Guidelines for International Breast Health and Cancer Control–Implementation

Supplement to ***Cancer***

Guideline Implementation for Breast Healthcare in Low- and Middle-Income Countries: Treatment Resource Allocation

Alexandru Eniu, MD, PhD[1]
Robert W. Carlson, MD[2]
Nagi S. El Saghir, MD[3]
Jose Bines, MD[4]
Nuran Senel Bese, MD[5]
Daniel Vorobiof, MD[6]
Riccardo Masetti, MD[7]
Benjamin O. Anderson, MD[8]
on behalf of the Breast Health Global Initiative Treatment Panel

[1] Department of Breast Tumors, Cancer Institute "Ion Chiricuta" Cluj-Napoca, Romania.

[2] Division of Oncology, Stanford University, Stanford, California.

[3] Division of Hematology-Oncology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon.

[4] National Cancer Institute-Brasil, Rua, Brazil.

[5] Cerrahpasa Medical School Department of Radiation Oncology, Cerrahpasa, Istanbul University, Istanbul, Turkey.

[6] Sandton Oncology Centre, Johannesburg, South Africa.

[7] Department of Surgery, Catholic University of Rome, Rome, Italy.

[8] Division of Public Health Sciences, University of Washington, Seattle, Washington and Fred Hutchinson Cancer Research Center, Seattle Washington.

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A key determinant of breast cancer outcome is the degree to which newly diagnosed cancers are treated correctly in a timely fashion. Available resources must be applied in a rational manner to optimize population-based outcomes. A multidisciplinary international panel of experts addressed the implementation of treatment guidelines and developed process checklists for breast surgery, radiation treatment, and systemic therapy. The needed resources for stage I, stage II, locally advanced, and metastatic breast cancer were outlined, and process metrics were developed. The ability to perform modified radical mastectomy is the mainstay of locoregional treatment at the basic level of breast healthcare. Radiation therapy allows for consideration of breast-conserving therapy, postmastectomy chest wall irradiation, and palliation of painful or symptomatic metastases. Systemic therapy with cytotoxic chemotherapy is effective in the treatment of all biologic subtypes of breast cancer, but its provision is resource intensive. Although endocrine therapy requires few specialized resources, it requires knowledge of hormone receptor status. Targeted therapy against human epidermal growth factor receptor 2 (anti-HER-2) is very effective in tumors that overexpress HER-2/*neu* receptors, but cost largely prevents its use in resource-limited environments. Incremental allocation of resources can help address economic disparities and ensure equity in access to care. Checklists and allocation tables can support the objective of offering optimal care for all patients. The use of process metrics can facilitate the development of multidisciplinary, integrated, fiscally responsible, continuously improving, and flexible approaches to the global enhancement of breast cancer treatment. ***Cancer*** **2008;113(8 suppl):2269–81.** *© 2008 American Cancer Society.*

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The BHGI Treatment Panel members included Baffour Awuah, Zeba Aziz, Rajendra Badwe, José Bines, Ashwini Budrukkar, Co-chair Robert W. Carlson, Nagi S. El Saghir, Co-chair Alexandru Eniu, Nagi Khouri, Richard R. Love, Riccardo Masetti, A. Nandakumar, Twalib Ngoma, Carlos Perez, Jose Miquel Reyes, Paula Trahan Rieger, Eeva Salminen, Rama Sivaram, Tomoo Tajima, Daniel Vorobiof, and Jo Anne Zujewski.

Address for reprints: Alexandru Eniu, MD, PhD, Cancer Institute "I. Chiricuta", Department of Breast Tumors, Republicii 34-36, 400015 Cluj-Napoca, Romania: Fax: (011) 40 264-450348; E-mail: aleniu@iocn.ro

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Guidelines for breast cancer treatment have been developed for countries with high-level healthcare resources.[1-3] The application of treatment guidelines for resource-rich countries can be cost prohibitive in low- and middle-income countries (LMCs). However, it remains possible to provide breast cancer treatment even with limited resources if selected healthcare resources are provided, organized, and sustained. The Breast Health Global Initiative (BHGI) previously published resource-sensitive guidelines for breast cancer treatment in LMCs[4,5] that were intended to assist ministers of health, policymakers, administrators, and institutions in prioritizing resource allocation as breast cancer treatment programs are implemented and developed in their resource-constrained countries. The guidelines presented here focus on the implementation of evidence-based expert consensus treatment guidelines stratified by the available level of healthcare resources in a geographic region, hospital, or individual clinic as well as process metrics to assess the quality of care provided by stage of disease and treatment modality at different levels of resource.

Successful delivery of breast cancer care is a multidisciplinary process that can include surgeons, radiologists, pathologists, primary care physicians, medical oncologists, radiation oncologists, nurses, pharmacists, psycho-oncologists, technicians, social workers, and others based on the available resources. In these guideline recommendations, the application of high-impact, selected, resource-efficient therapies is recommended. Priority is given to those interventions that provide the greatest benefit in prolonging disease-free and overall survival as resources increase. Unfortunately, some highly effective therapies are cost prohibitive in LMCs, restricting or preventing their application. In these settings in which effective therapy cannot be provided and/or cure will not be possible, palliation is emphasized.

A number of general principles addressing healthcare disparities underlie the efforts of the BHGI toward achieving equitable and optimal breast health for all women and were developed explicitly at the first BHGI Global Summit held in Seattle, Washington in 2002.[6] These principles include the right of all women to access healthcare, the equitable availability and application of healthcare within any given healthcare system, the need for educational and counseling efforts directed at both the healthcare system and the population at risk, and the recognition that healthcare delivery must be sensitive to the political, social, religious, and cultural environment in which it is applied.

The BHGI guidelines were expanded at the second BHGI Global Summit held in Bethesda, Maryland in 2005 to include a system for stratifying healthcare resources based on treatment efficacy and cost effectiveness.[5,7-9] In the updated BHGI treatment guidelines, resources were stratified according to a 4-tiered system, depending on the availability of resources (basic, limited, enhanced, and maximal) to account for discrepancies that exist among various regions of the world.[5] These treatment guidelines were assembled in conjunction with guidelines for early detection,[7] diagnosis,[8] and healthcare systems[9] to provide a comprehensive guide to breast program design for LMCs.

The purpose of the third BHGI Global Summit was to address guideline implementation as it relates to resource allocation in LMCs and to consider process metrics that may provide benchmarks for implementation success and possibly for programmatic expansion to the next higher resource allocation level. The 2007 BHGI Treatment Panel expanded on prior guideline iterations to examine how key therapeutic interventions can be integrated to form a functional treatment program in LMCs given differing levels of available resources. The previously formulated BHGI guidelines are broadened to include process metrics that can be used by medical professionals and healthcare authorities to assess the functionality of their breast health programs. Process metrics and other sources of data can help inform decisions on future resource allocation and can identify areas for local research and improvement efforts.

MATERIALS AND METHODS

The BHGI consensus conference methodology from the 2007 Global Summit held in Budapest, Hungary from October 1 through 4, 2007 was used previously for the creation of the 2 prior Global Summits and has been described previously.[10] Diagnostic resources were stratified according to the same 4-tiered system based on the availability of resources relevant to treatment:

- **Basic level**—These are core resources or fundamental services that are absolutely necessary for any breast healthcare system to function. By definition, a healthcare system that lacks any basic level resource would be unable to provide breast cancer care to its patient population. Basic-level services typically are applied in a single clinical interaction.
- **Limited level**—Second-tier resources or services that produce major improvements in outcome, such as increased survival, but that are attainable

with limited financial means and modest infrastructure are considered limited-level services and may involve single or multiple clinical interactions.
- **Enhanced level**—Third-tier resources or services at the enhanced level 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 at the maximal level may be used in some high-resource countries and/or may be recommended by breast care guidelines that assume unlimited resources but that should be considered a lower priority than those in the basic, limited, or enhanced categories on the basis of extreme cost and/or impracticality for broad use in a resource-limited environment. To be useful, maximal-level resources typically depend on the existence and functionality of all lower-level resources.

The evaluations of the Treatment Panel were considered in the context of required resources (surgery, radiation therapy, and systemic therapy), which then were stratified based on stage at presentation (stage I, stage II, locally advanced, or metastatic disease). The panel reviewed the previous stratification tables, discussed the core implementation issues related to these programs, and made relevant changes based on consensus opinion.

The Treatment Panel also provided recommendations for process metrics to assess the performance of a unit at the basic, limited, and enhanced levels of resources and to establish the threshold to be met to move the unit to the next level of resource allocation. This incremental nature of the allocation tables is associated with the key process metrics to monitor and evaluate the progress of medical units. A similar approach has been used in the United States by the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) to develop quality measures.[11] These quality measures were built on the parameters developed for ASCO's National Initiative on Cancer Care Quality and on the recommendations of the NCCN Breast Cancer Treatment Guidelines Panel. Measures were selected based on clinical impact, scientific acceptability, utility, potential for improvement, reliability, and feasibility. It is important to note that a process metric is not a treatment recommendation; rather, it identifies a homogeneous subgroup of patients by using specific criteria for which there is broad agreement on the treatment recommendation, and it provides a way of measuring the performance of the unit for the defined situation. These metrics are essential for the evaluation of the intervention and for guiding the decision-making for program improvement of a unit based on meeting the predefined quality and/or volume requirements. This sequential improvement strategy can prevent substantial inequity in the use of limited resources and can help prioritize resource use for the greatest benefit of the largest number of individuals possible.

The process metrics should be simple to measure to ensure reliability without excessive costs or infrastructure needs and to minimize the drain of scarce resources diverted for measuring indicators instead of offering therapy. It is not feasible or desirable to use performance metrics for each process or population; rather, it is important to identify a subgroup of patients that unequivocally should be treated in a certain way and to measure the performance of the medical unit for this particular subgroup intervention.

RESULTS

Overview

Prior reports published in 2005 from the BHGI presented an overview of treatment recommendation for stage I, stage II, locally advanced, and metastatic breast cancer, with a focus on limited resource countries.[5] This publication updates several therapeutic recommendations in view of recently published data; however, the primary focus of this report is allocation of resources and implementation of the BHGI recommendations. Specific details on the management and implementation of treatment for locally advanced breast cancer in LMCs and on radiotherapy delivery in LMCs also are presented in this supplement to *Cancer*.[12,13] The Treatment Panel recognized that future developments could modify the resource allocation in the tables. For example, research suggesting differences in effectiveness of treatment based on population genetics as well as individual genetic variations within populations may play a role in future guideline development. Such tools, most of which remain to be developed, could have a positive impact on breast cancer treatment, particularly if the tools are developed with cost containment in mind.

The results of the BHGI Treatment Panel consensus process are summarized in 2 types of tables: checklists (Tables 1-5) and resource allocation (Figs. 1-4). Checklists reflect the strengths and weaknesses of the major interventions used in the treatment of breast cancer, describe the benefits of each intervention, and discuss the resources required to deliver the care appropriately. Resource allocation tables

TABLE 1
Breast Cancer Surgery Checklist

Therapy	Strengths	Weaknesses	Required Resources
MRM	Rapid treatment	Disfiguring	Staff: Surgeon, anesthesiologist, pathologist, nurses, physiotherapist, medical social worker/counselor
	Curative for early breast cancer		Surgical resources: Operating theater, anesthetics, postoperative care system
	Technology to perform widely available		
BCS with axillary dissection	Rapid surgical treatment	Technically demanding	Surgical staff and resources as above under MRM
		Not appropriate for all patients	Resources included in Table 2
		Requires ability to assess margin status by breast imaging and pathology	
		Requires application of postoperative radiation therapy as potentially curative therapy for breast cancer	
SLN with blue dye	Allows for accurate identification of SLN	Requires experienced SLN team	Staff: Experienced surgeon, experienced pathologist
	Minimizes postsurgical morbidity in women with negative axillary lymph nodes	Rare allergic reactions	
SLN with radiotracer	Allows for accurate identification of SLN	Requires experienced SLN team	Staff: Experienced surgeon, experienced pathologist
	Minimizes postsurgical morbidity in women with negative axillary lymph nodes	Special handling of radiotracer	Other resources: Procedures, equipment, and facilities for radiotracer handling (nuclear medicine)

MRM indicates modified radical mastectomy; SLN, sentinel lymph node; BCS, breast-conserving surgery.

TABLE 2
Breast Cancer Radiotherapy Checklist

Therapy	Strengths	Weaknesses	Required Resources
Postmastectomy irradiation of the chest wall with or without regional lymph nodes	Reduces the risk of locoregional recurrence in women with positive axillary lymph nodes or with an advanced primary tumor	Chest wall irradiation in patients with 1-3 axillary lymph nodes still controversial	Equipment: Megavoltage teletherapy equipment, conventional simulator, dosimetry equipment
	Also may improve overall survival in women with axillary lymph node-positive breast cancer	Selection of the regional lymphatic fields controversial	Accessories for immobilization, shielding, and dose distribution
		Requires access to a radiotherapy facility	Quality assurance
			Staff: Radiation oncologist, medical physicist, radiotherapy technologist. maintenance technician*
			Support systems that allow receipt of radiation therapy for a period of several weeks
Post-BCS irradiation of the whole breast with or without regional lymph nodes	A 4- to 5-fold reduction in local recurrence and improvement in survival	Requires access to radiotherapy facility	Equipment: Megavoltage teletherapy equipment, conventional simulator, dosimetry equipment
	When added to BCS, equivalent to MRM	Treatment course is prolonged (6 to 6.5 wk)	Accessories for immobilization, shielding, and dose distribution
			Quality assurance
			Staff: Radiation oncologist; medical physicist; radiotherapy technologist; maintenance technician*
			Support systems that allow receipt of radiotherapy for a period of several weeks

BCS indicates breast-conserving surgery; MRM, modified radical mastectomy.
*Required if a linear accelerator is being used.

TABLE 3
Breast Cancer Cytotoxic Chemotherapy Checklist

Therapy	Strengths	Weaknesses	Required Resources
Cytotoxic chemotherapy	Established role in the treatment of women with invasive breast cancer	Costly in many instances	Laboratory facilities monitor CBC and blood chemistry; blood bank capabilities
Note: Combination chemotherapy is superior to single-agent chemotherapy		Absolute benefits decrease with increasing age	Pharmacy services: Compound the drugs, antiemetics, prophylactic and side-effect management drugs
		Requires a chemotherapy-experienced healthcare team	Physical facilities to administer intravenous chemotherapeutic drugs Medical services to monitor and manage the toxicities of treatment: Microbiology and general laboratory facilities, hydration facilities, transfusion services for erythrocytes, platelets; broad-spectrum antibiotics; growth factors Pulmonary and cardiac monitoring facilities
Regimen			
Classic (oral) CMF	Equivalent to regimens of anthracycline-based chemotherapy in certain situations	Treatment duration, 6 mo	Same as for cytotoxic chemotherapy (see above)
	An effective and less expensive adjuvant chemotherapy regimen	Multiple infusions	
		Variable patient compliance	
Anthracycline-based chemotherapy (eg, AC, EC, or FAC)	Superior overall to CMF chemotherapy in unselected patients	Potential cardiac toxicity	Same as for cytotoxic chemotherapy (see above)
	Generally a short course of therapy	Costly	
	Doxorubicin generally less expensive than epirubicin	Treatment duration, 4-6 mo	
Taxanes	Taxane chemotherapy may add benefit to anthracycline-based chemotherapy in some patients	Expensive	Same as for cytotoxic chemotherapy (see above)
		Additional toxicity (neurologic, bone marrow)	

CMF indicates cyclophosphamide, methotrexate, and 5-fluorouracil; AC, doxorubicin and cyclophosphamide; EC: epirubicin and cyclophosphamide; FAC: 5-fluorouracil, doxorubicin and cyclophosphamide.

summarize the recommendations for the stratification of breast cancer therapies based on the levels of resources and taking into account healthcare costs when assessing the relative benefits offered by different treatment modalities in terms of survival, disease-free survival, and quality of life. In the resource allocation tables, for each level of resources, key process metrics have been identified to monitor and evaluate the progress of the medical unit. The use of these parameters assumes that these selected key processes in the delivery of healthcare to selected patients will serve as indicators of the quality of care provided to patients with the given disease by the healthcare system as a whole.

Required Resources for the Delivery of Specific Therapies

Surgery and radiation therapy

The required resources for locoregional treatment are indicated in Tables 1 and 2. The availability of surgical therapy is considered a basic requirement for the management of patients with early-stage breast cancer. Most medical settings that provide at least minimally advanced healthcare in LMCs have the necessary resources for surgical therapy. The availability of radiation therapy allows for consideration of breast-conserving therapy, postmastectomy chest wall radiation, and the palliation of painful or symptomatic, localized metastases in many sites. However, access to radio-

TABLE 4
Breast Cancer Endocrine Therapy Checklist

Therapy	Strengths	Weaknesses	Required Resources
Adjuvant endocrine therapy	Adjuvant endocrine therapy in women with ER+ and/or PR+ or negative/unknown receptor status substantially reduces the risks of disease recurrence and death	Optimally requires availability of ER and PR determination	Pathology
	Limited toxicity	Benefits are limited in low-risk breast cancer	Tumor steroid hormone receptor content
	Easily administered by general practitioner or surgeon	Compliance varies	Tumor histologic grade
	Absolute benefits in adjuvant setting increase with increasing risk of recurrence	Need ability to manage rare but potentially serious side effects	Stage of disease (biochemistry and radiologic investigation)
			Resources for diagnosis and management of toxicities
			Pharmacy/drug distribution
Specific adjuvant endocrine therapies			
Tamoxifen	Improves disease-free and overall survival in all age groups and lymph node subsets and with or without chemotherapy in ER+ and/or PR+ or negative/unknown receptor status	Toxicity	Same as for adjuvant endocrine therapy (see above)
	Reduces risk of second, contralateral breast cancers	Hot flashes	Resources for management of toxicities should include gynecology
	Maintains bone mineral density in postmenopausal women	Thromboembolic disease	
	Inexpensive	Endometrial carcinoma	
	Known long-term toxicity profile	Rare ocular toxicities	
Aromatase inhibitors (AIs)	In postmenopausal women with ER+ and/or PR+ or negative/unknown, resected breast cancer:	Absolute difference between AIs and tamoxifen alone in terms of disease-free survival is small	Same as for adjuvant endocrine therapy (see above)
	Adjuvant AIs are superior to tamoxifen	No clear impact on survival	
	Sequential AI after 2-3 y of tamoxifen is superior to tamoxifen alone	Substantially higher cost compared with tamoxifen alone	
	Extended AI therapy after 5 y of tamoxifen is superior to 5 y of tamoxifen alone	Toxicity: increased risk of bone fracture, arthralgias	
	No increase in thromboembolic events or endometrial cancer		
Ovarian ablation (medical, surgical, radiotherapy)	Effective for premenopausal women with ER+ and/or PR+ or negative/unknown receptors status	Long-term adverse effects of estrogen deprivation in young women	Core surgical resources
	Combined medical oophorectomy (LHRH and tamoxifen) is equivalent to CMF chemotherapy	High cost of LHRH agonists	Access to radiotherapy
	Oophorectomy (surgery or radiation) plus tamoxifen may be considered an appropriate adjuvant endocrine therapy		Pathology: same as for adjuvant endocrine therapy (see above)
	Surgical and radiation induced ovarian ablation is likely to be cost-effective compared with chemotherapy alone		Resources for management of toxicities

ER indicates estrogen receptor, +,.positive; PR, progesterone receptor; LHRH, lutenizing hormone-releasing hormone; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil.

therapy services is very limited in the majority of LMCs.[14]

Systemic treatment (Tables 3-5)

The use of systemic therapy improves survival and disease-free survival in women with early breast cancer and can provide significant palliation in women with advanced disease.[15] In general, cytotoxic chemotherapy is effective for the treatment of all biologic subtypes of breast cancer, endocrine therapy is effective for the treatment of breast cancers that express hormone receptors for estrogen and/or progesterone, and HER-2-targeted therapy is effective for the treatment of tumors with HER-2 over expression or

TABLE 5
Breast Cancer Biologic Therapy Checklist

Therapy	Strengths	Weaknesses	Required Resources
Trastuzumab	In HER-2+ breast cancer, substantially reduces risks of disease recurrence and death as a component of adjuvant therapy;	Requires the availability of a reliable method for determining HER-2 over expression or gene amplification	Pathology (reliable HER-2 status)
	In metastatic HER-2+ breast cancer, provides substantial palliation and control of disease as a single agent and in combination with chemotherapy; limited acute and chronic toxicity	Administered in combination with cytotoxic therapy	Ability to monitor cardiac function (echocardiography, radionuclide left ventricular ejection fraction)
		Optimal duration of treatment unknown;	Pharmacy services to compound drug;
		Associated with increased risk of symptomatic congestive heart failure, especially when given with an anthracycline-containing chemotherapy regimen	Physical facilities to administer IV chemotherapeutic drug infusions
		Occasional allergic infusion reactions	Resources to administer cytotoxic chemotherapy
		Very high drug cost	
Bevacizumab	Improves time to progression when used with paclitaxel as first-line therapy for metastatic breast cancer	Associated with increased risk of bleeding, thrombosis, hypertension, and nephrotic syndrome	Pathology
		Optimal duration of treatment unknown	Resources to treat complications of treatment, especially bleeding, hypertension, and thrombosis
		Extremely high drug cost	Pharmacy services to compound drug
			Physical facilities to administer IV chemotherapeutic drugs

HER-2 indicates human epidermal growth factor receptor 2; +, positive; IV, intravenous.

amplification. The provision of endocrine therapy requires relatively few specialized resources but, optimally, requires knowledge of hormone receptor status to assure the treatment of patients who are most likely to benefit. The provision of chemotherapy requires specially trained healthcare providers, requires substantial supportive care systems, and varies greatly in cost, depending on the specific agents used. The ability to assess tumor HER-2 status and the use of HER-2-targeted therapy typically are prohibitively expensive in most healthcare settings in the world.

Resource Allocation by Stage

Stage I breast cancer (Figure 1)

Modified radical mastectomy is the mainstay of locoregional treatment at the basic level, because access to radiation therapy usually is not available in this setting. Breast-conserving surgery, sentinel lymph node biopsy, and breast reconstruction may be added at higher levels of resource allocation.

Similarly, oophorectomy in premenopausal patients and tamoxifen in both premenopausal and postmenopausal women is the recommended systemic therapy at the basic level, with the progressive addition of cytotoxic chemotherapy and other endocrine agents at higher levels of resource allocation. A process to establish estrogen receptor status should be in place at the basic level (for instance, by postal collaboration with a higher level institution) to allow the identification of patients who would benefit from endocrine treatment.

Despite the recently documented benefits of adjuvant trastuzumab in patients with HER-2-positive breast cancer in disease-free and overall survival, the requirement for laboratory facilities for determining HER-2 status and the very high costs of trastuzumab limit its applicability to the enhanced level. When and if trastuzumab becomes substantially less costly, it would move appropriately into the limited or basic category of resources.

Stage II breast cancer (Figure 2)

Important differences between treatment for stage I and stage II breast cancer include the use of cytotoxic chemotherapy at the basic level for stage II disease because of the higher risk of recurrence experienced by patients with stage II lymph node-positive breast cancer. Another difference is the earlier incorporation of chest wall and regional lymph node irradiation at lower resource levels because of

Treatment Resource Allocation and Process Metrics: Stage I Breast Cancer

Level of resources	Local-Regional Treatment		Systemic Treatment (Adjuvant)			Process Metrics
	Surgery	Radiation Therapy	Chemotherapy	Endocrine Therapy	Biological Therapy	
Basic	Modified radical mastectomy			Oophorectomy in premenopausal women Tamoxifen*		Pts diagnosed with cancer underwent MRM (min 75%, target 90%) Tamoxifen for postmeno pts w/ ER+ ca >1 cm (min 75%, target 90%) w/i 1 yr of diagnosis
Limited	Breast conserving surgery† Sentinel lymph node (SLN) biopsy with blue dye‡		Classical CMF§ AC, EC, or FAC§		‖	Chemo for premeno pts with ER- ca >1 cm w/i 120d (min 75%, target 90%) Sentinel node identification (min 75%, target 90%)
Enhanced	SLN biopsy using radiotracer‡ 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‖	Sentinel node identification (min 90%, target 95%) Chemo for premeno pts w/ ER- tumors >1 cm w/i 120d (min 90%, target 95%) Hormone tx for postmeno pts w/ ER+ ca >1 cm w/i 1yr (min 90%, target 95%) XRT post BCT for pts <70 yrs 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

FIGURE 1. Treatment resource allocation table and process metrics for stage I breast cancer. Pts indicates patients; MRM, modified radical mastectomy; min, minimum; postmeno, post menopausal; w/, with; ER, estrogen receptor; ca, cancer; w/i, within; yr, year; SNL, sentinel lymph node; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; AC, doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; Chemo, chemotherapy; premeno, premenopausal; d, day; LH-RH, luteinizing hormone-releasing hormone, HER-2/neu, human epidermal growth factor receptor 2; tx, treatment; XRT, external beam radiotherapy; BCT, breast conserving therapy. *ER testing by IHC is preferred for establishing hormone receptor status and is cost effective when tamoxifen is available. When tamoxifen is available at the basic level, then IHC testing of ER status also should be provided. †Breast-conserving surgery can be provided as a limited-level resource but requires breast-conserving radiation therapy. If breast-conserving radiation is unavailable, then patients should be transferred to a higher level facility for postlumpectomy radiation. ‡The use of SLN biopsy requires clinical and laboratory validation of the SLN technique. §Systemic chemotherapy requires blood chemistry profile and complete blood count testing for safety. When chemotherapy is available at the basic level, these tests also should be provided. ‖If the costs associated with trastuzumab were substantially lower, trastuzumab would be used as a limited-level. In this case, measurement of HER-2/neu overexpression and/or gene amplification would also need to be available at the limited level in order to properly select patients for this highly effective but expensive HER-2/neu targeted biological therapy. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. An empty matrix box indicates that additional resource allocation is not mandated beyond those resources required at lower levels. Maximal level resources should not be targeted for implementation in LMCs, even though they may be used in same higher income settings.

the higher risk of local recurrence. Again, process metrics are recommended to assist in determining when efforts should be made to move to the next higher level of resource allocation.

Locally advanced breast cancer (Figure 3)

Locally advanced breast cancer is a heterogeneous clinical entity that includes patients with T3 (>5 cm) primary breast tumors or T4 tumors (with chest wall involvement, skin edema or ulceration of the skin, satellite nodules, or inflammatory carcinoma) and/or extensive clinical lymph node involvement as defined by the N2 and N3 categories of the American Joint Committee on Cancer TNM classification system.[16] It is also the most common form of presentation for breast cancer patients in countries of limited resources,[17,18] and, along with stage IV disease, it represents from 60% to 80% of cases at presentation

Treatment Resource Allocation and Process Metrics: Stage II Breast Cancer

Level of resources	Local-Regional Treatment		Systemic Treatment (Adjuvant)			Process Metrics
	Surgery	Radiation Therapy	Chemotherapy	Endocrine Therapy	Biological Therapy	
Basic	Modified radical mastectomy	*	Classical CMF† AC, EC, or FAC†	Oophorectomy in premenopausal women Tamoxifen‡		Pts diagnosed with cancer underwent MRM (min 75%, target 90%) Chemo for premeno pts w/ ER- ca w/i 120d (min 75%, target 90%) Tamoxifen for postmeno pts w/ ER+ ca >1 cm (min 75%, target 90%) w/i 1 yr of diagnosis
Limited	Breast conserving surgery§ Sentinel lymph node (SLN) biopsy with blue dye‖	Postmastectomy irradiation of chest wall and regional nodes for high-risk cases*			¶	Post mastectomy chest wall radiation therapy for high risk women <70 yrs w/i 1 yr of mastectomy (min 75%, target 90%) Sentinel node identification (min 75%, target 90%)
Enhanced	SLN biopsy using radiotracer‖ 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¶	Sentinel node identification (min 90%, target 95%) Chemo for premeno pts w/ ER- ca w/i 120d (min 90%, target 95%) Hormone tx for pts with ER+ ca w/i 1 yr (min 90%, target 95%) XRT post BCT for pts <70 yrs w/i 1 yr (min 75%, target 90%)
Maximal			Growth factors Dose-dense chemotherapy			Maximal category process metrics determined based upon standards of care in high-income countries

FIGURE 2. Treatment resource allocation and process metrics table for stage II breast cancer. CMF indicates cyclophosphamide, methotrexate, and 5-fluorouracil; AC, doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; Pts, patients; MRM, modified radical mastectomy; min, minimum; Chemo, chemotherapy; premeno; premenopausal; w/, with; ER, estrogen receptor; ca, cancer; w/i, within; d, day; postmeno, postmenopausal; yr, year; SLN, sentinel lymph node; LH-RH, luteinizing hormone-releasing hormone; HER-2/neu, human epidermal growth factor receptor; tx, treatment; XRT, external beam radiotherapy; BCT, breast conserving therapy. *Chest wall and regional lymph node irradiation substantially decreases the risk of postmastectomy local recurrence. If available, it should be used as a basic-level resource. †Systemic chemotherapy requires blood chemistry profile and complete blood count testing for safety. When chemotherapy is available at the basic level, these tests also should be provided. ‡ER testing by IHC is preferred for establishing hormone receptor status and is cost effective when tamoxifen is available. When tamoxifen is available at the basic level, then IHC testing of ER status also should be provided. §Breast-conserving surgery can be provided as a limited-level resource but requires breast-conserving radiation therapy. If breast-conserving radiation is unavailable, then patients should be transferred to a higher level facility for postlumpectomy radiation. ‖The use of SLN biopsy requires clinical and laboratory validation of the SLN technique. ¶If the costs associated with trastuzumab were substantially lower, trastuzumab would be used at a limited level. In this case, measurement of HER-2/neu overexpression and/or gene amplification would also need to be available at the limited level in order to properly select patients for this highly effective but expensive HER-2/neu targeted biological therapy. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. An empty matrix box indicates that additional resource allocation is not mandated beyond those resources required at lower levels. Maximal level resources should not be targeted for implementation in LMCs, even though they may be used in same higher income settings.

in Arab countries.[19] The standard of care for patients with locally advanced breast cancer is primary systemic therapy with anthracycline-based chemotherapy. Neoadjuvant hormone therapy may be used in patients with estrogen receptor-positive disease who are not candidates for chemotherapy for medical reasons.[20] Therefore, primary systemic therapy should be made available at the basic level. All patients with locally advanced breast cancer require postoperative radiotherapy; therefore, radiotherapy should be made available at the basic level.

Metastatic (stage IV) and recurrent breast cancer (Figure 4)

The treatment of metastatic or recurrent breast cancer rarely is curative. However, the judicious application of surgery, radiation therapy, endocrine therapy,

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

FIGURE 3. Treatment resource allocation and process metrics table for locally advanced breast cancer. AC indicates doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; pts, patients; min, minimum; tx, treatment; w/, with; ER, estrogen receptor; ca, cancer; w/i, within; yr, year; MRM, modified radical mastectomy; LH-RH, luteinizing hormone-releasing hormone; HER-2/neu, human epidermal growth factor receptor 2; XRT, external beam radiotherapy. *Chest wall and regional lymph node irradiation substantially decreases the risk of postmastectomy local recurrence. If available, it should be used as a basic-level resource. †Systemic chemotherapy requires blood chemistry profile and complete blood count testing for safety. When chemotherapy is available at the basic level, these tests also should be provided. ‡ER testing by IHC is preferred for establishing hormone receptor status and is cost effective when tamoxifen is available. When tamoxifen is available at the basic level, then IHC testing of ER status also should be provided. §If the costs associated with trastuzumab were substantially lower, trastuzumab would be used at a limited level. In this case, measurement of HER-2/neu overexpression and/or gene amplification would also need to be available at the limited level in order to properly select patients for this highly effective but expensive HER-2/neu targeted biological therapy. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. An empty matrix box indicates that additional resource allocation is not mandated beyond those resources required at lower levels. Maximal level resources should not be targeted for implementation in LMCs, even though they may be used in same higher income settings.

cytotoxic chemotherapy, biologic therapy, and supportive therapy may provide substantial benefits in quality of life, control of metastatic disease, and limited average prolongation in overall survival. First recurrence of breast cancer in the ipsilateral breast after the use of breast-conserving therapy is a situation in which the intent of treatment for recurrent disease should be curative. In this situation, to perform a total mastectomy is cost-effective and often curative therapy. This therapy, thus, is allocated to the basic level of resources.

In patients with estrogen and/or progesterone receptor-positive disease, a wide variety of endocrine therapies provide substantial palliation and often long-term disease control with modest toxicity. Cytotoxic chemotherapy may provide substantial, short-term palliation for women with metastatic or recurrent breast cancer. Either combination chemotherapy or single-agent chemotherapy may be used. When given with chemotherapy, trastuzumab is highly active against breast cancers with HER-2 amplification or overexpression. When and if trastuzumab

Treatment Resource Allocation and Process Metrics: Metastatic (Stage IV) and Recurrent Breast Cancer

Level of resources	Local-Regional Treatment		Systemic Treatment (Palliative)			Process Metrics
	Surgery	Radiation Therapy	Chemotherapy	Endocrine Therapy	Supportive Therapy	
Basic	Total mastectomy for ipsilateral breast tumor recurrence after breast conserving surgery			Oophorectomy in premenopausal women Tamoxifen*	Nonopioid and opioid analgesics and symptom management	Pain control provided (min 80%, target 95%) Hormone tx for all patients with ER+ ca 120d of diagnosis (min 80%, target 90%)
Limited		Palliative radiation therapy	Classical CMF† Anthracycline monotherapy or in combination†			Palliative XRT for CNS mets (min 70%, target 80%) First line palliative chemo if ER- ca (min 80%, target 90%)
Enhanced			Sequential single agent or combination chemotherapy Trastuzumab Lapatinib	Aromatase inhibitors	Bisphosphonates	Second line chemo, if visceral metastasis and good performance status (min 90%, target 95%) Bisphosphonates for lytic/symptomatic bone disease (min 90%, target 95%)
Maximal			Bevacizumab	Fulvestrant	Growth factors	Maximal category process metrics determined based upon standards of care in high-income countries

FIGURE 4. Treatment resource allocation and process metrics table for metastatic (stage IV) and recurrent breast cancer. Min indicates minimum; ER, estrogen rector; ca, cancer; d, day; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil, XRT, external beam radiotherapy; CNS, central nervous system; mets, metastases; chemo, chemotherapy. *ER testing by IHC is preferred for establishing hormone receptor status and is cost effective when tamoxifen is available. When tamoxifen is available at the basic level, then IHC testing of ER status also should be provided. †Systemic chemotherapy requires blood chemistry profile and complete blood count testing for safety. When chemotherapy is available at the basic level, these tests also should be provided. Note that the table stratification scheme implies incrementally increasing resource allocation at the basic, limited, and enhanced levels. An empty matrix box indicates that additional resource allocation is not mandated beyond those resources required at lower levels. Maximal level resources should not be targeted for implementation in LMCs, even though they may be used in same higher income settings.

becomes more reasonably priced and affordable, it could be allocated at the basic level of resources for women with HER-2-positive, metastatic breast cancer.

Control of pain, nausea and vomiting, dyspnea, and other symptoms associated with metastatic breast cancer are central to providing optimal care. Furthermore, many agents that control these symptoms are available widely, do not require a specialist to administer, and are priced very cheaply.

DISCUSSION

Not every patient with breast cancer can receive the maximal level of care in countries with limited resources, which is the core reality on which the BHGI was founded. Most existing treatment guidelines are not applicable in countries with limited resources, because many diagnostic or therapeutic interventions simply are not available. The World Health Organization has stated that the initial priorities, particularly in developing countries, should be to develop national diagnostic and treatment guidelines that establish a minimum standard of care and to promote the rational use of existing resources and greater equity in access to treatment.[21] Consistent with this statement, the objective of the BHGI is to define reasonable priorities that ensure the evidence-based and equitable use of the available resources.

Some of the most effective agents in the treatment of breast cancer are cost-prohibitive for most

of the world. It is estimated that a year of adjuvant trastuzumab costs approximately $35,000 to $45,000 (US dollars) per patient (wholesale drug cost) in the United States, not including local pharmacy, infusion, monitoring, toxicity management, and mark-up costs. A year of an aromatase inhibitor therapy costs >$3300 for drug costs alone. Thus, we have highly effective therapies that are cost-prohibitive for most of the world. For many of these high-cost agents, cost-benefit analyses suggest that the agents may fall within the traditional cost-effectiveness range for the resource-rich countries. However, for LMCs, the application of these therapies to even a very few patients would require the withholding of effective therapy from many others. For some agents, such as adjuvant trastuzumab, which is administered in conjunction with rather than as a replacement for chemotherapy, the costs are additive and are not replacement costs. In the allocation of resource tables, the use of specific, highly active, systemic agents, including trastuzumab, taxanes, aromatase inhibitors, and possibly bevacizumab, would move appropriately to the basic- or limited-resource level if the cost of the agents were substantially lower.

The incremental, step-by-step allocation of resources tables account for the economic disparities across populations and provides a means for better ensuring equity in access to care. The use of allocation tables is a pragmatic approach, which recognizes that the ultimate objective of every healthcare system is to offer optimal care to all patients. However, resource constraints may necessitate intermediate steps toward achieving these objectives.

In applying this scheme, the short-term objective is to advance to the next higher level of care, and the long-term objective is to advance to the maximal level. It is worth noting that a given level refers to the set of therapies at that level. Depending on each country's unique situation, this level can be applied to any health unit; therefore, different levels may coexist within a country. For example, a country may have numerous community clinics that provide treatment at the basic level, a few hospitals that provide treatment at the limited level, and a single national cancer center that provides treatment at the enhanced or maximal level. How these facilities interconnect locally and nationally, for example, for patient referral, will be country specific.

The provision of treatment to patients with breast cancer is complex and requires substantial resource allocation. The recognition that not all regions of the world are able to afford optimal healthcare requires that resources be allocated equitably and judiciously if the negative impact of breast cancer is to be minimized. The checklists, resource allocation tables, and process indicators presented here are designed to facilitate the development of multidisciplinary, integrated, fiscally responsible, continuously improving, and flexible approaches to the global enhancement of breast cancer treatment.

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