

Surgery

Steve Kwon and T. Peter Kingham

1 Introduction

The International Agency for Research on Cancer predicts that the global burden of cancer incidence will reach 21.4 million by 2030 with the annual number of cancer deaths reaching 13.2 million [1]. The World Health Organization predicts approximately 60 % of all new cancer cases by 2020 will occur in low- and middle-income countries (LMIC) [2]. Yet, currently, there is a clear disparity in outcomes that correlate to the income level of countries [3]. The overall case fatality rate from cancer (percentage ratio of mortality to incidence) is around 75 % in low-income countries compared to 46 % in high-income countries [3]. The current challenge for us is to translate developments in cancer care from high-income countries (HIC) into LMIC, which will increasingly bear the world's cancer burden.

Surgery is a key component of all aspects of cancer care, ranging from diagnostic biopsies to therapeutic or palliative procedures. However, surgery is often overlooked in public health efforts to address cancer due to surgeon under-representation in the public health community [4]. Analysis using the WHO tool to look at surgical resources in LMICs revealed that 45 % of district hospitals did not have a functional anesthesia machine, and more than 52 % lacked a steady supply of sterile gloves [5]. Also, the extreme paucity of surgeons in LMICs is a significant barrier to surgical and thus cancer care. In a needs assessment of Sierra Leone, we found that in the ten government hospitals we surveyed, there were only ten fully trained Sierra Leonean surgeons to serve a population of 5.3 million [6].

S. Kwon, MD, MPH

Department of Surgery, Memorial Sloan Kettering, New York, NY, USA

e-mail: kwons@mskcc.org

T.P. Kingham, MD (✉)

Hepato-Biliary Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

e-mail: kinghamt@mskcc.org

2 Role of Surgery/Surgeons in Diagnosis

A major and distinguishing challenge when making the diagnosis of cancer in LMICs is the limited availability of trained personnel and modern equipment. Lack of access to pathology services is a major barrier to the diagnosis and staging of cancers in LMICs. Malawi, for example, had a single pathologist in 2010 serving a population of 15 million. This led to an approximate wait time of 3 months for pathologic reporting [7]. With increasing Internet access, teleoncology initiatives are being implemented that may help improve access to pathology [8].

In HIC, cancer diagnosis and staging relies heavily on radiographic examinations. A combination of computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI) is used. In comparison, physicians in LMIC rely on clinical examination, chest radiography, and ultrasound if available. Ultrasound can be especially useful for surgeons trying to make a diagnosis in resource-limited settings. In a large retrospective review from Cameroon, researchers looked at results from 1119 ultrasound examinations performed to make diagnoses ranging from gynecological to gastrointestinal. Abnormal findings were shown in 78 % of the ultrasound exams performed. In the 323 (28.8 %) patients where the diagnosis was certified, 67.8 % of the exams were deemed useful for diagnosis. Also in the certified group, ultrasound provided diagnosis in 31.6 % of the patients and allowed a differential diagnosis to be excluded in 36.2 % [9]. Although physicians in HICs rely on mammography and MRI for diagnosing breast cancer, it is possible that ultrasound could replace both in LMIC. Surgeons could be trained to use less expensive imaging tools such as ultrasonography to guide both radiologic diagnostics and biopsies [10].

Staging cancer patients is a significant problem in LMICs with no access to advanced equipment. For example, it was shown that Malawi's cancer registry had staging information for only 0.7 % of cancer cases [11]. Surgeons can use novel applications of technology, however, to help with staging. Examples are performing diagnostic laparoscopy to stage the abdomen and obtain tissue or capturing images via the use of smart phones to document cervical lesions.

Surgeons can play an important role in advocating for early diagnosis and developing low-cost, effective screening methodologies. For example, in cervical cancer, there has been a push to implement a screening procedure using visual inspection with acetic acid (VIA) and/or a low-cost rapid human papilloma virus (HPV) DNA-based test, rather than the more expensive Pap smear test [12, 13]. Such efforts are needed to avoid the late presentations that occur frequently in these countries because many common malignancies such as breast cancer, cervical cancer, gastrointestinal cancer, and Kaposi's sarcoma may be curable if detected and treated early. Surgeons also need to help build improved systems of educating communities about cancers and associated symptoms and also removing the fear that many in LMICs have of cancer being a death sentence [14]. Unfortunately, most available funds are spent on individual treatments and not in screening and diagnostic phases of cancer [3].

3 Role of Surgery in Treatment of Gastrointestinal Cancers

Many gastrointestinal cancers are curable with surgery. Despite this, surgery is rarely used. A retrospective study looking at characteristics of 206 patients diagnosed with hepatocellular carcinoma in Ghana showed that almost all patients received only supportive treatment and none received surgery, ablation, or transarterial chemoembolization. Further investigation revealed that less than 8 % had been eligible for resection, transplantation, or ablation, and up to 72 % had been eligible only for supportive care [15]. These results demonstrate the importance of performing further studies to estimate the contributions to lack of surgical use from both the presence of advanced disease and the lack of expertise. Distinguishing between the two will help focus efforts and more effectively manage these cancers in LMICs (i.e., screening and early detection vs. personnel training).

In colorectal cancers, surgery plays a crucial role because of the scarcity of adjunct treatments as well as the need to palliate symptoms (Table 1). However, there are certain limiting factors with surgery, especially with rectal cancers, due to lack of experience in sphincter-preserving rectal surgery, cost of certain stapling devices used for this surgery, and lack of neoadjuvant treatments to downstage these tumors [16, 17]. Perhaps due to these limiting factors, more than 40 % of patients with rectal cancer undergo abdominal perineal resection [16, 17], which is an important consideration in certain countries where stomas are not culturally accepted. A first step toward more sphincter-preserving rectal surgery may be further training of surgeons and better access to stapling devices that help facilitate these surgeries.

In gastric cancers, the morbidity and mortality rates are high. Major complications such as anastomotic leak and hemorrhage occur in as many as 30 % of the patients undergoing gastric resections [18], and operative mortality rates range from

Table 1 Availability of chemotherapies in sub-Saharan Africa

Available	Available by request, if patient can afford	Rarely available
Capecitabine	Bleomycin	Bevacizumab
Cisplatin	Carboplatin	Erlotinib
Cytarabine	Dacarbazine	Ibandronic acid
Dactinomycin	Epirubicin	Imatinib
Daunorubicin	Fludarabine	Rituximab
Doxorubicin	Gemcitabine	Sunitinib
Etoposide	Ifosfamide	Temozolomide
Fluorouracil	Interferon alfa	Trastuzumab
Folinic acid	Irinotecan	
Hydroxyurea	Oxaliplatin	
Melphalan	Pamidronic acid	
Mercaptopurine	Taxanes	
Methotrexate	Topotecan	
Thioguanine	Vinorelbine	
Vincristine	Zoledronic acid	

This table was adapted from Kingham et al. [33]

16 to 36 % [19]. The high complication and mortality rates are likely related to the fact that outcomes in gastric cancer surgery are closely associated with stage of disease at diagnosis. Early surgical intervention, before tumor enlargement and involvement of nearby structures, may improve these rates. Most patients, however, present with gastric outlet obstruction, hematemesis, or perforation. Access to surgeons trained in endoscopy is necessary when patients have persistent symptoms of dyspepsia, epigastric pain, or nausea to identify early gastric cancers and to lower these mortality and morbidity rates.

4 Role of Surgery in Treatment of Prostate Cancer

Prostate cancer is the second most frequently diagnosed cancer among men and the sixth leading cause of cancer death among men globally [1]. The treatment for prostate cancer in LMICs is limited by late presentation, advanced disease, and scarcity of urologists, pathologists, radiation treatment, and androgen-deprivation therapies. Compared to the 99 % 5-year survival rates in HIC for all stages of prostate cancer, a study from Nigeria showed that 16 % of patients died from this disease within a 3-year follow-up period [20, 21].

Currently, subcapsular orchiectomy and diethylstilbestrol are the two most widely used treatments in low-income countries [21]. Subcapsular orchiectomy is a good example of a cost-effective alternative treatment that can be performed surgically in place of a medical treatment (chemical castration). Unfortunately, due to lack of access and the high cost of prostate-specific antigen tests and transrectal ultrasonography, digital rectal examination alone remains for screening. The specificity, however, of digital rectal examination has been shown to be only 61 % [22]. Increasing access to diagnostic tools, such as transrectal ultrasound for earlier detection of prostate cancer, and increasing access to adjunct treatments, such as radiation therapy, hormone therapy, and chemotherapy, are key to improving survival in these patients.

5 Role of Surgery in Treatment of Cervical Cancer

Cervical cancer is the leading cause of cancer mortality in low-income countries [23]. For example, in Africa, 80,000 cases of cervical cancer are diagnosed per year in women older than 15 years. More than 50,000 of these women die from their disease. This is mostly due to late presentation, because cervical cancer is often curable when found in early stages. It is clear then that efforts should focus on cost-effective screening that is easily available.

As mentioned above, one approach to reducing costs is to replace the traditional screening tests, cytology, and colposcopy, with VIA and/or rapid HPV DNA-based

testing. These single-visit tests are appealing alternatives also because treatment, if needed, could be provided in the same day. Goldie et al., with data from five developing countries, demonstrated that if 35-year-old women were screened just once in their lives with VIA, their lifetime risk of invasive cervical cancer can decrease by 25 %. If screened twice with VIA, at ages 35 and 40, lifetime risk can decrease by 35 % [24]. HPV DNA-based testing was shown to be more effective at reducing the occurrence of advanced precancerous lesions over time. A study from India demonstrated that HPV DNA-based testing resulted in a greater mortality reduction than using VIA or Pap smear for screening [25]. However, HPV DNA-based testing is still relatively expensive and requires 7 h for laboratory processing. Therefore, a major focus should be on developing a low-cost screening test that would provide immediate and accurate results to enable screening, diagnosis, and treatment in the same visit. New, rapid HPV DNA-based testing is being developed for this purpose [26].

6 Role of Surgery in Treatment of Breast Cancer

Understanding how breast cancer in LMICs differs from breast cancer in high-income countries is crucial for surgeons. For example, patient characteristics in the high-risk groups are not identical from one region to the next. Notably, patients with breast cancer in sub-Saharan Africa tend to be premenopausal, multiparous, and have a history of protracted breastfeeding [27]. Such information can help clinicians target high-risk groups more effectively and reduce the current mean delay (11.2 months) from onset of symptoms to presentation [27].

Also, breast cancer biology in LMICs may differ from that in high-income countries. For example, in one study, researchers compared women with breast cancer in the United States to women with breast cancer in Ghana. Results showed that 76 % of the Ghanaian women had estrogen receptor-negative tumors in contrast with 22 % of the white American women. Also, 82 % of the Ghanaians had triple-negative disease in contrast with 16 % of the white Americans [28]. While such discrepancies may be in part due to inaccurate immunohistochemistry results, administering tamoxifen without confirming positive receptor status wastes valuable resources. Understanding the differences in tumor biology while also improving the accuracy of immunohistochemistry results may lead to more cost-effective interventions.

Lastly, it is important to realize that procedures that are offered in HICs may not be available in LMICs. For example, mastectomy is the most frequently offered breast cancer surgery in LMIC and is challenging culturally. It is estimated that 38.3 % of patients undergoing mastectomies are divorced within 3 years [29]. Surgeons should be attentive to this cultural barrier and work with the whole family in coming to an understanding of breast cancer and its treatments. Unfortunately, due to lack of resources, radiation therapy, chemotherapy, sentinel lymph node assessment, and breast-conserving surgery are rarely performed.

7 Chemotherapy and Radiation

Three major obstacles to delivery of appropriate multidisciplinary cancer care in LMIC are lack of personnel, high cost, and cultural beliefs. First, chemotherapy regimens are administered under direction of either surgeons or physicians, without specialized training in cancer care. With multidisciplinary cancer management adoption by tertiary hospitals, this will improve. Second, generic drugs are often used because the cost of patented drugs is prohibitive. This has negative effects because in the absence of regulatory bodies to control the influx of these medications, the bioequivalence, side-effect profile, and efficacy of generic drugs may differ from those of the originals. It is important for countries to identify which drugs are available (Table 1) and to calculate the cost to patients. It is also important to calculate the cost of chemotherapy maintenance as many drugs to treat chemotherapy-associated toxicities are either expensive or not readily available (Table 2). This information will help resource-limited LMICs to select the most cost-effective chemotherapy drugs. Cultural beliefs, patient denial, especially after complete surgical resection, and physician ignorance are all barriers to access. Also, traditional healers offer the promise of a cure without the side effects of chemotherapy such as hair loss, erectile dysfunction/infertility, or neuropathy.

Similarly, use of radiation therapy is limited due to its cost and lack of availability. In one study from Australia looking at the use of radiotherapy in LMICs, researchers showed that although 83 % of the breast cancer patients could be expected to have received radiotherapy, only 10.8 % received this treatment [30]. In Ethiopia alone, where it is estimated that 74 to 85 radiation machines are needed to meet patient requirements, there is only one machine available [30]. One way to reduce costs and improve access is to perform intraoperative radiotherapy. Researchers in South Africa studied the effectiveness of intraoperative radiation therapy. Baatjes et al. reported that after 7 years of follow-up, only one of 39 (2.6 %) women with breast cancer had a local recurrence, four (10.3 %) had regional recurrences, and three (7.7 %) had systemic relapses. The estimated cost of intraoperative radiotherapy was \$1300 per patient, far less than \$9000 per patient for standard external beam radiation therapy [31].

Table 2 Availability of supportive drugs to manage chemotherapy-associated toxicities in sub-Saharan Africa

Available by request, if patient can afford	Rarely available
Metoclopramide	Domperidone
Dexamethasone	Granisetron
Ondansetron	Erythropoietin
Lorazepam	Granulocyte colony-stimulating factor

This table was adapted from Kingham et al. [33]

8 Directions for the Future

Five key components that should be implemented in low-resource setting are improvements in the pathology services, access to surgery, radiology services, reliable data collection, and the modification of guidelines. The pathological and radiological components have been discussed in the Diagnosis section. Data collection is a difficult but crucial component to improve cancer management in low-income countries. A simple intervention can be introduction of patient data cards containing information on a patient's age, sex, date of diagnosis, presenting symptoms, significant family history and social habits, studies performed, estimate of tumor stage, treatment to date, and pathological stage when possible. A similar approach has been used to improve adherence to childhood vaccinations [32]. Lastly, development and implementation of modified guidelines are important because there are regions where surgery may be the only therapeutic option.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 127:2893–2917
2. Kachroo S, Etzel CJ (2009) Decreasing the cancer burden in developing countries: concerns and recommendations. *Eur J Cancer Care (Engl)* 18:18–21
3. Farmer P, Frenk J, Knaul FM et al (2010) Expansion of cancer care and control in countries of low and middle income: a call to action. *Lancet* 376:1186–1193
4. Farmer PE, Kim JY (2008) Surgery and global health: a view from beyond the OR. *World J Surg* 32:533–536
5. Kushner AL, Cherian MN, Noel L, Spiegel DA, Groth S, Etienne C (2010) Addressing the Millennium Development Goals from a surgical perspective: essential surgery and anesthesia in 8 low- and middle-income countries. *Arch Surg* 145:154–159
6. Kingham TP, Kamara TB, Cherian MN et al (2009) Quantifying surgical capacity in Sierra Leone: a guide for improving surgical care. *Arch Surg* 144:122–127; discussion 8
7. Gyorki DE, Muyco A, Kushner AL, Brennan MF, Kingham TP (2012) Cancer surgery in low-income countries: an unmet need. *Arch Surg* 147:1135–1140
8. Hazin R, Qaddoumi I (2010) Teleoncology: current and future applications for improving cancer care globally. *Lancet Oncol* 11:204–210
9. Steinmetz JP, Berger JP (1999) Ultrasonography as an aid to diagnosis and treatment in a rural African hospital: a prospective study of 1,119 cases. *Am J Trop Med Hyg* 60:119–123
10. Bumpous JM, Randolph GW (2010) The expanding utility of office-based ultrasound for the head and neck surgeon. *Otolaryngol Clin North Am* 43:1203–1208
11. Msyamboza KP, Dzamalala C, Mdokwe C et al (2012) Burden of cancer in Malawi; common types, incidence and trends: national population-based cancer registry. *BMC Res Notes* 5:149
12. Sahasrabudde VV, Parham GP, Mwanahamuntu MH, Vermund SH (2012) Cervical cancer prevention in low- and middle-income countries: feasible, affordable, essential. *Cancer Prev Res (Phila)* 5:11–17
13. Sahasrabudde VV, Bhosale RA, Kavatkar AN et al (2012) Comparison of visual inspection with acetic acid and cervical cytology to detect high-grade cervical neoplasia among HIV-infected women in India. *Int J Cancer* 130:234–240
14. Vento S (2013) Cancer control in Africa: which priorities? *Lancet Oncol* 14:277–279

15. Gyedu A, Shrauner WR, Kingham TP (2015) No patients to resect or transplant: an analysis of patients with hepatocellular carcinoma admitted to a major African referral hospital. *World J Surg* 39:231–236
16. Saidi H, Nyaim EO, Githaiga JW, Karuri D (2008) CRC surgery trends in Kenya, 1993–2005. *World J Surg* 32:217–223
17. Dakubo JC, Naaeder SB, Tettey Y, Gyasi RK (2010) Colorectal carcinoma: an update of current trends in Accra. *West Afr J Med* 29:178–183
18. Ahmed A, Ukwenya AY, Makama JG, Mohammad I (2011) Management and outcome of gastric carcinoma in Zaria, Nigeria. *Afr Health Sci* 11:353–361
19. Osime OC, Momoh MI, Irowa OO, Obumse A (2010) Gastric carcinoma—a big challenge in a poor economy. *J Gastrointest Cancer* 41:101–106
20. Siegel R, DeSantis C, Virgo K et al (2012) Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin* 62:220–241
21. Bowa K (2010) An overview of the diagnosis and management of prostate cancer in Nigeria: experience from a north-central state of Nigeria. *Ann Afr Med* 9:111–112
22. Ahmed M (2011) Prostate cancer diagnosis in a resource-poor setting: the changing role of digital rectal examination. *Trop Doct* 41:141–143
23. Yang BH, Bray FI, Parkin DM, Sellors JW, Zhang ZF (2004) Cervical cancer as a priority for prevention in different world regions: an evaluation using years of life lost. *Int J Cancer* 109:418–424
24. Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD et al (2005) Cost-effectiveness of cervical-cancer screening in five developing countries. *N Engl J Med* 353:2158–2168
25. Sankaranarayanan R, Nene BM, Shastri SS et al (2009) HPV screening for cervical cancer in rural India. *N Engl J Med* 360:1385–1394
26. Qiao YL, Sellors JW, Eder PS et al (2008) A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncol* 9:929–936
27. Adesunikanmi AR, Lawal OO, Adelusola KA, Durosimi MA (2006) The severity, outcome and challenges of breast cancer in Nigeria. *Breast* 15:399–409
28. Stark A, Kleer CG, Martin I et al (2010) African ancestry and higher prevalence of triple-negative breast cancer: findings from an international study. *Cancer* 116:4926–4932
29. Odigie VI, Tanaka R, Yusufu LM et al (2010) Psychosocial effects of mastectomy on married African women in Northwestern Nigeria. *Psychooncology* 19:893–897
30. Barton MB, Frommer M, Shafiq J (2006) Role of radiotherapy in cancer control in low-income and middle-income countries. *Lancet Oncol* 7:584–595
31. Baatjes KJ, Apffelstaedt JP (2012) 7-year follow up of intra-operative radiotherapy for early breast cancer in a developing country. *Breast* 21:326–329
32. Usman HR, Rahbar MH, Kristensen S et al (2011) Randomized controlled trial to improve childhood immunization adherence in rural Pakistan: redesigned immunization card and maternal education. *Trop Med Int Health* 16:334–342
33. Kingham TP, Alatise OI, Vanderpuye V et al (2013) Treatment of cancer in sub-Saharan Africa. *Lancet Oncol* 14(4):e158–e167