time patients who had a confirmed diagnosis were registered. Patients were initially scheduled for follow-up every 1 to 2 months, with the imatinib dose adjusted on the basis of CBC monitoring and review of patient-reported adverse effects (Box 1).

In the majority of cases, follow-up molecular testing and bone marrow biopsy were not performed due to limited resources. Patients who were asymptomatic and in complete hematologic remission (CHR), as defined below, were scheduled for visits every 3 to 4 months. Socioeconomic supports, including nutritional supplementation and transport vouchers, were available for patients in need. CHW accompaniment was offered to vulnerable patients residing within the hospitals’ catchment districts.

Data Collection

We conducted a retrospective review of patients with confirmed BCR-ABL–positive CML who were enrolled between July 1, 2009 and June 30, 2014. Manual chart abstraction was performed twice by independent observers at each site, with discrepancies resolved by a third observer. Data included baseline patient demographics, diagnostic work up, treatment, clinical examination, and laboratory
testing at 3, 6, and 12 months (± 30 days for all time points) of follow-up. Only clinical and laboratory examinations that fell within these date ranges were included. If there were multiple visits within each range, the most complete examination was included in analysis.

Patients with incomplete documentation of BCR-ABL status were excluded from the analysis. Patients who had been diagnosed and/or initiated imatinib treatment before establishing care at Rwinkwavu or Butaro hospitals were excluded from the baseline characteristics analysis (Table 1), but were included in all other analyses. Patients who were lost to follow-up (LTFU), as defined below, were included in survival analysis. The follow-up period was counted from the date of imatinib initiation at Rwinkwavu or Butaro hospital (even if the patient had received imatinib before establishing care there), until the last follow-up visit. Telephone calls with patients, or visits on behalf of patients by family members or CHWs, were not recorded as follow-up visits.

Definitions
The primary outcome for this study was CHR, which was defined according to conventional guidelines as WBC count less than 10,000/μL, absence of splenomegaly on clinical examination, and platelet count less than 450,000 cells/μL. When spleen size was not consistently documented, CHR was replaced with CBC remission, defined as WBC count less than 10,000 cells/μL and platelet count less than 450,000 cells/μL. A secondary outcome was OS, defined as time from imatinib initiation to death from any cause or LTFU. LTFU was defined as having no visit for 9 or more months—the equivalent to three missed visits—before the study end date.

Ethics
This protocol of this study was approved by institutional review boards in Rwanda (National Health Research Council and Rwanda National Ethics Committee) and the United States (Partners Human Research Committee).

Statistical Analysis
All analyses were performed using STATA/IC software version 12 (StataCorp, College Station, TX). OS was calculated from the start of imatinib treatment to death, censoring at last follow-up visit for patients who were alive. The Kaplan-Meier product-limit method was used to estimate OS probabilities. An α level of 0.05 was set to determine statistical significance.

RESULTS
Baseline Characteristics
A total of 49 patients were treated for CML at Rwinkwavu (n = 25) and Butaro (n = 24) hospitals during the study period. Six patients (12%) were excluded due to incomplete documentation of BCR-ABL status, leaving 43 patients in this cohort (among these, one patient had a single visit). Of the 31 imatinib-naïve patients, 17 (54.8%) were men and none were HIV positive. The median age at diagnosis was 36.9 years (interquartile range [IQR]: 29-42 years). Patients presented from all provinces in Rwanda, and 11 (35.5%) patients were from neighboring countries. Two-thirds of patients (n = 21) were enrolled in a public health insurance scheme.

The duration of symptoms before diagnosis ranged from 2 to 144 months (IQR: 4-48 months) among the 23 patients with adequate documentation. Six (19.4%) patients reported having consulted a traditional healer before presenting for care. The most common presenting signs and symptoms, in descending order of predominance, were splenomegaly (74.2%), weight loss (38.7%), and fatigue (35.5%).

Treatment
Twelve (27.9%) patients had been treated with imatinib before presentation at Rwinkwavu or Butaro hospitals. An additional 12 (27.9%) patients had received other treatment, primarily hydroxyurea, whereas the remaining 19 (44.2%) had never been treated for CML. All patients were initiated or continued on imatinib. (The IQR was...
0 to 166 days for the 31 patients who had not previously been on imatinib; of the 12 patients who had previously been on imatinib, all except for one were initiated on imatinib on the day of enrollment. Imatinib dose reduction was instituted for 16 (37.2%) patients, and discontinued for five.

Table 2 summarizes reasons for dose reduction, with the leading reasons being isolated thrombocytopenia (31.3%) and neutropenia (31.3%). During the course of study follow-up, reduced doses of imatinib ranged from 100 mg (n = 4, 9.5%), to 200 mg (n = 8, 19.1%), to 300 mg (n = 4, 9.5%). Four (9.5%) patients required dose increases to 600 mg.

Outcomes

Of the 43 patients treated at our centers, 32 (82.1% of those with adequate documentation) remained in CBC remission as of their last evaluation, with a maximum follow-up of 58 months (median follow-up, 22.6 months). Twenty-eight (100% patients with adequate documentation), 27 (90.0%), and 17 (77.3%) patients were in CBC remission at 3, 6, and 12 months of follow-up, respectively. CHR was achieved in 12 (75.0% of patients with adequate documentation), 11 (68.8%), and seven (63.6%) patients, respectively, for the same time points (Table 3).

Figure 1 summarizes patient outcomes at 12 months of follow-up. Seventeen patients were in CBC remission. Five patients were not in CBC remission (of these, two were in CBC remission at 3 months and subsequently progressed, whereas the remaining three patients had inadequate documentation to assess CBC remission before 12 months). A total of 21 patients did not have adequate documentation to determine CBC remission status; of these, 12 had been in CBC remission at 3 months.

As of June 30, 2014, three patients were known to have died. Two deaths of patients residing outside of Rwanda occurred in the community as a result of unclear causes within 12 months of follow-up. The third death was of a patient admitted to a national referral hospital, who was in presumed blast crisis after being intermittently treated with imatinib for 4 years. Five (11.6%) patients were transferred to other facilities. Four patients were LTFU. The estimated OS at 12 months was 94.7% (95% CI, 0.80 to 0.99); the OS was the same at median follow-up (Fig 2).

DISCUSSION

In this study, we demonstrate the successful delivery of CML therapy in two rural district hospitals in Rwanda. Most published studies on CML management and outcomes in LMICs describe programs in private and/or urban academic centers. In contrast, our experience is one of
the few documented that describes care in a low-income country and serves poor patients in rural areas, with care directed by generalist physicians and nurses. In our cohort, treatment was successful for the majority of patients, with CBC remission exceeding 60% at 3 months of therapy. The CHR at that time was only 28%, although the actual rate of hematologic response was probably higher but difficult to ascertain as a result of poor documentation of spleen size. Treatment was well tolerated, with relatively few dose reductions and no durable treatment stops for toxicity.

Our findings are similar to reports from other LMICs including Sudan, Nigeria, Kenya, Togo, South Africa, Iraq, China, and Mexico, although few of these sites treat patients in settings as remote as Butaro or Rwinkwavu.6,8-17 In the largest of these studies, conducted at centers in India, OS at median follow-up of 47 months was 94% and progression-free survival was 76%.13 In 2013, Mendizabal et al analyzed the GIPAP database of 33,985 patients treated for CML in Asia, Africa, Latin America, and Southern/Eastern Europe. OS at 3 years was 89.4% (95% CI, 88.9 to 89.9),17 identical to the 5-year OS rate in the IRIS study of 89%.4 In the same study, Mendizabal et al demonstrated a lower age at diagnosis of CML in LMICs (37.8 years) when compared with high-income countries (eg, 64.0 years in the United States). This is also consistent with our study findings, where the median age was 36.9 years. Although reasons for this difference have not yet been elucidated, environmental risk factors may be contributing and need to be studied further.17

In our cohort of 43 patients, OS at median follow-up of 22.6 months was 94.7% and LTFU was 11.8%. These results are encouraging and demonstrate that CML can be treated successfully in extremely resource-constrained settings, where imatinib is the only available therapeutic intervention and other more complex treatments (eg, alternative tyrosine kinase inhibitors or stem cell transplantation) are not yet available. Furthermore, these outcomes have been attained without the availability of molecular assessment of response to therapy, as is standard in high-resource settings. Monitoring on the basis of only clinical and hematologic assessment was a necessity given the available resources, with neither cytogenetic nor molecular testing available within the country. Additionally, molecular monitoring is costly and had little practical implication given that if resistance to imatinib had developed, other treatment options were not available. Similar constraints have resulted in hematology-based monitoring approaches in Sudan,10 with reasonable outcomes (87.5% CHR after 8 weeks of treatment, 16% deaths after 63 months of follow-up in a cohort of 31 pediatric patients). In-country capacity to detect BCR-ABL translocations will soon be available using the Xpert BCR-ABL Monitor (Cepheid, Sunnyvale, CA). Although less expensive than sending specimens abroad, this testing is not without cost and effort. It should be used with the introduction of therapeutic options if molecular relapses are detected.

Our study has several limitations. One is that because of the retrospective design, documentation was not always complete (including spleen size and blood testing), which limited reporting on CHR. In addition, some patients were referred from other facilities with inadequate documentation. Bone marrow biopsies were not performed in all patients as a result of limited resources; hence, we were not able to describe CML phase at presentation or follow-up, nor progression-free survival. The use of consistent bone marrow biopsies is now a priority in the programs at Rwinkwavu and Butaro and is being integrated into routine care. Our study was further limited in its characterization of imatinib-related toxicity. Nonhematologic adverse effects such as nausea, rash, edema, and muscle cramps cited in other studies4,5,17 were probably underreported because clinicians may not have actively assessed for these. Finally, given the absence of a universal standardized definition

<table>
<thead>
<tr>
<th>Remission Type</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC remission</td>
<td>28 (100%)</td>
<td>27 (90%)</td>
<td>17 (77.3%)</td>
</tr>
<tr>
<td>CHR</td>
<td>16</td>
<td>16</td>
<td>11</td>
</tr>
</tbody>
</table>

Abbreviation: CHR, complete hematologic remission.

Table 2 – Toxicity and Reasons for Imatinib Dose Reduction in 16 Patients

<table>
<thead>
<tr>
<th>Reason for Imatinib Dose Reduction</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia alone</td>
<td>5</td>
<td>31.3</td>
</tr>
<tr>
<td>Thrombocytopenia alone</td>
<td>5</td>
<td>31.3</td>
</tr>
<tr>
<td>Thrombocytopenia and neutropenia</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Thrombocytopenia and anemia</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Table 3 – Trend in CBC Remission Over Time
of LTFU for CML, we were not able to compare our rates to those seen in other programs.

Adherence to medication regimens has been shown to be an issue in both resource-rich and resource-constrained settings. A recent United States–based study revealed that high adherence rates were critical to achieving and maintaining major molecular response in CML.\(^\text{15}\) Drug cost, inconvenience, toxicity, and lack of understanding of the importance of compliance all contribute to poor drug adherence. The fact that our patients achieved and maintained hematologic remission suggests that there is an acceptable rate of medication adherence, although formal evaluation of adherence should be performed in the future. Ongoing adherence support initiatives include standardized patient education and telephone check-in.

Approximately one-third of patients required a dose reduction as a result of toxicity, which was monitored with symptom review and hematologic testing performed at follow-up visits. The incidence of thrombocytopenia and neutropenia was similar to that reported in the IRIS study.\(^\text{4,5}\) Importantly, this suggests that imatinib is well tolerated and retains its therapeutic benefit in this setting, despite the expected higher prevalence of malnutrition, malaria, and other comorbidities, and presentation with more long-standing disease among our patients.

Compared with patients in high-income countries, many patients in our setting presented with long-standing disease. Possible reasons for late presentation are multifactorial. Many patients consult traditional healers first (almost one-third reported...
having done so among our patients), many wait until symptoms are debilitating because of limited funds to travel the long distances required to reach facilities where treatments are available, and many lack awareness of cancer and the potential gravity of illness. Other reasons for delay may reflect limited knowledge about CML of primary care clinicians and operational challenges in diagnostic work up for patients.17

A relatively small number of patients were LTFU. Retention supports are particularly important in our setting, given the long duration of follow-up, the socioeconomic vulnerability of most patients, and the long distances that many must travel to access care. Several initiatives exist to support patient follow-up. Missed visits are flagged in the electronic medical records system, oncology nurse coordinators make routine telephone calls to inquire if patients have missed appointments, and transport vouchers and CHW accompaniment are available. We believe that provision of these coordination and socioeconomic supports has been instrumental in achieving high retention among patients with CML. However, follow-up remains a challenge, particularly for patients residing outside the hospitals’ catchment districts, as a result of distance from facilities, frequent changes in cell phone numbers, relocations, and lack of community-based mechanisms to reach patients. All four patients who were LTFU resided outside the hospitals’ catchment districts.

Our findings also highlight the importance of developing strategies to bring high-cost, life-saving treatment to people who do not have the ability to pay. The model that GIPAP and the Max Foundation have developed with Novartis demonstrates the feasibility of doing this safely and effectively. Without GIPAP, imatinib would have been unaffordable for these programs and patients, and all of them would have died early of preventable deaths. We hope this serves as a model for other pharmaceutical companies to develop similar programs to bring their life-saving medications to people in need.

In conclusion, our experience indicates that CML can be effectively managed in a resource-constrained rural setting with promising outcomes, despite limited availability of on-site diagnostic resources or specialty oncology personnel. The simple daily oral regimen and subsidized availability of imatinib make life-prolonging treatment of CML possible in these settings. This was achieved through a public-private partnership designed to transfer knowledge, skills, medications, and technology. Expansion of services in Rwanda is underway, including a nationally approved diagnostic and treatment protocol for CML, a national scale-up of cancer programs, expansion of the imatinib-procurement process through GIPAP, and diversification of in-country testing via Xpert BCR-ABL Monitor.

DOI: 10.1200/JGO.2015.001727
Published online on jgo.asco.org on February 3, 2016.

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Manuscript writing: All authors
Final approval of manuscript: 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 jco.ascopubs.org/site/ifc.

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Pulmonary Nodules in Patients With Nonpulmonary Cancer: Not Always Metastases

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Introduction The differential diagnosis of pulmonary nodules (PNs) includes metastases, lung cancers, infectious diseases, and scar tissue, among others. Because data regarding whether and when to perform a PN biopsy in patients with cancer are scarce, clinicians tend to assume that PNs are metastatic disease based solely on imaging. The current study evaluated the findings of PN biopsies in a population of patients with cancer and sought to determine the variables that correlated with higher odds of metastatic disease.

Patients and Methods We conducted a retrospective, single-institution study that included consecutive patients with nonpulmonary solid malignancies who underwent PN biopsy from January 2011 to December 2013. Imaging and clinical variables were analyzed by logistic regression to determine the correlation between such variables and the odds of metastatic disease. Patients with previously known metastatic disease or primary hematologic malignancies were excluded.

Results Two hundred twenty-eight patients were included in the study. Metastatic disease was found in 146 patients (64%), 60 patients (26.3%) were diagnosed with a second primary lung tumor, and 22 patients (9.6%) had no cancer on biopsy. On multivariate analysis, the presence of multiple PNs (> 5 mm) and cavitation/necrosis were the only variables associated with higher odds ($P<.05$) of metastatic disease. We registered six (2.6%) procedure complications demanding active interventions, and no procedure-related death occurred.

Conclusion Multiple PNs (> 5 mm) and cavitation were the two characteristics associated with the highest chances of metastatic disease. Our findings demonstrate that PNs should not be assumed to be metastases without performing a biopsy. This assumption may lead to high rates of misdiagnosis. Tissue sampling is fundamental for accurately diagnosing patients with cancer.

INTRODUCTION

Pulmonary nodules (PNs) are frequently encountered on imaging studies and represent a diagnostic challenge. Among patients already diagnosed with cancer, data regarding optimal investigation of PNs are scarce. Usually, the emergence of PNs during treatment or follow-up leads clinicians to favor the hypothesis that disease has metastasized to the lungs. In some malignancies, such as colorectal cancer and osteosarcoma, patients with few pulmonary metastases and good control of the primary site are considered for surgical resection. However, most patients thought to have pulmonary metastases are deemed incurable and are assigned to palliative treatment. This assumption directly affects the treatment and prognosis of patients.

There is no consensus or guideline regarding investigation of a PN in patients with extrapulmonary malignancies, and clinicians are commonly challenged to balance the benefit of obtaining tissue sampling for accurate diagnosis with the potential risks involved in a pulmonary biopsy procedure. Retrospective data in populations of patients with cancer show a high frequency of benign lesions (up to 58%) and primary lung cancers (up to 50%) found after biopsies or surgery for PNs. Some characteristics, such as primary site, nodule size, the presence of concomitant extrapulmonary lesions on imaging studies, and multiple PNs, have been predictive of malignancy in previous studies. To estimate the prevalence of metastatic disease in patients with cancer presenting with a PN and evaluate the variables associated with higher odds of finding metastatic disease on biopsy, we conducted a retrospective study.

PATIENTS AND METHODS

This retrospective, observational, single-institution study was approved by the institutional review board.
board and local ethics committee of the Instituto do Câncer do Estado de São Paulo in Brazil. We reviewed electronic charts of all patients older than 18 years of age undergoing a PN percutaneous computed tomography (CT)-guided core biopsy at the Instituto do Câncer do Estado de São Paulo consecutively from January 2011 to December 2013. All biopsy specimens were referred to the pathology department and were reviewed by a pathologist. The results were registered uniformly and electronically in patients’ charts. All patients had a previous biopsy-proven diagnosis of a solid tumor and were not known to have metastatic disease. Patients with the following characteristics were excluded from enrollment: no previously confirmed cancer diagnosis; primary lung cancer (because the objective of the majority of these biopsies was to obtain tissue sampling for mutational testing) or hematologic malignancy (less likely to present with PNs and could present a bias to our final analysis); and known metastatic disease, defined by biopsy of the metastatic site. Patients presenting with PNs and concomitant extrathoracic nodules in CT scans (eg, liver, bones) were included in the analysis, provided that they did not have biopsy-proven metastatic disease. Patients who received previous thoracic radiotherapy as a part of breast cancer adjuvant treatment were included in this analysis. We established 0.5 cm as the minimum diameter for a lesion to be considered as a PN. Postprocedure complications were evaluated and described.

At our institution, the standard practice is to perform PN biopsies on lesions \( \geq 0.5 \) cm in patients without a diagnosis of metastatic disease. However, the final decision is made by the patient’s respective clinician. Some patients presenting with multiple new PNs or imaging study features suggestive of metastatic disease may not have undergone biopsy because of their clinician’s decision.

Patients were classified according to primary site: colorectal, head and neck, urologic (kidney, testicular, prostate, and bladder), gastrointestinal noncolorectal (esophageal, gastric, pancreatic, small bowel, and biliary tract), breast, melanoma, gynecologic (ovarian, endometrial, and cervical), others (sarcomas, thyroid cancer, squamous cell), and unknown primary. In those cases in which the PN was found to be a metastasis from a primary breast cancer, a comparison between the immunohistochemical profiles of the primary tumor and the metastases was performed regarding estrogen receptors and progesterone receptors (PRs), using the Allred score.\(^8\) Human epidermal growth factor receptor 2 status was assessed by means of immunohistochemical analyses (with 3+ indicating positive status) or fluorescence in situ hybridization (with an amplification ratio \( \geq 2.0 \) indicating positive status), or both.

### Statistical Analysis

Statistical analyses were performed using SPSS, version 21.0 (SPSS, Chicago, IL). We analyzed clinical and radiologic variables possibly

#### Table 1 – Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>( N = 228 )</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>61.8 (18-88.8)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>122 (53.5)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>106 (46.5)</td>
<td></td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRC</td>
<td>59 (25.8)</td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>44 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Urologic</td>
<td>33 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal non-CRC</td>
<td>25 (10.9)</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>24 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>15 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Gynecologic cancers</td>
<td>14 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Other primary sites</td>
<td>14 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Cavitary or necrotic PN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>202 (88.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Concomitant extrathoracic nodules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>169 (74.1)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>59 (25.9)</td>
<td></td>
</tr>
<tr>
<td>Number of PNs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>112 (49.1)</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>116 (50.9)</td>
<td></td>
</tr>
<tr>
<td>PN size, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-20</td>
<td>114 (50.0)</td>
<td></td>
</tr>
<tr>
<td>20-30</td>
<td>65 (28.5)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td>49 (21.5)</td>
<td></td>
</tr>
<tr>
<td>Previous thoracic radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>209 (91.7)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current or former smoker</td>
<td>139 (61.0)</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>69 (30.3)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>20 (8.7)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CRC, colorectal cancer; PN, pulmonary nodule.
associated with higher odds of finding metastatic disease on biopsy, including primary tumor site, location of the nodules (superior or inferior lobes), previous thoracic radiotherapy, time from cancer diagnosis until biopsy, concomitant extrathoracic nodules, smoking history, presence of cavitation or necrosis, single or multiple nodules, and size of the biopsied nodule. To estimate the relationship between those variables and the biopsy result (metastatic vs nonmetastatic disease), a multivariable logistic regression analysis was performed. These results are presented as OR (odds ratio) with its respective 95% confidence interval. Significance was set at an alpha error of .05.

RESULTS

Patient Characteristics

From January 2011 to December 2013, 487 patients underwent PN biopsies. After exclusion of 259 patients who did not meet the inclusion criteria, 228 were included in our final analysis. Patient characteristics are listed in Table 1, and the data collection flowchart is shown in Figure 1. Most patients were male (53.5%), colorectal cancer was the most common primary tumor site (25.8%), concomitant extrathoracic nodules were present in 25.9% of patients, multiple PNs were present in 50.9% of patients, and 30.3% of patients were never smokers.

Biopsy Results

The majority of the PNs were found to be metastatic lesions from the primary tumor (64%). The remainder 36% were mostly either primary lung lesions (71.4% of nonmetastatic patients) or benign lesions (27.4% of nonmetastatic patients), as listed in Table 2. Figures 2 and 3 show two CT-guided PN biopsies performed in patients included in the present analysis. Of note, after the biopsy result, none of the study patients underwent rebiopsy. Among 24 patients with a primary breast cancer, we observed an immunohistochemistry profile difference between the primary breast tumor and the metastatic PN (primary tumor was negative for PR, and the metastasis was positive) in only one case. Patients with concomitant extrapulmonary nodules had a metastatic disease rate of 62.7%.

Multivariate Analysis

Multivariable logistic regression analysis results are listed in Table 3. The presence of multiple PNs was significantly correlated with higher odds of finding metastatic disease on biopsy (OR, 5.08; 95% CI, 2.62 to 9.84; *P* < .01). Also, the presence of PN cavitation or signs of necrosis on CT scan was associated with statistically increased odds of finding metastatic disease (OR, 2.9; 95% CI, 1.03 to 8.21; *P* = .04). Of note, despite the small sample size, a PN in melanoma patients showed a trend toward increased odds of finding metastatic disease on biopsy, with an OR of 9.09 (95% CI, 0.83 to 99.73; *P* = .07). To evaluate which covariates were associated with a higher likelihood of finding metastatic disease on PN biopsy in patients presenting solely with PN, a similar analysis was performed, excluding patients who presented with concomitant extrapulmonary nodules. Interestingly, both multiple PNs and the presence of cavitation or necrosis were associated with metastatic disease to the lungs (OR, 4.24; 95% CI, 1.97 to 9.14; *P* < .01 and OR, 4.01; 95% CI, 1.24 to 13.01; *P* = .02, respectively). All other variables analyzed were not associated with higher odds of finding metastatic disease in the current study.

Procedure Complications

All patients underwent chest imaging (CT or x-ray) after biopsy. Of the 228 biopsies analyzed, 152 (66.6%) were uncomplicated. Among 76 complications, we observed one case of parenchymal

Table 2 – Biopsy Results in Nonmetastatic Patients

<table>
<thead>
<tr>
<th>Biopsy Results</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary lung tumor</td>
<td>60 (71.5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10 (11.9)</td>
</tr>
<tr>
<td>Mycobacterial infections</td>
<td>4 (4.8)</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Adenomatous hyperplasia</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Solitary fibrous tumor</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Melanoma (new primary tumor)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Anthracosis</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>
hemorrhage and 75 cases of pneumothorax. Most pneumothoraces (70) resolved spontaneously, and only five patients with pneumothorax required CT-guided percutaneous drainage for up to 5 days. The patient with parenchymal hemorrhage was monitored at the intensive care unit for 48 hours and was discharged. No patient required a blood transfusion, and there were no procedure-related deaths.

DISCUSSION
In our sample of 228 patients with nonpulmonary cancer presenting with PNs, more than one third (36.9%) of the PNs were unrelated to patients’ primary tumor, including 9.6% of benign lesions, such as infectious diseases or anthracosis. The biopsy procedure has demonstrated to be safe, with only 2.6% of patients presenting clinically relevant complications after biopsy. Among the 36.9% of patients with nonmetastatic lesions, PN biopsy resulted in a radical change in the patient’s final diagnosis and therapeutic plan. Infectious diseases were treated with antimicrobial drugs, benign lesions were observed, and new primary cancers were staged and treated accordingly. If all PNs were presumed to be metastatic disease, more than one third of these patients would have received inappropriate treatment.

Although not within the scope of our study, we also observed that one of 24 patients with breast cancer presented a change in immunohistochemical profile: the primary tumor was estrogen receptor negative and PR negative, and the PN was PR positive. This finding has been previously reported and has clinical implications because it may provide an opportunity for the patient to receive...
more effective treatment for breast cancer recurrence.9,10

Our results are comparable to other series.5-7 In 1978, Cahan et al5 described 35-year thoracotomy results in more than 800 patients presenting with PNs and observed that the PNs represented primary lung cancer, metastases, or nonneoplastic lesions. Since then, efforts to better understand the etiology of PNs in patients with cancer have become necessary.

Other series have also found different rates of malignant nodules on histologic analysis of PNs of patients with cancer. In a study with 1,104 patients undergoing PN resection, Mery et al6 observed a 63% malignancy rate in 337 patients with previous cancer history. Their study included patients with lung cancer as well as patients without a cancer diagnosis, who were not included in our analysis. A lower rate of malignant PNs was found by Khokhar et al.7 In 151 patients with extrapulmonary cancers who underwent PN biopsy, 42% of the nodules were found to be malignant, including newly diagnosed lung cancers.

The presence of multiple PNs and cavitary/necrotic lesions were associated with higher odds of finding metastatic disease, regardless of the presence of concomitant extrapulmonary nodules. We did not find a significant association between the site of the primary tumor and higher odds of metastatic disease, as observed in a previous study.11 However, a trend toward increased odds of metastatic disease was shown for primary melanoma. The fact that this correlation did not reach statistical significance might be attributed to the relatively small number of melanoma patients (n = 15) included in our analysis.

Despite the associations observed, as a result of the high prevalence of nonmetastatic disease and the low incidence of procedure-related complications observed in the current study and in other series, PN biopsy should be routinely recommended for patients with nonpulmonary cancer presenting with PNs. Perhaps in patients expected to have a higher risk of lung biopsy complications, the presence of multiple and/or cavitated nodules could favor metastatic disease and guide therapy, although no established guidelines currently exist.

This analysis has some limitations because of its retrospective nature. Referral for PN biopsy was a choice of the patient’s clinician. Therefore, because this was an exploratory study, it was not possible to quantify the number of patients presenting with PNs who would be eligible for our study but who were not referred for biopsy, representing a possible selection bias. Additionally, this was a single-center analysis, in which the prevalence of infectious disease, such as tuberculosis, might be distinct from other centers worldwide. Although the procedural complication rate in this study was low and seemed acceptable and manageable, such occurrences are not trivial.12

Our institution is a high-volume tertiary-care institution with expertise in image-guided invasive procedures. The logistics involved in the procedure and related follow-up are complex. Our results only apply to institutions with such a profile. Patients presenting with concomitant extrathoracic nodules detected on CT scans were included in the present analysis if they did not have biopsy-proven metastatic disease. This might represent a confounding factor because

### Table 3 – Multivariate Analysis of Covariates Associated With Metastatic Disease

<table>
<thead>
<tr>
<th>Covariate</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple nodules</td>
<td>5.08</td>
<td>2.62 9.84</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nodule size, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-20</td>
<td>0.66</td>
<td>0.14 3.23</td>
<td>.61</td>
</tr>
<tr>
<td>20-30</td>
<td>0.56</td>
<td>0.11 2.82</td>
<td>.48</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>0.53</td>
<td>0.09 2.95</td>
<td>.46</td>
</tr>
<tr>
<td>&gt; 1 year from diagnosis</td>
<td>1.49</td>
<td>0.78 2.86</td>
<td>.23</td>
</tr>
<tr>
<td>Cavitation or necrosis</td>
<td>2.90</td>
<td>1.03 8.21</td>
<td>.04</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior lobe</td>
<td>0.70</td>
<td>0.36 1.36</td>
<td>.29</td>
</tr>
<tr>
<td>Inferior lobe</td>
<td>0.60</td>
<td>0.22 1.66</td>
<td>.32</td>
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<tr>
<td>Primary site</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Unknown</td>
<td>0.78</td>
<td>0.01 43.07</td>
<td>.90</td>
</tr>
<tr>
<td>CRC</td>
<td>2.08</td>
<td>0.30 14.29</td>
<td>.46</td>
</tr>
<tr>
<td>Other</td>
<td>1.45</td>
<td>0.10 21.76</td>
<td>.79</td>
</tr>
<tr>
<td>Breast</td>
<td>1.22</td>
<td>0.15 9.69</td>
<td>.85</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>1.01</td>
<td>0.11 9.41</td>
<td>.99</td>
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<tr>
<td>Urologic</td>
<td>0.53</td>
<td>0.07 4.07</td>
<td>.54</td>
</tr>
<tr>
<td>Gastrointestinal non-CRC</td>
<td>0.63</td>
<td>0.08 5.13</td>
<td>.66</td>
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<tr>
<td>Head and neck</td>
<td>1.10</td>
<td>0.15 8.22</td>
<td>.93</td>
</tr>
<tr>
<td>Melanoma</td>
<td>9.09</td>
<td>0.83 99.73</td>
<td>.07</td>
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<tr>
<td>Previous thoracic radiotherapy</td>
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<td>0.23 2.61</td>
<td>.69</td>
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<tr>
<td>Smoking history</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>0.70</td>
<td>0.22 2.25</td>
<td>.55</td>
</tr>
<tr>
<td>Smoker/former smoker</td>
<td>0.47</td>
<td>0.16 1.41</td>
<td>.18</td>
</tr>
<tr>
<td>Extrathoracic nodules</td>
<td>1.81</td>
<td>0.87 3.76</td>
<td>.11</td>
</tr>
</tbody>
</table>

Abbreviations: CRC, colorectal cancer; OR, odds ratio.
PNs in these patients are supposed to have higher odds of being metastatic disease. Interestingly, on multivariate analysis, the presence of concomitant extrathoracic lesions was not associated with higher odds of finding metastatic disease. Moreover, a subsequent multivariate analysis excluding this subgroup of patients demonstrated results similar to the first analysis. Of note, patients with non-neoplastic diseases, such as tuberculosis and fungal infections, can present with extrathoracic nodules. Given the small number of these patients in our study, it is difficult to draw definitive conclusions, but the results indicate that in patients presenting with PNs and concomitant extrathoracic nodules on CT scans, the nodules should not be assumed to be metastatic without biopsy confirmation. Further studies to address this question are necessary.

In conclusion, this study demonstrated that the majority of PNs observed in patients with cancer were metastases from the primary tumor. Despite this, more than one third of the patients did not have metastatic cancer. Percutaneous CT-guided PN biopsy is safe and can provide valuable information. Because no validated clinical tools exist to predict whether a PN is a metastasis, biopsy is recommended. Our data demonstrate that assuming that all PNs observed in patients with cancer are metastatic disease will lead to high rates of inaccurate diagnosis and inappropriate subsequent treatments. Tissue sampling is still fundamental for accurately diagnosing and treating patients with cancer.

DOI: 10.1200/JGO.2015.002089
Published online on jgo.ascopubs.org on February 3, 2016.

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Manuscript writing: All authors
Final approval of manuscript: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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No relationship to disclose

REFERENCES


Cheaper Options in the Prevention of Chemotherapy-Induced Nausea and Vomiting

Chemotherapy-induced nausea and vomiting (CINV) is a common challenge in modern oncology practice. For many patients with cancer, CINV is one of their worst fears. Studies have shown that CINV can adversely affect quality of life, lead to change in treatment plans, and increase the use of health care resources. It has also been demonstrated that clinicians frequently underestimate the incidence of CINV. The economic feasibility of anticancer treatment has been a matter of huge debate and discussion. The National Comprehensive Cancer Network (NCCN) has recently announced that it will publish cancer treatment guidelines that cater to the needs of resource-limited countries. Such guidelines for cervical cancer are already in place, and a position paper by the European Society for Medical Oncology regarding decreasing the cost of anticancer treatment has also been published. Despite the enthusiasm for reducing the high cost of cancer treatment, the high cost of supportive care for patients with cancer is frequently ignored. Antiemetics used in the prevention of CINV are often expensive, and because they are used with every treatment cycle, the cost of these agents adds significantly to the overall cost of treatment. The current guidelines-based practice for highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC) include the use of antiemetic drugs aprepitant and palonosetron; both of these agents are expensive. In resource-limited settings, the cost of these agents can be greater than the cost of the chemotherapy with which they are prescribed, and justifying the cost to patients is difficult. These agents are also not easily available in developing and underdeveloped countries; however, evidence exists that supports the use of other less costly alternatives that are also effective in preventing CINV. In this article, we will review updates in the prevention of CINV that explore economically cheaper options. Oncologists in both developing and developed countries should be familiar with these approaches because it is common for patients not to be able to afford these expensive treatments, which can make guideline-based practice impossible. Furthermore, reducing the overall cost of cancer treatment is a collective responsibility we all share.

METHODS
A literature search was conducted in PubMed by using the search terms chemotherapy-induced nausea and vomiting, CINV, chemotherapy, nausea, vomiting, and emesis in various combinations. The search was conducted in June 2015 without any date restrictions. We included only those studies published in English and that were relevant to cost reduction in CINV treatment. We...
also conducted a manual search of the reference lists of the selected studies to incorporate a comprehensive list of studies for this review.

Olanzapine

Olanzapine is a relatively inexpensive and widely available agent that has been in use for a long time as an atypical antipsychotic. It targets not only the dopaminergic receptors (D1 to D5) that are responsible for antipsychotic properties but also the serotonergic, adrenergic, histaminergic, and muscarinic receptors. These receptors are known to play a role in the emesis reflex, and the ability to target multiple receptors with a single oral medication is an advantage of this drug. Olanzapine has now been included as an alternative to an aprepitant-containing regimen in the NCCN guidelines for the prevention of CINV resulting from HEC and MEC.9

Use of olanzapine represents a cost reduction of approximately US$100 to US$500 in one cycle (Table 2), which is significant for both patients and health care systems. Evidence for the use of olanzapine to prevent emesis associated with HEC comes from a randomized study by Navari et al17 that compared treatment with aprepitant, palonosetron, and dexamethasone (APD) with treatment with olanzapine, palonosetron, and dexamethasone (OPD) in 257 patients. The primary end point was overall complete response (CR). The study found a numerical advantage for the OPD regimen with regard to overall CR, acute CR, and delayed CR, and OPD demonstrated both a numerical and a statistical advantage for overall nausea control and delayed nausea control (Table 3).17 No treatment-related adverse effects were observed in either arm, and there were no significant differences in the two arms with regard to any of the MD Anderson Cancer Center symptom scores. This study has been criticized for being open label and for not indicating whether it was a superiority or an inferiority trial18,19; however, there is still credible evidence to support the use of olanzapine because vomiting is a parameter that is not affected by blinding, and all patients were chemotherapy naïve and had not previously received either of the antiemetic regimens. Moreover, the control of delayed and overall nausea was improved by > 30%. It should be noted that the OPD regimen contained only a single dose of dexamethasone 20 mg on day 1 and a dosage of olanzapine 10 mg/d was continued for < 4 days. Another phase III trial randomly assigned 229 Chinese patients being treated with HEC or MEC to treatment groups of either olanzapine, azasetron, and dexamethasone or azasetron and dexamethasone.20 The trial found that the addition of olanzapine significantly improved the CR rates of delayed nausea and vomiting as well as quality of life (QoL), with no significant difference for acute nausea and vomiting.20 An important caveat of this study, however, is the use of azasetron as a 5-HT3 (5-hydroxytryptamine-3) inhibitor, which was later shown to be inferior to ondansetron for the prevention of delayed CINV.21 Nevertheless, this study demonstrated impressive improvements in delayed nausea CR (HEC, 39.2%; MEC, 25.0%), delayed vomiting CR (HEC, 22.0%; MEC, 13.4%), overall nausea CR (HEC, 41.3%; MEC, 26.6%), and overall vomiting CR (HEC, 22.0%; MEC, 13.4%). This study also showed improvements in QoL. Some beneficial antidepressant effect of this atypical antipsychotic also cannot be ruled out in this setting.20

### Table 1 – Cost of Commonly Used Antiemetic Drugs in CINV in the United States

<table>
<thead>
<tr>
<th>Antiemetic Drug</th>
<th>Cost in US Dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aprepitant set (125, 80, 80 mg)</td>
<td>647.50</td>
</tr>
<tr>
<td>Palonosetron 0.25 mg IV</td>
<td>493.20</td>
</tr>
<tr>
<td>Ondansetron 8 mg</td>
<td>40</td>
</tr>
<tr>
<td>Olanzapine 10 mg</td>
<td>23.30</td>
</tr>
<tr>
<td>Metoclopramide 10 mg</td>
<td>2.48</td>
</tr>
<tr>
<td>Dexamethasone 8 mg</td>
<td>1.98</td>
</tr>
<tr>
<td>Prochlorperazine 10 mg</td>
<td>2.73</td>
</tr>
</tbody>
</table>

NOTE: Cost in US dollars has been referenced from Lexicomp in June 2015 and may vary. Wherever possible, oral medications have been chosen for cost calculation. All costs except aprepitant are per tablet and dose. Abreviation: CINV, chemotherapy-induced nausea and vomiting.

### Table 2 – Cost Analysis of OPD Versus APD Regimen by Country

<table>
<thead>
<tr>
<th>Country</th>
<th>Cost of APD Regimen, Dollars</th>
<th>Cost of OPD Regimen, Dollars</th>
<th>Cost Saving, Dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>1,143.00</td>
<td>589.00</td>
<td>554.00</td>
</tr>
<tr>
<td>Australia</td>
<td>169.00</td>
<td>72.00</td>
<td>97.00</td>
</tr>
</tbody>
</table>

NOTE: Cost in Australia has been referenced from Hocking and Kichenadasse.16 Abbreviations: APD, aprepitant (days 1 to 3), palonosetron (day 1), dexamethasone (days 1 to 4); OPD, olanzapine (days 1 to 4), palonosetron (day 1), dexamethasone (day 1).
A randomized study that compared olanzapine with aprepitant was presented at the 2009 ASCO Annual Meeting. This was a double-blind, placebo-controlled study in 18 chemotherapy-naïve patients who were receiving HEC, and results showed that olanzapine obtained a numeric advantage in all parameters—acute CR, delayed CR, and rates of nausea in anticipatory, acute, and delayed periods—compared with aprepitant.

A meta-analysis of six studies involving 726 patients, of whom 441 were Chinese, who received HEC and MEC found that olanzapine-containing antiemetic regimens were more effective than non-olanzapine-containing regimens, especially for delayed CINV. However, only two of these studies used the standard guideline regimen (5-HT3 + dexamethasone + neurokinin 1 [NK-1] antagonist) as the control arm. Another meta-analysis of 488 patients from three trials further confirmed the efficacy and safety of olanzapine-containing regimens for CINV prevention as well as for olanzapine as a single agent for treatment of breakthrough CINV.

Many studies have demonstrated that it is more difficult to control nausea than it is vomiting; however, olanzapine studies have shown that the agent is particularly helpful in controlling nausea. It should be noted, however, that OPD has been approved only in the NCCN guidelines, whereas guidelines by ASCO and the European Society for Medical Oncology/Multinational Association of Supportive Care in Cancer have yet to include olanzapine for CINV prevention.10,24

Although debate exists over the prophylactic use of olanzapine for the prevention of HEC and MEC CINV, use of olanzapine in breakthrough CINV is relatively well accepted. In a double-blind, phase III randomized trial among 276 patients receiving HEC, olanzapine was found to be significantly better than metoclopramide in the control of breakthrough emesis and nausea. During the 72-hour observation period, the percentages of patients with no vomiting and no nausea were 70 and 68 versus 31 and 23 in olanzapine versus metoclopramide groups, respectively (P < .01 for both vomiting and nausea).25

Common adverse effects associated with olanzapine, as experienced from its use in psychiatric patients, include sedation, sleepiness, weight gain, hyperglycemia, dyslipidemia, orthostatic hypotension, extrapyramidal symptoms such as akathisia, and anticholinergic effects of dry mouth, constipation, asthenias, tremors, dyspepsia, and dizziness. Decreased seizure threshold, diabetes, prolongation of QTc interval, and, although rare, neuroleptic malignant syndrome have also been reported with use of olanzapine in psychiatric practice.18 Weight gain and increased appetite could actually be positive effects, given that many patients with cancer are cachectic. Care should be taken with patients on antihypertensive agents because olanzapine can potentiate hypotension. Olanzapine has been included in the Beers list of drugs to avoid in older adults with syncope and seizures. Of note, these adverse effects were conspicuously absent in the clinical studies of olanzapine in CINV, which suggests that the short-term use of the drug in such instances as in the prevention or treatment of CINV is safe.

The risk of drug interaction must be considered when administering any antiemetic. Olanzapine is metabolized by CYP1A2 and CYP2D6, and, as a result, inhibitors of CYP1A2, such as fluvoxamine, decrease olanzapine clearance, whereas inducers of CYP1A2, such as omeprazole, rifampin, and carbamazepine, increase olanzapine clearance. Inhibitors of CYP2D6 have a relatively weaker impact on olanzapine clearance. It is important to note that drug interactions with olanzapine are few compared with aprepitant.

In conclusion, an olanzapine-containing regimen is a cost-reducing alternative to an aprepitant-containing regimen. The role of other 5-HT3 antagonists in combination with olanzapine and dexamethasone should also be explored because the cost of palonosetron is more than ten times that of first-generation 5-HT3 antagonists. Although a randomized, double-blinded study is desirable, all available studies suggest favorable outcomes with olanzapine. Moreover, there are many hurdles to conducting large, phase III trials in the supportive care field. As currently available data support the use of olanzapine, and as there is no clear data to...

---

**Table 3 – Efficacy of OPD Versus APD Regimen**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>APD Regimen</th>
<th>OPD Regimen</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR acute</td>
<td>87</td>
<td>97</td>
<td>NS</td>
</tr>
<tr>
<td>CR delayed</td>
<td>73</td>
<td>77</td>
<td>NS</td>
</tr>
<tr>
<td>CR overall</td>
<td>73</td>
<td>77</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea control acute</td>
<td>87</td>
<td>87</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea control delayed</td>
<td>38</td>
<td>69</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Nausea control overall</td>
<td>38</td>
<td>69</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

NOTE. Taken from the Navari et al.17

**Abbreviations:** APD, aprepitant (days 1 to 3), palonosetron (day 1), dexamethasone (days 1 to 4); CR, complete response (no emesis, no rescue); OPD, olanzapine (days 1 to 4), palonosetron (day 1), dexamethasone (day 1); NS, not significant.
suggest that administering an NK-1 inhibitor is superior, an olanzapine-containing treatment regimen should be an obvious choice, especially for patients who cannot afford costlier drugs. The cost savings associated with the use of OPD versus APD in various countries is highlighted in Table 2.

Ginger

Ginger is known to exert antiemetic properties. Although the exact mechanism of action is unknown, possible mechanisms hypothesized include regulation of GI secretions and motility as well as interaction with 5-HT3 receptors. Ginger has been known to be effective in cisplatin-induced emesis in animal models.

In a large, double-blind, randomized study, 744 patients with cancer were randomly assigned to three different doses of ginger (0.5 g, 1.0 g, or 1.5 g) or a placebo. All patients received a 5-HT3 antagonist on day 1 of all cycles and three capsules of ginger 250 mg or placebo twice a day for six days, beginning three days before day 1. Of 576 patients included in the final analysis, of which 91% were female, all doses of ginger significantly reduced the severity of acute nausea on day 1 compared with placebo (P = .003). The largest reduction in nausea intensity was observed with doses 0.5 g and 1.0 g (P = .017 and .036, respectively). In the delayed phase, no significant benefit was noted. Similar results in acute phase, but not delayed phase, CINV were obtained in an open-label study of ginger plus granisetron plus dexamethasone in patients with breast cancer. These studies suggest a use for ginger in the treatment of CINV, at least for acute nausea. However, other studies have found a role for ginger in the treatment of delayed nausea as well.

Another advantage of ginger lies in the fact that it does not have significant adverse effects. In fact, it is commonly used as a spice or flavoring agent in the food of many South Asian countries. The reported adverse effects of ginger include abdominal discomfort, heartburn, diarrhea, and inhibition of platelet aggregation leading to bleeding; however, these are of a more theoretical interest.

A systematic review of the efficacy of ginger in CINV that was performed in 2013 reviewed seven randomized controlled studies, of which all but two favored the use of ginger in the prevention of CINV. The two studies that failed to show a benefit were severely flawed. The first study enrolled only 36 participants, of which 13 were excluded as a result of nonadherence. The second study had a larger sample size (N = 129) but compared ginger versus a placebo in combination with 5-HT3 with or without aprepitant. Of the participants, > 31% and > 43% had received aprepitant and palonosetron, respectively. Because effective antiemetics had already been administered to many participants, ginger could not have provided any additive effect. These ginger studies have several problems, one of which is the standardization of dose in ginger capsules, and a second being that the aroma or smell of ginger makes true blinding difficult. However, blinding strategies have been developed and used effectively.

In conclusion, ginger seems to be a cheap and attractive adjunct for CINV prevention. Pillai et al found that, compared with placebo, ginger plus ondansetron plus dexamethasone was effective in the prevention of both acute and delayed CINV in children and young adults receiving HEC. This is a promising finding, and such strategies should be investigated and validated in larger patient populations. If validated, this regimen could be of immense value in terms of cost savings. On the basis of a study by Ryan et al, thus far the largest, well-conducted study of the effect of ginger in CINV, ginger could at least be encouraged in the setting of the trial inclusion criteria, that is, for patients with a history of CINV in a previous cycle and for those with controlled emesis but continued nausea.

Dexamethasone Sparing

For HEC and MEC, guidelines recommend the use of dexamethasone for the first 4 days and the first 3 days of the treatment cycle, respectively, for the prevention of delayed nausea and vomiting. In 2010, Aapro et al investigated whether dexamethasone could be omitted altogether on days 2 and 3 in 300 chemotherapy-naïve patients receiving an antiemetic regimen of palonosetron plus dexamethasone with AC (anthracycline, cyclophosphamide) -based chemotherapy. Their results showed that dexamethasone on only the first day of treatment with AC was not inferior to dexamethasone continued for the first 3 days with respect to acute CR (69.5 v 66.8%, respectively), delayed CR (62.3 v 65.8%, respectively), and overall CR (53.6 v 53.7%, respectively). An Italian phase III, open-label study, randomly assigned 332 patients receiving MEC to palonosetron and dexamethasone on day 1 only versus palonosetron on day 1 only and dexamethasone on days 1 to 3. This study showed that a dexamethasone-sparing strategy was not inferior in terms of overall, acute,
and delayed CR rates, especially for non–AC-containing MEC. A prespecified retrospective analysis of the two studies found that a dexamethasone-sparing regimen is not associated with a significant loss in overall antiemetic protection in women undergoing AC-containing chemotherapy, regardless of age.

A recent phase III, randomized, open-label Japanese study of 305 patients also demonstrated that dexamethasone may be omitted on days 2 and 3 for non–AC-containing MEC, with administration of palonosetron and dexamethasone on day 1 only, showing no inferiority in overall CR compared with palonosetron and dexamethasone on days 1 to 3 (66.2% vs 63.6%, respectively). This study administered palonosetron 0.75 mg, which is the commonly used dose in Japan. Netupitant-palonosetron is a netupitant (an NK-1 antagonist) plus palonosetron combination that has recently been included in the NCCN guidelines. Netupitant-palonosetron and dexamethasone are also administered on day 1 only, whereas dexamethasone is not necessary to be administered on subsequent days.

A nonrandomized, phase II Italian trial demonstrated that dexamethasone can be safely omitted from AC-containing MEC in patients with breast cancer (with palonosetron administered on day 1 only) because other corticosteroids, such as prednisone and hydrocortisone, are used by default for chemotherapy premedication.

Although dexamethasone is not expensive, a dexamethasone-sparing strategy is cheaper when considering the overall cost of managing the wide variety of adverse effects that are associated with corticosteroid use, such as insomnia, GI upset, agitation, increased appetite, weight gain, and skin rash. This implies that a dexamethasone-sparing strategy can both save money and improve QoL.

Aprepitant Sparing for Delayed Emesis

A recent study by the Italian Group for Antiemetic Research explored an aprepitant-sparing strategy for the prevention of delayed CINV in AC-containing MEC (dexamethasone v aprepitant on days 2 and 3) after APD on day 1. This study showed that dexamethasone and aprepitant had similar efficacy and toxicity in preventing delayed emesis, which represents cost savings of approximately US$350 for dexamethasone over aprepitant. Although these studies have been criticized for the potential confounding by palonosetron, it should be noted that APD followed by aprepitant is a guideline-based practice. That APD followed by dexamethasone alone is effective is important, given the cost savings of this strategy.

One multiarm, double-blind, randomized trial showed that palonosetron and granisetron had similar efficacy in preventing delayed nausea (prochlorperazine and not dexamethasone was administered on days 2 and 3), and that effects from the addition of prochlorperazine was similar to those of the addition of aprepitant. The primary end point of this study was average nausea assessed four times per day on days 2 and 3, which is a matter for criticism. However, an important finding from this study is that dexamethasone and prochlorperazine could substitute for aprepitant to prevent delayed nausea (86% of patients experienced no benefit from aprepitant over prochlorperazine), and that palonosetron is similarly effective compared with granisetron. Most of the studies on aprepitant in delayed nausea have compared aprepitant with placebo or dexamethasone or 5-HT3 alone and found positive results. However, this study, where aprepitant was compared with dexamethasone and prochlorperazine, and another study by Schmoll et al., in which aprepitant was compared with dexamethasone and 5-HT3, showed no difference between groups for delayed nausea. Thus, dexamethasone and prochlorperazine could potentially provide a cheaper efficacious alternative to the expensive aprepitant.

Metoclopramide

Metoclopramide is a dopamine receptor antagonist that was used as a first-line therapy for the prevention of CINV before 5-HT3 antagonists were introduced. Current guidelines, however, suggest metoclopramide only for the treatment of breakthrough emesis. A randomized, double-blind trial by the Italian Group for Antiemetic Research investigated the role of metoclopramide versus aprepitant in the prevention of cisplatin-induced, delayed CINV. All patients received APD on day 1 and were then randomly assigned to aprepitant 80 mg orally once per day on days 2 and 3 and dexamethasone 8 mg on days 2 to 4 versus metoclopramide 20 mg four times daily on days 2 to 4 and dexamethasone 8 mg twice a day on days 2 to 4. Although limited by poor accrual, this study showed a numeric advantage for metoclopramide plus dexamethasone over aprepitant and dexamethasone for CR rate (82.5% vs 80.3%, respectively). However, it failed to show the superiority of aprepitant and dexamethasone over metoclopramide and dexamethasone in the prevention of delayed emesis in HEC. Secondary
end points—complete protection, total control, no vomiting, no nausea, and score of functional living—were similar between both cohorts.\textsuperscript{59} Given that the efficacy of both regimens were similar and that the cost of aprepitant is seven times that of metoclopramide, the choice of regimen is obvious, especially in economically constrained situations.

The adverse effects of metoclopramide include neurologic effects, such as extrapyramidal symptoms and tardive dyskinesia. Therefore, the European Medicines Agency, but not the US Food and Drug Administration, has restricted the use of metoclopramide to a maximum of 5 days, 30 mg/d.\textsuperscript{60} Metoclopramide is also a drug to avoid in older adults according to the Beers Criteria\textsuperscript{29}; however, no extrapyramidal adverse effects were observed in the Italian study of metoclopramide in CINV prevention.\textsuperscript{59} Although the loss of power resulting from poor accrual of this study has been pointed out as a pitfall by some critics,\textsuperscript{19} the authors’ defense of having taken a lower margin of difference for sample calculation, numeric advantage of metoclopramide arm in all but one of the primary and secondary end points as well as corroboration by similar findings in the past attest to the reliability of this study. Therefore, this study should not be regarded as having poor accrual and, therefore, no validity, but should be taken by clinicians as a viable alternative, especially in resource-limited settings or settings for which alternatives are needed. Further research on cost effectiveness by testing this with a first-generation 5-HT\textsubscript{3} regimen on day 1 or with OPD is needed.

In conclusion, there has been substantial research and progress in exploring cheaper alternatives for the prevention of CINV. With scientific data supporting the use of alternative antiemetic regimens, we should not hesitate to practice cheaper CINV prevention strategies, especially in resource-limited settings. Because trials in alternative drugs have shown better or comparable results to expensive counterparts, these regimens should also be explored in developed countries. A dexamethasone-sparing strategy could be used when aprepitant and palonosetron regimens are used, as shown by the trials. The efficacy of ginger in preventing CINV may be considered by oncologists in resource-limited settings who care for poor patients.

DOI: 10.1200/JGO.2015.002477
Published online on jgo.ascopubs.org on March 16, 2016.

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Manuscript writing: All authors
Final approval of manuscript: 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.

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Nursing’s Potential to Address the Growing Cancer Burden in Low- and Middle-Income Countries

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INTRODUCTION
Cancer has become a major noncommunicable disease (NCD) in low- and middle-income countries (LMICs) where an inadequately prepared and insufficient nursing workforce exists. Successful cancer care requires a team approach, and knowledgeable oncology nurses play a crucial role in a functioning team. The goals of reducing cancer incidence, improving survival, and providing better palliative care cannot be met without the efforts of these nurses. Oncology nurses who work in the community and at the bedside can deliver needed patient, family, and community education; implement early detection programs; administer treatments; identify complications; provide palliative care; and lead and collaborate on clinical research. Well-prepared oncology nurses have demonstrated a wide-ranging impact across the spectrum of cancer care in high-income countries (HICs). To benefit from this expertise, LMICs need workforce capacity—building efforts to educate nurses in cancer care initiatives, expand the scope of nursing practice, and increase task sharing. Adequately educated nurses can play many vital roles across the cancer control continuum to help to improve cancer control in LMICs and create an additional point of access to cancer care, particularly in settings where specialized care is rare and existing resources are strained. By highlighting the ways nurses can contribute to the improvement of oncology care in LMICs, this report addresses the issues that face the workforce and includes recommendations to illustrate how health and educational systems can be used to strengthen the expertise and expand the role of oncology nurses in LMICs. Nursing education, the nursing practice environment, and opportunities for role expansion research have not kept pace with the growing need.

NURSING’S POTENTIAL CONTRIBUTIONS TO CANCER CARE: WHAT CAN BE DONE IN LMICs
In all aspects of the fight against cancer, nurses participate dynamically as part of an interdisciplinary team. A well-prepared oncology nursing workforce includes generalist nurses who are prepared at the basic level and provide health promotion, risk assessment, and care for people who receive cancer treatment in their general practice; specialized nurses whose primary focus is the delivery of cancer care and who care mostly for people with or at risk for cancer; and advanced practice oncology nurses who provide cancer care at the master’s degree level of education or higher. Oncology nurses with master’s and doctoral education contribute through advanced practice, education, and scientist roles. Adequately educated nurses can play many vital roles across the cancer control continuum; however, not all countries use nurses to their fullest capacity. As part of their Global Action Plan for NCDs, the WHO recommended that nations “optimize” the scope of nurses’ and allied health professionals’ practice to contribute to the prevention and control of non-communicable

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Authors’ disclosures of potential conflicts of interest and contributions are found at the end of this article.

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disease, including addressing barriers to that contribution,⁶ and many opportunities exist to maximize the impact of oncology-trained nurses in addressing the cancer burden.

Nurses’ intimate knowledge of patient populations make them an obvious partner among oncology specialists to address the increasing public health burden of this group of diseases. Nurses trained as specialists in oncology could address public health cancer risks, such as smoking and obesity, as well as cancer-causing environmental and occupational hazards in their local areas. Oncology nurse researchers in LMICs could collaborate with epidemiologists, medical anthropologists, environmental health scientists, public health professionals, and health economists to gather the much-needed data to measure the efficacy of cancer prevention activities, cancer incidence and prevalence, and outcomes of people treated for cancer. This section outlines what has been done in oncology from prevention through end-of-life care and survivorship by nurses who work in countries of various resource levels and what can be done in LMICs specifically to improve cancer-related outcomes around the globe.

Cancer Education

In LMICs, a patient’s first encounter with the health system often is with a community health worker (CHW) at the dispensary (community) level; however, CHW and nurses’ knowledge of cancer and cancer risk factors, signs, and symptoms in many LMICs is low.⁷-¹⁰ Oncology nurses placed throughout the country could dramatically increase the number of cases diagnosed in early stages. In addition, oncology nurses can educate CHWs about cancer to raise awareness and appropriately refer a patient for further evaluation.⁷,¹¹ Further, nurses can increase adherence to screening guidelines because they are viewed as trusted members of their society.⁶ Thus, nurses can act more efficiently as patient navigators through the continuum of care to link the patient to local health systems and decrease delay in care.¹²,¹³

Prevention: The Unique Role of Nurses

One-third or more cancer diagnoses can be avoided by reducing risk factors, such as tobacco use, poor diet, low levels of physical activity, alcohol consumption, workplace and environmental carcinogens, and exposure to radiation; immunizing against hepatitis B and C viruses and the human papillomavirus (HPV); and preventing infection with Helicobacter pylori and schistosomiasis.¹⁴ Nurses are uniquely positioned to successfully implement preventive interventions at both the individual and the community level given their accessibility to and active role in the community. Disease prevention and health promotion have long been a part of nursing’s scope of practice. Nurses are trained to identify risk factors, and they have the communication and teaching skills to work with individuals, families, and communities to change behaviors to reduce risk factors.¹⁵-¹⁷

A Cochrane review of 16 studies about tobacco cessation conducted in various HICs showed evidence that the likelihood of reaching the positive outcome of quitting smoking is increased when nursing-specific interventions are used.¹⁸ Emerging research has demonstrated that nurses are instrumental in providing effective smoking cessation intervention in LMICs as well.¹⁹ In vaccination programs, nurses also have been instrumental in educating the public about the importance of vaccinations and in implementing these programs in LMICs for viruses such as HPV, the cause of cervical cancer, and hepatitis B virus, which is associated with an increased incidence of liver cancer. A school-based, opt-out HPV vaccination program in Rwanda has used nurses to reduce the two-decade delay in vaccine introduction between HICs and LMICs to 5 years.²⁰

Screening and Early Detection: Opportunities for Expanded Care

To improve outcomes, prevention must be coupled with screening and early detection measures. Early detection decreases the overall costs of cancer treatment.²¹ With additional training, nurses can perform the broad range of interventions that contribute to screening,¹⁷ early detection, and even treatment of precancerous lesions.⁵ With nurses performing these activities, the few available physicians and oncologists can focus on tasks that require their specialized skills.²³,²⁴ Various programs have demonstrated that nurses play a vital role in screening. Studies in HICs have shown that nurses can perform flexible sigmoidoscopy or colonoscopy with ratings in patient satisfaction, safety, and effectiveness similar to those for procedures done by general surgeons and GI fellows.²⁵-²⁸ These findings suggest that appropriately trained oncology nurses in LMICs could assume this level of care as part of the task shifting that has already been demonstrated to be successful (eg, for colposcopy). However, challenges related to scope of practice for oncology nurses in LMICs remain.
Research findings in the Philippines, Indonesia, and Malaysia have demonstrated that clinical breast examinations done by nurses are a sustainable form of early detection and primary screening. In promoting general breast health awareness, nurses are a well-suited professional group to desigmatize disease within their respective communities. Nurses in LMICs knowledgeable about breast health and with skills in clinical breast examination can contribute to reaching the goal of downstaging the presentation of breast cancer in these countries.

The Cervical Cancer Prevention Program in Zambia demonstrates the value nurses provide in cervical cancer control through the Screen and Treat program. Similar programs have been successfully implemented in other LMICs, including India.

**Treatment: Roles in Surgery, Chemotherapy, and Radiotherapy**

Nurses around the globe play a vital and central role in the delivery of all cancer treatment modalities, particularly surgical, radiation, and medical oncology. For patients undergoing surgical intervention, nurses teach patients what to expect before, during, and after procedures. The nurse assesses the patient during the postoperative period by monitoring wound healing, preventing infection, managing pain, and facilitating return to activities of daily living. Surgical interventions such as mastectomy, orchiectomy, or colectomy may require nurses to assist patients to adapt to altered physical or emotional functioning. Surgical nurses in LMICs participate in multidisciplinary training to improve surgical outcomes in people with cancer. Despite this evidence, nursing management and care of patients undergoing surgical intervention remain suboptimal in many countries due to lack of adequate resources and targeted nursing education. For example, in Paraguay, postoperative pediatric neurosurgical management does not prevent the high infection rate that leads to early mortality for children with brain tumors. Well-educated pediatric oncology nurses could support efforts to improve neurosurgical interventions in LMICs.

Although radiation therapy is an important component of cancer control, of the 139 LMICs (as categorized by the World Bank), almost one-half (55) have no radiation facilities, and only four have adequate equipment. Nurses who work in radiation oncology units clinically assess and educate patients about radiotherapy by addressing patient fears and providing information about potential adverse effects. Nurses need to be knowledgeable about the specific radiation field so that they can educate patients to identify adverse effects early and so that steps can be taken to avoid complications, avoid treatment delays, or conclude radiation treatment prematurely, as has been demonstrated in Indonesia.

Nurses who work in medical oncology practices in LMICs often administer and prepare chemotherapy and generally without personal protective equipment or a biologic safety cabinet. They need to be meticulous in this practice, particularly in math calculations to reconstitute chemotherapy agents, calculate body surface area, and assure appropriate dosing that is consistent with treatment protocols. Many nurses in LMICs, however, are not formally trained in chemotherapy administration and would like further education on the subject.

Because of the lack of education, protective equipment, and trained pharmacists in many locations around the globe, chemotherapy preparation and administration poses a significant risk to nurses. Training for the safe handling of hazardous drugs is essential to protect both the nurses and their patients and families. Personal protective equipment, which includes chemotested gloves, disposable gowns, masks with eye shields or goggles, and a biosafety cabinet, must be available and used properly to protect nurses within their practice setting.

Chemotherapy preparation ideally is the scope of the pharmacist and should be conducted in appropriate pharmacy facilities, even in LMICs. In fact, the inclusion of an oncology-trained pharmacist is a cost-effective way for an LMIC setting to improve chemotherapy preparation and handling; nurse and patient safety; and inventory control, patient and family education, hazardous drug waste management, and pharmaceutical cost savings. Nonetheless, the reality in many LMICs is that a shortage of either educated pharmacists or safety equipment exists and that nurses ultimately are responsible for both preparing and administering chemotherapy and therefore need to be properly educated about safety measures. Other professionals, such as engineers, are needed to develop low-cost, effective chemotherapy preparation facilities and equipment.

**Treatment: Provision of Supportive Care in All Modalities**

Patients who undergo cancer treatment benefit from supportive care, or the prevention and management of adverse effects. Oncology nurses
are skilled at conducting a comprehensive assessment of the health and supportive care needs of patients with cancer. In addition, oncology nurses can educate and provide psychosocial and spiritual support by sharing and applying their knowledge of cancer and treatment modalities and adverse effects.\(^5\),\(^52\)

Cancer and treatment-related symptoms are major stressors in patients with cancer. In LMICs, symptom burden that patients with cancer experience may be even worse than the experience of patients in HICs because supportive care, including symptom management, often is a low priority in LMICs, and essential medicines (eg, to control pain) may be unavailable.\(^53\),\(^54\) However, lack of information and education about cancer treatment and the management of its adverse effects are major barriers to effective cancer treatment in LMICs because supportive care often is inadequately addressed.\(^32\),\(^55\),\(^56\)

Various studies have reported that patients who do not receive adequate symptom management can experience an increase in psychological distress, treatment delays or noncompliance, a prolonged hospital stay, and negative effects on quality of life.\(^52\),\(^57\)-\(^59\) By educating patients so that they have a better understanding about their treatment, adherence to treatment could be enhanced and, in turn, could result in better treatment outcomes.\(^50\)-\(^62\)

Studies in HICs have reported positive effects of nursing interventions on the management of symptoms\(^57\),\(^63\),\(^64\) to minimize the consequence of cancer treatment\(^57\),\(^65\),\(^66\) and promote quality of life\(^67\)-\(^69\) among patients. Oncology nurses are the closest to the patient and, therefore, have the unique opportunity and privilege to advocate for and support the patient and his or her family. They also play a significant role in assuring that the highest quality of care is delivered to achieve the best possible outcome.\(^70\),\(^71\)

An Opportunity to Improve Outcomes Through Research and Evidence-Based Practice

Nurses have a unique perspective on health care systems that can contribute effectively to research and evidence-based interventions that inform service delivery, education and training, and policy recommendations. Nursing research has had a significant impact on health promotion and disease prevention in LMICs for health issues such as HIV/AIDS,\(^72\)-\(^74\) maternal and child health,\(^75\),\(^76\) and mental health\(^77\) and can have a similar impact on oncology care. Nursing research and multidisciplinary research led by a team of nurses, physicians, statisticians, and others could assist in developing strategies for resource-appropriate best practices. In addition, nurses could make pivotal contributions to translational research for the development of evidence-based practice.

The WHO Global Forum for Government Nursing and Midwifery Officers (the Global Forum) calls for nursing and midwifery research on efficacy and cost-effectiveness of interventions, translational research, and collaborative partnerships for funding research and innovative projects.\(^19\) To enhance nurse and midwife capacity to address NCDs such as cancer, the Global Forum suggests research focused on expanding settings for implementing interventions, integrating risk assessment with clinical practice, surveying the prevalence of risky health behaviors, and training to enhance knowledge and skills on cancer and its risk factors.\(^19\) The advancement of nursing research in LMICs not only will enhance the cadre of cancer researchers\(^78\) but also will improve service delivery, training, policy, and health outcomes.\(^79\),\(^80\)

As a result of challenges that stem from the hierarchy of power; lack of resources, mentors, and subject matter experts; limited oncology education and training opportunities; and lack of funding, nurses in LMICs interested in research usually have fewer opportunities compared with colleagues in HICs.\(^81\) They must also confront the perception that nurses are not fit to be researchers and the lack of integration of research with service delivery, treatment, and care. Capacity building for nurse-led research in LMICs is critical in elevating nurses as research scholars,\(^82\) translating nursing research into evidence-based practice, and recognizing nurses as potential policymakers,\(^83\) which thus improves health outcomes.

Palliative Care and Hospice: Managing Symptoms From Diagnosis Through End of Life

Palliative care supports patients with cancer and their families throughout the trajectory of illness. It might become even more significant in countries where late-stage diagnosis, for example,\(^84\) and low resource levels for treatment are most prevalent. As with care during treatment, nurses assess, identify, and manage not only pain but also the physical, psychosocial, spiritual, and cultural needs of patients and their families at the end of life.\(^85\) Nurses trained in pain management; palliative care; and management of grief, death, and dying can positively affect the end-of-life experience, help patients to achieve a peaceful death, and help their families to cope with loss and grief.\(^86\)-\(^88\) These skills are especially important
for nurses in LMICs where the majority of patients present with advanced disease and where effective treatments to cure or even control the disease are limited.\textsuperscript{44,89}

It is estimated that of the 20 million people needing palliative care at the end of life, around 80\% live in LMICs.\textsuperscript{90} In most LMICs, however, palliative care is not considered an essential part of cancer care.\textsuperscript{91} and the majority of these countries do not meet basic international guidelines for the delivery of palliative care.\textsuperscript{90,96} Barriers to effective palliative care in LMICs include the limited availability of opioids and other medications to manage symptoms, inadequate knowledge, and a lack of country-level palliative care policies or integrated services.\textsuperscript{89,93,94} The WHO estimates that 5.5 million patients with cancer die in pain annually because they do not have access to opioid medications.\textsuperscript{95} Reasons include legal and regulatory restrictions on the use of opioids due to concerns about diversion, addiction, and misuse and cultural perceptions about pain and its treatment.\textsuperscript{96}

Efforts are under way to improve nurses’ ability to provide adequate end-of-life care, such as the End-Of-Life Nursing Education Consortium curriculum, which has been adapted to serve the needs of an international nursing audience. This curriculum has been used to train nurses from LMICs, including Eastern Europe, Central Asia, and Africa.\textsuperscript{97} The Institute of Hospice and Palliative Care in Uganda also leads regional efforts to train nurses.\textsuperscript{98}

Nurses can act as advocates for improved end-of-life care in their country. They can work with government officials and nongovernmental organizations to develop policies that improve the availability of opioids. When nurses lead and participate in the development of hospice and palliative care services, access is expanded.\textsuperscript{96,99}

Because nurses often are the health care provider with the closest connection with the community, they can help to overcome cultural barriers against the use of opioid medications by educating patients, families, and their colleagues.\textsuperscript{100}

Survivorship

The term cancer survivor, as used in this section, is defined as individuals who have completed primary cancer treatment.\textsuperscript{101} The incidence of cancer has been increasing steadily in the past decade as has the number of cancer survivors. In 2012, 14.1 million people were given a diagnosis of cancer, and globally, 32.6 million people have lived within 5 years of diagnosis;\textsuperscript{102,102a} however, the prolonging of the lifespan of survivors does not necessarily mean that their well-being is improved. Cancer survivors continue to experience late effects of treatment and psychosocial complications after treatment.\textsuperscript{103,104} Cancer survivors have been reported to experience a poorer quality of life than the general population.\textsuperscript{105,106} Prolonged experience of complications and a poorer quality of life may be detrimental to survivors’ health and, in turn, increase health care use and the burden on existing health care services.\textsuperscript{107,108} Although health care professionals in HICs have highlighted the use of cancer survivorship care plans,\textsuperscript{109} which aim to assist in providing a patient with a smooth transition from active treatment at a cancer center to post-treatment care in the community,\textsuperscript{110} this kind of supportive care service for cancer survivors in LMICs has not been addressed.

Various studies have reported positive outcomes of health care services for survivors that are led by nurses or include nurse involvement. Nurse-led efforts in psychosocial support and healthy lifestyle promotion have shown benefits for quality of life and behavioral outcomes for patients,\textsuperscript{111,112} and nurses have been involved in protocol design for post-treatment follow-up care.\textsuperscript{113} Although most of the studies were conducted in HICs, the findings provide strong evidence that nurses in LMICs who received oncology-specific education and training could make comparable contributions to supportive care services for cancer survivors.

Across the cancer continuum and around the world, nurses play an integral role throughout a patient’s cancer journey. Nurses must be educated and positioned to practice to their utmost potential to improve patient outcomes at all points of care and in all locations.\textsuperscript{114}

In conclusion, the burden of cancer is increasing worldwide,\textsuperscript{115} and cancer is one of the NCDs prioritized by the agendas of the WHO, the United Nations, and other international organizations. Unfortunately, the health care professionals who provide care across the cancer continuum, from prevention and detection to treatment, end-of-life care, and survivorship, are seriously lacking in LMICs. Initiatives have addressed cancer in LMICs by using the limited health care staff available; however, the current mortality statistic for patients with cancer in these countries is 72\% to 75\%, which is devastating.\textsuperscript{116} When governments and donors commit to supporting sustainable development of the health care infrastructure, including the personnel and material resources required, this statistic can be changed, and nurses must be central to designing the solutions.

DOI: 10.1200/JGO.2015.001974
Published online on jgo.ascopubs.org on February 3, 2016.
AUTHOR CONTRIBUTIONS
Manuscript writing: All authors
Final approval of manuscript: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Nursing’s Potential to Address the Growing Cancer Burden in Low- and Middle-Income Countries
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 jco.ascopubs.org/site/ifc.

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No relationship to disclose
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No relationship to disclose
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No relationship to disclose

ACKNOWLEDGMENT
Other members of the Key Stakeholder Group for Strengthening Oncology Nursing in Low- and Middle-Income Countries: Stella Bialous and Greta Cummings, International Society of Nurses in Cancer Care, Vancouver, British Columbia, Canada; Sara W. Day, St Jude Children’s Research Hospital, Memphis, TN; Kathy Houlihan, Dana-Farber Cancer Institute and Boston Children’s Hospital, Boston, MA; Brenda Nevidjon, Oncology Nursing Society, Pittsburg, PA; Julie Schneider, National Cancer Institute, Bethesda, MD; Marina Teahan, Union for International Cancer Control, Geneva, Switzerland; and Pamela (Akiiny) Were, EMBLEM Project, Kenya. We thank Matthew Pun (Duke University, Durham, NC), intern with the National Cancer Institute Center for Global Health, for assistance with the organization of this article.

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TO THE EDITOR:

In their recent article in *Journal of Global Oncology*, Al-Wassia et al reported on the outcomes of Saudi Arabian patients with nasopharyngeal cancer treated with primarily neoadjuvant chemotherapy followed by concurrent chemoradiotherapy. We have a few questions about the study.

Why was neoadjuvant chemotherapy given when the meta-analysis of chemotherapy in nasopharyngeal cancer clearly showed no benefit? What were the doses of the docetaxel, cisplatin, 5-fluorouracil regimen used as neoadjuvant therapy? How were the patients selected for cisplatin either 100 mg/m² every 3 weeks or 30 mg/m² once per week? Did patients receive adjuvant chemotherapy?

On what basis were patients selected for neoadjuvant chemotherapy followed by concurrent chemoradiotherapy, neoadjuvant chemotherapy followed by radiotherapy, or concurrent chemoradiotherapy alone? Did any patients undergo resection of residual neck nodes after completion of therapy? How were the patients with relapse managed?

Finally, was Epstein-Barr virus testing performed and was there any association with tobacco or alcohol consumption?

DOI: 10.1200/JGO.2016.003418

Published online on jgo.ascopubs.org on May 18, 2016.

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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In a letter to the editor in response to our recent article in Journal of Global Oncology titled “Outcomes of Saudi Arabian Patients With Nasopharyngeal Cancer Treated With Primarily Neoadjuvant Chemotherapy Followed by Concurrent Chemoradiotherapy,”1 Dhanushkodi2 raises some interesting points. The Meta-Analysis of Chemotherapy in Nasopharynx Carcinoma (MAC-NPC) demonstrated improved overall survival (OS) by adding concomitant chemotherapy to radiotherapy (RT) in patients with NPC, but the potential effect of neoadjuvant chemotherapy (NACT) and adjuvant chemotherapy on OS was not established. Six trials comparing RT plus concomitant chemotherapy with the same RT with or without concomitant chemotherapy plus induction (NACT) chemotherapy were included in this meta-analysis. There was a statistically significant improvement in progression-free survival at 5 years (47% vs 39%; hazard ratio, 0.81; 95% CI, 0.69 to 0.95) but 5-year OS was not significant (57% vs 55%; hazard ratio, 0.96; 95% CI, 0.80 to 1.16) with induction chemotherapy.3 From our experience, NACT was useful for prompt symptom relief from large primary tumors (T4 lesions) or advanced nodal disease, or when delivery of a full course of RT was not possible because of critical surrounding structures, which was the case in the majority of our patients. Nonetheless, the meta-analysis did not examine such a potential beneficial effect of NACT on symptom relief and RT planning and delivery. Hence, the notion of no benefit of such an approach is not correct. We used induction TPF with docetaxel 75 mg/m² on day 1, cisplatin 75 mg/m² on day 1, and 5-FU 750 mg/m²/day for 5 days (1→5).

Palliative RT to the primary tumor was given to four patients (10%); two patients had metastatic disease and two patients had a poor performance status, which prevented the administration of systemic chemotherapy.

As indicated in our review, selecting patients for NACT was based on the treating medical and radiation oncologists’ preferences, but overall, patients with nodal disease received NACT regardless of the tumor extent.1 Likewise, and because of the retrospective nature of this review, the choice between once per week and every 3 weeks cisplatin was at the treating physician’s discretion. No patient underwent resection of residual cervical lymphadenopathy. Molecular testing for Epstein-Barr virus markers on archived tumor samples is underway. The data on managing subsequent relapses and the possibility of a tobacco and alcohol association with NPC are beyond the scope of this review.

DOI: 10.1200/JGO.2016.003517
Published online on jgo.ascopubs.org on May 18, 2016.

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No relationship to disclose

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