



Breast Cancer Diagnosis and Treatment in Low- and Mid-Resource Settings: the Role of Resource-Stratified Clinical Practice Guidelines

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Published online: 24 July 2018

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Abstract

Purpose of Review One of the most important recent advances in the management of cancer patients have become the development of guidelines. Guidelines are usually evidence-based or international consensus guidelines. Those guidelines may not be applicable worldwide, especially where resources are limited. This prompted initiatives for the development of resource-stratified guidelines so that health care providers and authorities can do the best they can with the resources they have, while working on improving their resources. We will describe the process of development of those guidelines and briefly review recommendations for awareness, screening, diagnosis, and treatment of breast cancer, focusing on countries and special populations with limited resources.

Recent Findings The World Health Organization (WHO) described three resource scenarios (low-resource, middle-resource, and high-resource scenarios) in order to facilitate the establishment of national cancer control plans. The Breast Health Global Initiative (BHGI), as an initiative group with goals to improve the care of patients with breast cancer in low- and mid-resource settings, identified four levels of resource availability (basic, limited, enhanced, and maximal) with comprehensive sets of recommendations for each. BHGI published resource-stratified breast cancer guidelines starting in 2006, and later on updated them and focused on implementation and health systems. The National Comprehensive Cancer Network (NCCN) initiated a program, building upon the BHGI experience to resource stratify cancer treatment guidelines across multiple cancer types and published NCCN Framework for resource stratification in breast cancer in 2016. Subsequently, the NCCN has published multiple additional resource stratification frameworks that use slightly different definitions of resource level than use by the BHGI. The American Society of Clinical Oncology (ASCO) has also assembled a Guidelines Advisory Group for Resource Stratification for different cancers, and published its first comprehensive resource-stratified guidelines for cancer of the cervix.

Summary International efforts to improve management and reduce disparities in the outcome of breast cancer patients' worldwide focus on recommendations for better allocation of available resources in different countries. The WHO, BHGI, NCCN, ASCO, and other international initiatives issued various resource-stratified guidelines (RSG) based on levels of resources in different countries. We shed the light on the development of these guidelines and discuss awareness, prevention of advanced disease at presentation, and management. Future research is needed to update and improve dissemination and implementation of RSG, as well as building infrastructure, reforming of health systems, and better allocating resources.

Keywords Resource-stratified guidelines (RSG) · Low- and/or middle-income countries (LMICs) · Breast cancer · Breast Health Global Initiative (BHGI) · NCCN Framework

This article is part of the Topical Collection on *Global Breast Cancer*

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Introduction

Efforts to improve the quality of health care in the setting of rapidly increasing scientific evidence have led to the widespread use of clinical practice guidelines in medicine. The clear majority of clinical practice guidelines, such as those developed by the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), Cancer Care Ontario (CCO), and others, are developed for use in

high-resource settings. The development and increasing reliance on those guidelines can be considered as one of the major achievements over the last two decades. However, they are paralleled with concerns that they are not generally applicable in countries with limited resources. This prompted the development of resource-stratified guidelines.

It is estimated that there are approximately 7.4 million new cancer cases and 4.7 million cancer deaths per year in the world, and that 4.2 million new cases and 3.1 million deaths occur in less developed regions of the world [1]. Comprehensive strategies for cancer control are needed to effectively manage the disease burden [2]. To address the cancer problem in less developed regions of the world, the World Health Organization (WHO) described in 2002 three resource scenarios A, B, and C (low-resource, middle-resource, and high-resource scenarios) to facilitate the establishment of national cancer control plans and ensure efficient use of existing resources in each country and setting [3]. The WHO called for the development of resource-stratified guidelines for use in oncology care, although how those stratified guidelines would be developed and organized was not addressed.

BHGI Guidelines Development

The Breast Health Global Initiative (BHGI) first met in 2002 to improve the care of patients with breast cancer in low- and mid-resource settings [4]. The BHGI later extended this work and published resource-stratified breast cancer guidelines in 2006 that addressed awareness and public education, prevention, early diagnosis, treatment, and health care systems and public policy [5] by advocating for better utilization of resources, and that countries do the best they can with the resources that they have, while working on improving resources, infrastructure, and human capabilities. BHGI then also focused on implementation of guidelines [6] and supportive and palliative care [7••].

The BHGI guidelines were unique at the time in that they identified four levels of resource availability, each of which had a different, cumulative set of recommendations [8] (Table 1). This allowed the BHGI guidelines to be used in multiple resource settings with minimal modification to accommodate regulatory environments, the nature of the cancer care work force, and societal factors. BHGI guidelines assist health care authorities and institutions for prioritizing resource allocation in resource-constrained countries [5].

NCCN Resource-Stratified Guidelines

The rapidly increasing use of the NCCN Clinical Practice Guidelines globally led the NCCN to initiate a program building upon the BHGI experience to resource stratify cancer treatment guidelines across multiple cancer types, including breast cancer [9••]. The first of these was a resource-stratified cervical cancer guideline released in March, 2015. The first NCCN Framework for resource stratification in breast cancer was published in 2016. Subsequently, the NCCN has published multiple additional resource stratification frameworks that use slightly different definitions of resource level than use by the BHGI (see Table 2).

Stratified Guideline Development

The development of resource-stratified guidelines typically begins with the identification of a high-quality guideline developed for use in high-resource settings. Multidisciplinary experts then score the recommendations on the high-resource guideline based upon both resource utilization and magnitude of impact on the disease-related outcomes. Interventions that require low levels of resources and that provide large improvement in outcome are assigned to the first level of the guidelines. Additional levels of guidelines utilize more resources

Table 1 BHGI resource stratification definitions [8]

Basic level	Core resources or fundamental services absolutely necessary for any breast health care system to function. By definition, a health care system lacking any basic-level resource would be unable to provide breast cancer care to its patient population. Basic-level services are typically applied in a single interaction.
Limited level	Second-tier resources or services that produce major improvements in outcome, such as increased survival, but which are attainable with limited financial means and modest infrastructure. Limited-level services may involve single or multiple clinical interactions.
Enhanced level	Third-tier resources or services that are optional but important. Enhanced-level resources may produce minor improvements in outcome but increase the number and quality of therapeutic options and patient choice.
Maximal level	High-level resources or services that may be used in some high-resource countries, but nonetheless should be considered lower priority than those in the basic, limited, or enhanced categories on the basis of cost or impracticality for limited-resource environments. In order to be useful, maximal-level resources typically depend on the existence and functionality of all lower-level resources.

Table 2 Resource level definitions used in the NCCN Frameworks for resource stratification

Basic Resources	Include essential services needed to provide basic minimal standard of care that improves disease-specific outcomes.
Core Resources	Include services provided in the Basic Resources Framework plus additional services that provide major improvements in disease outcomes (e.g., survival) and that are not cost prohibitive.
Enhanced Resources	Enhanced resources include services provided in the Core Resources Framework plus additional services that provide lesser improvements in disease outcomes and/or services that provide major improvements in disease outcomes but are cost prohibitive in lower-resource settings.
NCCN Guideline	Evidence-based, consensus-driven recommendations made by the NCCN Guidelines panels. They include services provided in the Enhanced Resources Framework plus additional services that provide minor improvements in disease outcomes, interventions that are cost prohibitive in lower-resource settings, and/or services that do not provide improvement in disease outcomes but are desirable services.

and/or recommend interventions that provide less overall benefit to disease-related outcomes. Finally, the resulting recommendations are collated into a graphical format (e.g., NCCN Stratification Framework) (see Fig. 1) or into a tabular format (e.g., BHGI, ASCO) (see Fig. 2).

Available Breast Cancer Guidelines with Resource Stratification

There are two major clinical practice guidelines for breast cancer that incorporate a resource stratification methodology—the NCCN Framework for Breast Cancer and the BHGI stratification tables. The BHGI stratification tables are primarily a proof of concept document and have not been actively maintained since 2007. The NCCN Framework for Breast Cancer was first published in 2016, and has been updated, most recently in April 2018. A derivative of the NCCN Framework for Breast Cancer is a harmonization process that takes the frameworks and adapts them for use in a given region of the world considering health care expertise, resource availability, regulatory environment, and societal considerations. The NCCN Harmonized Guidelines for Sub-Saharan Africa, including a Harmonized Guideline for Breast Cancer, were first made available in November 2017 as part of an expanding library of harmonized guidelines in oncology care [11].

Uses and Applicability of Stratified Guidelines

Clinical practice guidelines are used at the point of care to add practitioner and patient decision-making on appropriate medical care. In this context, the clinical practice guidelines provide a distillation of expert assessment of the scientific evidence, and when there is an absence of evidence, expert clinical experience and knowledge upon which decisions may be based. In low- and/or middle-income countries (LMICs), the use of resource-stratified guidelines provides guidance on the optimal use of resources that are available. Substantial evidence exists in high-resource settings that the use of appropriately developed clinical practice guidelines improves patient outcomes and decreases costs of care [12–17]. It is important that such assessments also be performed in limited-resource settings to determine whether the use of RSGs also improves outcomes and decreases costs of care.

Awareness, Early Detection, and Screening

Awareness, breast self-examination (BSE), clinical breast examination (CBE), and mammography are primary modalities for breast cancer early detection. Although recent controversies arose regarding screening mammography in High-income countries (HICs), it is still widely practiced in HIC; and although thought impractical in LMICs, many countries do make plans for early detection and screening. BHGI and NCCN recommend increasing public awareness about risks and symptoms of breast health, and both BSE and CBE as important methods for breast cancer early detection stages of disease; thus, reducing late stages at presentation in these countries [18–21].

Diagnosis

Resource-stratified guidelines (RSG) [22] emphasize adequate history and physical examination, basic imaging, tissue diagnosis with FNA, and/or biopsy according to availability of services and pathologists. RSG recommend basic laboratory tests and staging imaging. CT scans and nuclear bone scans, or even PET scans that are increasingly used in HICs, are becoming available in many middle-income countries and may become additional burdens on patients and health systems in many LMICs, if not judiciously used and regulated.

It is recommended that biopsies be performed by ultrasound-guided core needle technique. Surgical excision should be done only if needle biopsy is technically

Treatment Resource Allocation and Process Metrics:
Locally Advanced Breast Cancer

Level of resources	Local-Regional Treatment		Systemic Treatment (Adjuvant or Neoadjuvant)			Process Metrics
	Surgery	Radiation Therapy	Chemotherapy	Endocrine Therapy	Biological Therapy	
Basic	Modified radical mastectomy	*	Preoperative chemotherapy with AC, EC, FAC or CMF [†]	Oophorectomy in premenopausal women Tamoxifen [†]		Neoadjuvant systemic therapy for all pts (min 75%, target 90%) Hormone tx for all pts w/ ER+ ca w/i 1 yr (min 75%, target 90%) Pts that received neoadjuvant therapy underwent MRM (min 75%, target 90%)
Limited		Postmastectomy irradiation of chest wall and regional nodes*			§	Post mastectomy chest wall radiation therapy for women <70 yrs w/i 1 yr of mastectomy (min 75%, target 90%)
Enhanced	Breast-conserving surgery Breast reconstruction surgery	Breast-conserving whole-breast irradiation as part of breast-conserving therapy	Taxanes	Aromatase inhibitors LH-RH agonists	Trastuzumab for treating HER-2/neu positive disease [§]	Neoadjuvant systemic therapy for pts <70 yrs (min 90%, target 95%) Post-mastectomy chest wall XRT for pts <70 yrs w/i 1 yr of mastectomy (min 90%, target 95%) Hormone tx for all pts w/ ER+ ca w/i 1 yr (min 90%, target 95%)
Maximal			Growth factors Dose-dense chemotherapy			Maximal category process metrics determined based upon standards of care in high-income countries

Fig. 1 Resource allocation and process metrics for locally advanced breast cancer by level of resources as recommended by the Breast Health Global Initiative. Reproduced with permission [10]

not feasible. RSG recommend an immunohistochemistry (IHC) analysis for estrogen receptors since this will determine prognosis and predicts sensitivity to hormonal therapy.

Availability of human and infrastructure services to support pathology remains limited in many LMICs. While HER2 testing is not recommended by either BHGI or NCCN Guidelines for basic and limited-resource settings, in view of the significant increase in survival rates with trastuzumab, [23] and its addition to the WHO Essential Medications Lists, LMICs may have to start planning for assessment of HER2 receptors. It is important to note that a trastuzumab biosimilar [24] is now available and approved by the FDA and recommended by the ABC4 International Consensus Guidelines Panel. The panel noted that a significant reduction in the price of biosimilar is essential to make it beneficial for larger numbers of patients and to reduce economic burden worldwide [25].

Staging

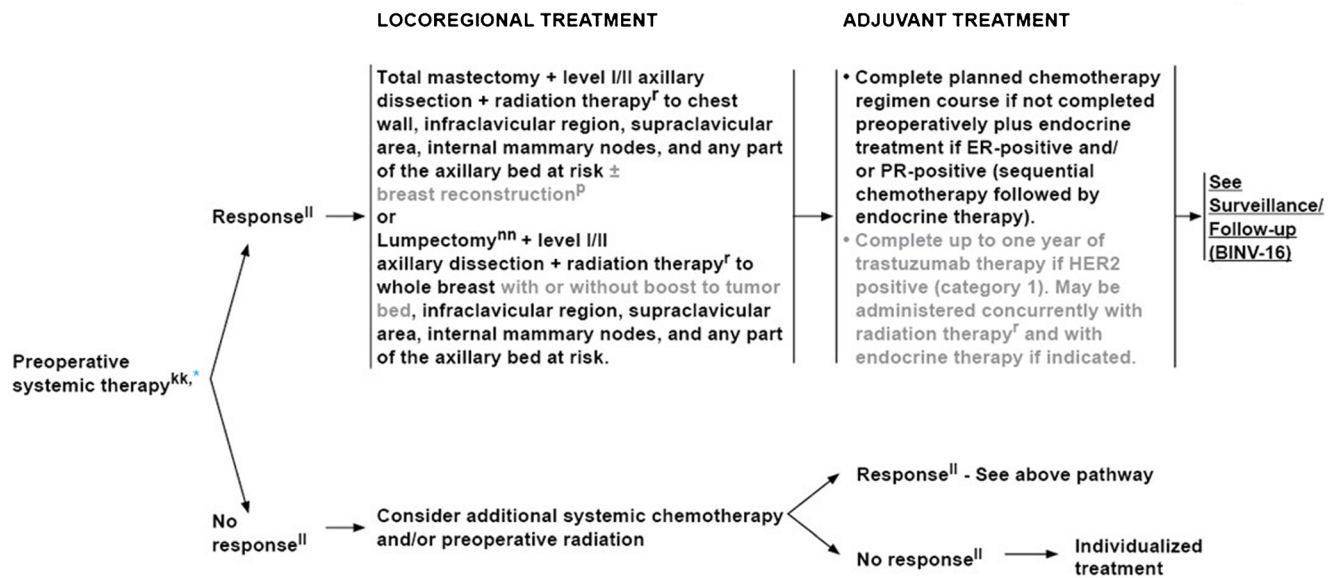
Staging should be performed to assess the extent of disease. Basic staging traditionally includes routine lab tests including complete blood counts (CBC), chest X-ray

(CXR), and abdominal ultrasound. Radionuclide bone scan may or may not be available based upon level of resources. CT scans can delineate better the extent of disease but are of limited availability in low-resource settings. More recently, PET/CT scanning has been increasingly used, especially in locally advanced disease, but it requires extensive resources and comes with high costs. The BHGI consensus recommendations published in 2011 [6, 26] and the NCCN Framework RSG recommend very limited staging in early clinical stages at the basic level of resources, beginning with obtaining history and physical examination, mammography, CBC, CXR if clinical symptoms are present, and abdominal ultrasound. For higher resource settings, the use of CT scans instead of ultrasound evaluation, bone scanning, and liver function testing, are progressively added as indicated (BHGI tables; NCCN tables).

Surgery

RSG recommendations call for [10] mastectomy if radiation therapy is not available or accessible. In LMICs where there are surgeons trained in partial mastectomy and even in sentinel lymph node biopsy using blue dye, women, especially young

PREOPERATIVE SYSTEMIC THERAPY FOR INOPERABLE OR LOCALLY ADVANCED BREAST CANCER (NON-INFLAMMATORY)



*Preoperative chemotherapy versus adjuvant therapy alone has similar overall survival statistics.

^pSee Principles of Breast Reconstruction Following Surgery (BINV-H).

^fSee Principles of Radiation Therapy (BINV-I).

^{kk}See Principles of Preoperative Systemic Therapy (BINV-L).

^{ll}The accurate assessment of in-breast tumor or regional lymph node response to preoperative systemic therapy is difficult, and should include physical examination and performance of imaging studies (mammogram and/or breast MRI) that were abnormal at the time of initial tumor staging. Selection of imaging methods prior to surgery should be determined by the multidisciplinary team.

ⁿⁿFor patients with skin and/or chest wall involvement (T4 non-inflammatory) prior to preoperative systemic therapy, breast conservation may be performed in carefully selected patients based on a multidisciplinary assessment of local recurrence risk. In addition to standard contraindications to breast conservation (see BINV-G), exclusion criteria for breast conservation include: inflammatory (T4d) disease before preoperative systemic therapy and incomplete resolution of skin involvement after preoperative systemic therapy.

Fig. 2 Representative algorithm from NCCN Framework for Invasive Breast Cancer version 2.2017 at the Core Level of Resources relating to management of locally advanced breast cancer. Additional algorithm pages cover the continuum of care, and other resource levels. The dark black text represents interventions recommended at the given resource level, while the gray text are interventions recommended in the high-resource level parent guideline that are not recommended for use at the Core Level (https://www.nccn.org/professionals/physician_gls/pdf/breast_core.pdf, accessed April 20, 2018). Reproduced with permission from the NCCN Framework for Resource Stratification of NCCN

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women, could be offered breast conservation surgery. Referral of patients to a central regional major center in an LMIC is often required.

Capacity building for surgery, infrastructure, equipment, anesthesia, and human expertise, in addition to benefit for patients, was found to be also beneficial for society by The Lancet Oncology Commission on Global Cancer Surgery [27]. It concluded that surgery is essential for global cancer care and must be at the heart of global and cancer control planning.

Radiation Therapy

Radiation therapy is an essential component of breast cancer patient curative and/or palliative management. Availability of radiation therapy remains a problem in many LMICs, as the availability of such centers is reflected by the country’s economic status: The African continent has the least resources

for RT. [28] Making radiation therapy available requires investment in technology, infrastructure, and human resources and may be economically profitable. In fact, the Lancet Oncology Commission on Expanding Global Access to Radiotherapy concluded that investment in radiotherapy not only enables treatment of cancer cases to save lives and provide palliative care but also may bring positive economic benefits [29]. In fact, Commission estimates that scaling up radiotherapy capacity in LMICs could lead to saving 26.9 million life-years and investment in radiation therapy and efficiency models would save hundreds of millions of dollars by the year 2035 [29].

Systemic Therapy

Chemotherapy The BHGI outlined appropriate basic resources and supportive care for the safe administration of systemic therapy [10]. In addition to medical

oncologists and trained nurses, physical infrastructure including hospital day centers, pharmacies, and clinical laboratories is essential. Proper training for chemotherapy regimen selection, dosing, sterile handling, and administration is necessary. Basic chemotherapy agents are recommended in BHGI and NCCN Frameworks and are widely available in LMICs. Filgrastim generics and biosimilars have become widely available, are less expensive than original colony stimulating factors, and can be added at increasing resource levels as appropriate.

Endocrine Therapy Patients with estrogen receptor-positive tumors should receive endocrine adjuvant therapy, typically with tamoxifen at the lower-resource levels. Although generic AI are now widely available, they are still priced much more expensive than tamoxifen. For estrogen receptor-positive metastatic breast cancer, with no evidence of visceral crisis, hormonal therapy is recommended at all levels of resources. Fulvestrant, and CDK4/6 inhibitors, and mTOR inhibitors remain too expensive for countries with limited resources.

Targeted Therapy As described above, trastuzumab is recommended for adjuvant therapy in HER2-positive early breast cancer and is now on the “Essential Medications List” of the WHO for early breast cancer [30]. However, trastuzumab remains prohibitively expensive for routine use in low-resource settings. There are studies that showed benefit, though slightly less, from shorter than 12 months duration of trastuzumab adjuvant therapy [31–33]. Use of biosimilars also is a possible cost-saving strategy [34••]. This is an area where local adaptation guidelines can be used to optimize benefit of available resources for the largest number of patients.

Advanced Breast Cancer Management in Low-Resource Settings

Inoperable locally advanced and metastatic breast cancer remains very common in LMICs [35]. In this setting, the BHGI Guidelines (ref. [35], NCCN Framework ref. [9])... and International ABC Guidelines [25] all emphasize palliation of symptoms and signs of disease, with the least side effects at all levels or resources (see Figs. 1 and 2).

Systemic Chemotherapy Chemotherapy in advanced breast cancer is generally palliative. Open discussions with patients are as important in limited-resource settings as they are in high-resource ones. In LMICs, families are usually involved in management decisions and culturally sensitive methodology and practices are required. Patients should not be given false hopes, nor should they be abandoned.

Patients should be offered the options of hormonal therapy or less toxic chemotherapy where appropriate.

Supportive Care and Survivorship Patients with advanced breast cancer usually require a wide range of medical, nursing, and psychological support including support during systemic therapy, pain management, and palliative end-of-life care [36]. Availability in LMICs and access to pain medication is variable and limited in many countries [37]. Prevention and management of treatment complications require education, infrastructure setup, building human resource, continuing education and training of physicians, nurses, and allied professionals [38].

Multidisciplinary Management

Multidisciplinary treatment units and tumor boards that include experts from different specialties addressing patient diagnosis and management are essential for optimal multidisciplinary management. In many LMICs, a full team is not available, but mini-tumor boards can be conducted with the available specialists. [39–42]

Equitable Distribution of Cancer Care Resources

Equity and justice in the distribution and application of health care within a given society is an appropriate goal. The WHO defines equity in health systems as “the absence of avoidable or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, or geographically” [43]. The use of resource-stratified clinical practice guidelines provides a benchmark against which health care may be measured to assure an equitable and just distribution of health care resources within a region or country.

Assessment of Quality of Care

Evidence-based clinical practice guidelines also allow for an assessment of quality of care. In LMICs, measuring quality is more appropriately accomplished by those services and outcomes that are based upon the utilization of resources that are available, as opposed to measuring based upon a maximal level of resources that is available at only a few, select, high-resource centers worldwide.

Aspiration In evolving health care systems, the use of resource-stratified guidelines can provide an aspirational model and tool to predict what additional resources are most likely

to provide meaningful improvements in patient-related outcomes and be cost effective for that resource level.

Role of the Primary Care Physician

One of the solutions in LMICs and an increasing cancer population is to increase the role of the primary care providers (PCP) in providing a wide range of services for these patients. The use of detailed clinical practice guidelines developed for the specific resource levels available can facilitate the delivery of such care. In addition, curricula to train PCPs in LMICs in cancer etiology, cancer prevention, early detection, and early warning signs of cancer and to provide basic cancer care are available. In addition, knowledge about resources available in their country for cancer diagnosis and treatment, and how to help and provide support to patients under treatment, is important [44].

Educational Instruments

Appropriately developed clinical practice guidelines incorporate not only recommendations for care across a continuum of clinical cancer care but also provide assessments of levels of evidence and detailed information outlining the rationale for the recommendations and options provided in the guidelines.

Forecasting Resource Requirements, Such as Chemotherapy or Pathology Services

Policymakers play a major role in developing cost-effective and resource-appropriate strategies for cancer patients. The policies can target multiple steps in cancer care, from prevention [45] of the disease to screening mammograms [46], and then treatment [47] and finally palliative care [48].

To operate optimally, health care systems need to be able to predict and anticipate demand for a variety of needs: human resource, structural, pharmaceutical, financial, and others. The use of resource-stratified guidelines allows for health ministries, administrators, and others within the health care system to enhance access to care, save, improve patient outcome, and decrease disparities between communities, regions, and countries.

Guideline Use for Refugees and Displaced [49]

According to the United Nations High Commissioner for Refugees (UNHCR), there are 65.6 million refugees and displaced people worldwide. When diagnosed with cancer, they are often at a stage of advanced disease and suffer more

complications. Although international agencies and volunteer organizations provide various kinds of needed support, these patients have poor outcomes because of limited health education, limited resources, poor hygiene and living conditions, and limited access to care and they are given low priority.

In refugees as in the general population, cancer can present with a good prognosis and patients may have a real chance of being cured from the disease. The United Nations, other international agencies, host countries, and medical oncology communities should avail themselves of resource-stratified guidelines to manage cancer in refugee patients and consider applying the principle of doing the best we can with the resources that we have. In addition, UNHCR and other humanitarian agencies need and should be allocated more money and resources [50••].

Conclusions

Resource-stratified clinical practice guidelines in breast cancer care provide a resource to optimize the delivery of oncology care given the available medical resources. In addition, stratified guidelines can help to assure equity in care, assessment of quality, inclusion of primary care providers, education, and forecasting of resource demand.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

1. International Agency for Research on Cancer. World Health Organization, gco.iarc.fr/today/home, Accessed March 29, 2018.
2. Anderson BO, Ilbawi AM, El Saghir NS. Breast cancer in low and middle income countries (LMICs): a shifting tide in global health. *Breast J.* 2014;21:111–8. <https://doi.org/10.1111/tbj.12357>.
3. WHO. National cancer control programmes: policies and managerial guidelines. Geneva: WHO; 2002. Access at <http://www.who.int/cancer/media/en/408pdf>, April 17, 2018
4. Anderson BO, Braun S, Carlson RW, et al. Overview of breast health care guidelines for countries with limited resources. *Breast J.* 2003;2:S42–5035.
5. Anderson BO, Yip C, Ramsey SD, et al. Breast cancer in limited-resource countries: health care systems and public policy. *Breast J.* 2006;12(s1):S54–69.

6. Anderson BO, Cazap E, El Saghir NS, et al. Optimisation of breast cancer management in low-resource and middle-resource countries: executive summary of the Breast Health Global Initiative consensus, 2010. *Lancet Oncol.* 2011;12:387–98.
7. •• Distelhorst SR, Cleary JF, Ganz PA, et al. Optimisation of the continuum of supportive and palliative care for patients with breast cancer in low-income and middle-income countries: executive summary of the Breast Health Global Initiative, 2014. *Lancet Oncol.* 2015;16(3):e137–47. [https://doi.org/10.1016/S1470-2045\(14\)70457-7](https://doi.org/10.1016/S1470-2045(14)70457-7). ISSN 1470–2045, (<http://www.sciencedirect.com/science/article/pii/S1470204514704577>). **This article combined the three successive BHGI panel recommendations into a comprehensive summary, including the importance of supportive and palliative care in breast cancer patients in LMICs as much as recommendations with curative intents.**
8. Anderson BO, Shyyan R, Eniu A, Smith RA, Yip CH, Bese NS, et al. Breast cancer in limited-resource countries: an overview of the Breast Health Global Initiative 2005 guidelines. *Breast J.* 2006 Jan-Feb;12 Suppl 1:S3–15. <https://doi.org/10.1111/j.1075-122X.2006.00199.x>.
9. •• Carlson RW, Scavone JL, Koh WJ, et al. NCCN Framework for resource stratification: a framework for providing and improving global quality oncology care. *J Natl Compr Cancer Netw.* 2016;14: 961–9. **This study shows the need and necessity of having RSGs to treat better cancer patients in LMICs, and offers the most updated RSGs made in 2016 by the NCCN Framework.**
10. Eniu A, Carlson RW, El Saghir NS, Bines J, Bese NS, Vorobiof D, et al. Guideline implementation for breast healthcare in low- and middle-income countries: treatment resource allocation. *Cancer.* 2008 Oct 15;113(8 Suppl):2269–81. <https://doi.org/10.1002/cncr.23843>.
11. National Comprehensive Cancer Network. NCCN Harmonized Guidelines™ for Sub-Saharan Africa. *Breast Cancer.* (Version 2.2017 – November 3, 2017). https://www.nccn.org/professionals/physician_gls/pdf/breast_harmonized-africa.pdf. Accessed June 24 2018.
12. Erickson Foster J, Velasco JM, Hieken TJ. Adverse outcomes associated with noncompliance with melanoma treatment guidelines. *Ann Surg Oncol.* 2008;15:2395–402. <https://doi.org/10.1245/s10434-008-0021-0>.
13. Neubauer MA, Hoverman JR, Kolodziej, et al. Cost effectiveness of evidence-based treatment guidelines for the treatment of non-small-cell lung cancer in the community setting. *J Oncol Pract.* 2010;6(1):12–8. <https://doi.org/10.1200/JOP.091058>.
14. Visser BC, Ma Y, Zak Y, Poultides GA, Norton JA, Rhoads KF. Failure to comply with NCCN Guidelines for the management of pancreatic cancer compromises outcomes. *HPB.* 2012;14:539–47. <https://doi.org/10.1111/j.1477-2574.2012.00496.x>.
15. Molena D, Mungo B, Stem M, Poupore AK, Chen SY, Lidor AO. Does quality of care matter? A study of adherence to National Comprehensive Cancer Network Guidelines for patients with locally advanced esophageal cancer. *J Gastrointest Surg.* 2015;19:1739–47. <https://doi.org/10.1007/s11605-015-2899-8>.
16. Delhorme J, Antoni D, Mak KS, et al. Treatment that follows guidelines closely dramatically improves overall survival of patients with anal canal and margin cancers. *Crit Rev Oncol Hematol.* 2016;101: 131–8. <https://doi.org/10.1016/j.critrevonc.2016.03.001>. ISSN 1040–8428. (<http://www.sciencedirect.com/science/article/pii/S1040842816300427>)
17. Schwam ZG, Sosa JA, Roman S, et al. Receipt of care discordant with practice guidelines is associated with compromised overall survival in nasopharyngeal carcinoma. *Clin Oncol (R Coll Radiol).* 2016;28:1–8.
18. Yip CH, Smith RA, Anderson BO, et al. Guideline implementation for breast healthcare in low- and middle-income countries: early detection resource allocation. *Cancer.* 2008;113(8 Suppl):2244–56.
19. Dey S. Preventing breast cancer in LMICs via screening and/or early detection: the real and the surreal. *World J Clin Oncol.* 2014;5:509–19.
20. El Saghir NS, Farhat RA, Charara RN, et al. Enhancing cancer care in areas of limited resources: our next steps. *Future Oncol.* 2014;10: 1953–65.
21. Hayek F, Berro B, Fayad W. Awareness campaign for the early detection of growth disorders in public school children in North Lebanon. *Ethn Dis.* 2016;26(3):417–26. <https://doi.org/10.18865/ed.26.3.417>.
22. Shyyan R, Sener SF, Anderson BO, Fernández Garrote LM, Hortobágyi GN, Ibarra JA Jr, et al. Guideline implementation for breast healthcare in low- and middle-income countries: diagnosis resource allocation. *Cancer.* 2008;113(8 Suppl):2257–68.
23. Mayor S. Radiation in combination with immune-checkpoint inhibitors. *Lancet Oncol.* 2015;16:e162. [https://doi.org/10.1016/S1470-2045\(15\)70118-X](https://doi.org/10.1016/S1470-2045(15)70118-X).
24. Rugo HS, Barve A, Waller CF, et al. Heritage: a phase III safety and efficacy trial of the proposed trastuzumab biosimilar Myl-14010 versus Herceptin. *ASCO Annual Meeting; Chicago, IL; Jun 3–7, 2016.* LBA503.
25. Cardoso E, Senkus A, Costa E, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC4). *Ann Oncol.* 2018. <https://academic.oup.com/annonc/advance-article/doi/10.1093/annonc/mdy192/5055519>.
26. Yip CH, Cazap E, Anderson BO, et al. Breast cancer management in middle-resource countries: consensus statement from the Breast Health Global Initiative. *Breast.* April 2011; 20 (TBD).
27. Sullivan R, Alatisse OI, Anderson BO, Audisio R, Autier P, Aggarwal A, et al. Global cancer surgery: delivering safe, affordable, and timely cancer surgery. *Lancet Oncol.* 2015;16:1193–224.
28. Grover S, Xu MJ, Yeager A, et al. A systematic review of radiotherapy capacity in low- and middle-income countries. *Front Oncol.* 2015;4:380. <https://doi.org/10.3389/fonc.2014.00380>. eCollection 2014
29. Atun R, Jaffray DA, Barton MB, Bray F, Baumann M, Vikram B, et al. Expanding global access to radiotherapy. *Lancet Oncol.* 2015;16:1153–86.
30. Robertson J, Barr R, Shulman LN, Forte GB, Magrini N. Essential medicines for cancer: WHO recommendations and national priorities. *Bull World Health Organ.* 2016;94:735–42. <https://doi.org/10.2471/BLT.15.163998>.
31. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol.* 2013;14(8):741–8.
32. Joensuu H, Fraser J, Wildiers H, et al. A randomized phase III study of adjuvant trastuzumab for a duration of 9 weeks versus 1 year, combined with adjuvant taxane-anthracycline chemotherapy, for early HER2-positive breast cancer. The Synergism Or Long Duration (SOLD) trial. Presented at: 2017 San Antonio Breast Cancer Symposium; December 5–9, 2017; San Antonio, TX. Abstract GS3–04.
33. Joensuu H, Bono P, Kataja V, Alanko T, Kokko R, Asola R, et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. *J Clin Oncol.* 2009;27:5685–92.
34. •• El Saghir NS, Kreidieh FY, El-Baba S, Anderson BO. Management of locally advanced and metastatic breast cancer: guidelines, infrastructures and low resource settings. *Breast Cancer Manage.* 2016;5(2):69–77. **This article tackles a specific group of patients in LMICs, which is the locally advanced/metastatic breast cancer group. It is important to know that resources needed in the management of cancer at this advanced stage requires proper infrastructure that is not always present in low-resource**

- countries. In this article, disparities in the breast cancer outcomes and requirements for optimal management are reviewed, including infrastructure needs for optimal surgery, radiation treatment, and systemic therapy. In addition, the article mentions controversies related to drug pricing and availability and process and delays in registration of new drugs as well as resource stratification.**
35. El Saghir NS, Adebamowo CA, Anderson BO, et al. Breast cancer management in low resource countries (LRCs): consensus statement from the Breast Health Global Initiative. *Breast*. 2011;20: S3–S11.
 36. Ganz PA, Yip CH, Gralow JR, Distelhorst SR, Albain KS, Andersen BL, et al. Supportive care after curative treatment for breast cancer (survivorship care): resource allocations in low- and middle-income countries. A Breast Health Global Initiative 2013 consensus statement. *Breast*. 2013;22:606–15.
 37. Lopes G, Eniu A, El Saghir N. Developing resource-stratified guidelines in oncology to improve cancer care worldwide. 2015. *Asco Post*, <https://am.asco.org/developing-resource-stratified-guidelines-oncology-improve-cancer-care-worldwide>.
 38. Cazap E, Distelhorst SR, Anderson BO. Implementation science and breast cancer control: a Breast Health Global Initiative (BHGI) perspective from the 2010 Global Summit. *Breast*. 2011;20(suppl 2):S1–2.
 39. Charara RN, Kreidieh FY, Farhat RA, al-Feghali KA, Khoury KE, Haydar A, et al. Practice and impact of multidisciplinary tumor boards on patient management: a prospective study. *J Glob Oncol*. 2016;3:242–9. <https://doi.org/10.1200/JGO.2016.004960>.
 40. El Saghir NS, Carlson RW, Khoury KE, Fallowfield L. Tumor boards: optimizing the structure and improving efficiency of multidisciplinary management of cancer patients worldwide. *Am Soc Clin Oncol Educ Book*. 2014;2014:e461–6.
 41. El Saghir N, El Asmar N, Hajj C, et al. Survey of utilization of multidisciplinary management tumor boards in Arab countries. *Breast*. 2011;20(Suppl 2):S70–4.
 42. El Saghir NS, Charara RN, Kreidieh FY, et al. Global practice and efficiency of multidisciplinary tumor boards: results of an American Society of Clinical Oncology international survey. *J Global Oncol*. 2015;1:57–64.
 43. WHO. Health systems: equity; <http://www.who.int/healthsystems/topics/equity/en/> Accessed March 30, 2018.
 44. Hortobagyi GN, El-Saghir NS, Cufer T, et al. The American Society of Clinical Oncology's efforts to support global cancer medicine. *J Clin Oncol*. 2016;34(1):76–82. <https://doi.org/10.1200/JCO.2015.61.7696>.
 45. B O. Anderson, A Dvaladze, A Ilbawi, et al. Prevention: breast cancer risk factors and risk reduction https://www.fredhutch.org/en/labs/phs/projects/breast-cancer-initiative_2-5/knowledge-summaries.html. Accessed on June 26, 2018.
 46. B O. Anderson, A Dvaladze, A Ilbawi, et al. Early detection: screening mammography programs. https://www.fredhutch.org/en/labs/phs/projects/breast-cancer-initiative_2-5/knowledge-summaries.html. Accessed on June 26, 2018.
 47. B. O. Anderson, A Dvaladze, A Ilbawi, et al. Treatment: systemic therapy: chemotherapy for breast cancer. https://www.fredhutch.org/en/labs/phs/projects/breast-cancer-initiative_2-5/knowledge-summaries.html. Accessed on June 26, 2018.
 48. B O. Anderson, A Dvaladze, A Ilbawi et al. Palliative care during treatment for breast cancer. https://www.fredhutch.org/en/labs/phs/projects/breast-cancer-initiative_2-5/knowledge-summaries.html. Accessed on June 26, 2018.
 49. El Saghir NS. Conflict medicine and cancer care in refugees and displaced people. *Asco Connection* 2017, <https://connection.asco.org/blogs/conflict-medicine-and-cancer-care-refugees-and-displaced-people>.
 50. El Saghir NS, Perez de Celis ES, Fares JE, Sullivan R. Cancer care for refugees and displaced populations: Middle East conflicts and global natural disasters. 2018 American Society of Clinical Oncology ASCO Educational Book: http://ascopubs.org/doi/abs/10.1200/EDBK_201365. **This article brings a new dimension to the subject of underprivileged cancer patients, which are refugees and displaced populations. It incites the WHO, UN, BHGI, ASCO, NCCN, and others to think about solutions for cancer patients in these communities.**