CONTEXT-RELEVANT GUIDELINES IN CANCER CARE: BREAST CANCER EARLY DETECTION, DIAGNOSIS AND TREATMENT IN LOW- AND MIDDLE-INCOME COUNTRIES

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Resource constraints in developing health systems require difficult allocation decisions to optimize cancer outcomes. Cancer care guidelines developed in high-income countries have limited utility in developing countries, because many of the resources described in the ideal health care delivery system are unavailable or unaffordable, making it unclear where to begin in creating a realistic and sustainable cancer control strategy. New approaches to health care system design require that an evidence-based approach to resource prioritization be established. Co-founded by Susan G Komen for the Cure and the Fred Hutchinson Cancer Research Center, the Breast Health Global Initiative (BHGI) has created resource-stratified guidelines that provide a framework for programme development and a template for gap analysis to determine how existing resources can be applied in the most effective way to improve breast cancer outcomes. These approaches can be applied to other common malignancies that have a significant potential for improved outcome but are hindered by significant infrastructure limitations.

Resource allocation for developing cancer programmes

Physicians working in low- and middle-income countries (LMIC) may be forced to make decisions contrary to their best medical knowledge. Despite knowing the optimal management for a given patient based on guidelines developed in wealthy countries, less-than-optimal solutions are offered to patients because diagnostic and/or treatment resources are lacking. The constraint of limited resources generates tension for the clinician who is unable to offer "gold standard" treatments to any or all of the patients. This tension is amplified by the clinicians' added responsibility of having to manage an inadequate, fixed amount of resources from an insufficient cancer programme budget. Does a clinician decide to treat 10 patients with an older, less expensive chemotherapy regimen, or to treat two patients, with a newer, more efficacious but also more expensive regimen? It is important to determine which resources commonly applied in resource-abundant countries are most needed in limited-resource settings, where patients typically present with advanced disease at diagnosis.

Initial attempts at establishing a cancer treatment programme require treatment approaches that favour simple and highly efficacious therapies. Key treatment alternatives should be discussed, considering both relative costs of the interventions, efficacy differences, and the expected availability of resources and personnel to implement programmatic policies. Flexibility in recommendations is important, because heterogeneity exists in social, economic and health system barriers to improvement among countries or even among regions of the same country, making universal recommendations impractical.

The need for cancer care guidelines addressing issues in LMIC

Early detection and comprehensive cancer treatment play synergistic roles in creating improved breast cancer outcomes. In economically developed countries, guidelines outlining optimal approaches to early detection, diagnosis and treatment of breast cancer are defined and have been

disseminated[1-3]. In 2002, the World Health Organization (WHO) pointed out that these guidelines have limited utility in resource-constrained countries[4]. They fail to include implementation costs and provide no guidance as to how an existing system could be improved incrementally towards an ideal delivery system based on available resources.

Guidelines for LMIC must offer practical solutions to the implausibility of applying cancer guidelines developed for high-resource countries to LMIC. Guidelines from high-resource countries may be inappropriate for a number of reasons, including inadequate numbers of trained health care providers; inadequate diagnostic and treatment infrastructure such as pathology, pharmacy, infusion centres, and microbiology laboratories; lack of drugs; lack of radiographic film; and inadequate transportation systems. Thus, in a country with limited resources, many barriers lie between the average patient and the level of care dictated by guidelines applicable to high-resource settings.

Breast cancer as a model for resource-stratified guideline development

As the world's most common cancer among women, and the most likely reason that a woman will die of cancer around the globe, breast cancer affects countries at all economic levels. Each year, breast cancer is newly diagnosed in more than 1.1 million women, representing more than 10% of all new cancer cases. Breast cancer is becoming an increasingly urgent problem in low-resource regions where incidence rates have been rising by up to 5% per year[5]. Despite the common misconception that breast cancer is primarily a problem of high-income countries, the majority of the 425,000 breast cancer deaths in 2010 occurred in developing (not developed) countries[6]. The number of young lives lost is even more disproportionate. In 2010, breast cancer killed 68,000 women aged 15–49 years in developing countries versus 26,000 in developed countries[7]. Countries with established and adequately funded health care systems have higher breast cancer diagnosis rates, but also have improved breast cancer survival[8].

Standards of care are defined by the environment in which they are practiced. It is incorrect to assume that methods of breast cancer diagnosis and treatment that have evolved in high-income countries should directly translate into applications in LMIC. Some tools considered indispensable tools by US or Western European standards are less useful in limited resource environments, because the more advanced stage of disease at diagnosis makes their findings less relevant. For example, diagnostic mammography in high-income countries is considered mandatory for the performance of breast conservation surgery[9], because the early breast conservation trials required preoperative diagnostic mammography for entry in the study[10,11]. Certainly, in countries where screening mammography is commonly employed and non-palpable, non-invasive cancers are often diagnosed, diagnostic mammography is critical for determining the extent of disease in the breast to properly select patients for breast conserving surgery versus mastectomy. However, in LMIC where women present with palpable disease at the time of diagnosis, a preoperative mammogram may not be essential for selecting patients for breast conserving surgery. Nadkarni, Badwe and colleagues reviewed their institutional experience in Mumbai, India to assess how often diagnostic mammography added to clinical assessment in the selection of patients for breast conserving surgery[12]. The investigators examined their experience in 2004 and found that if mammography had not been performed in the 735 patients undergoing surgery, breast conservation would have been performed erroneously in only 38 (5%) patients (13 with impalpable multicentric disease, 25 with extensive microcalcifications). The remaining patients were corrected assessed for breast conservation versus mastectomy on the basis of clinical assessment performed by an experienced surgeon. Furthermore, had breast conservation been attempted in the 38 patients with clinically occult disease, most (if not all) would have been recognized and rectified postoperatively on the basis of positive surgical margins seen on final pathology. Thus, the availability of diagnostic mammography cannot be asserted to be mandatory in countries lacking screening mammography, especially when patients commonly present with clinically obvious disease.

Established in 2002, the Breast Health Global Initiative (BHGI) created an international health alliance to develop evidence-based guidelines for LMIC to improve breast health outcomes. BHGI held four Global Summits to address health care disparities (Seattle, Washington, 2002)[13], evidence-based resource allocation (Bethesda, Maryland, 2005)[14], guideline implementation (Budapest, Hungary, 2007)[15] and optimizing outcome (Chicago, 2010)[16] as related to breast cancer in LMIC. Modeled after the approach of the National Comprehensive Cancer Network (NCCN), BHGI developed and applied a consensus panel process, now formally endorsed by the US Institute of Medicine, to create resource-sensitive guidelines for breast cancer early detection[17], diagnosis[18], treatment[19] and health care systems[20] as related to breast health care delivery in LMIC.

Principles of BHGI guideline development

To begin the guideline development process, two axioms were adopted as principles in considering available evidence

regarding breast cancer early detection, diagnosis and treatment. First, it was assumed that all women have the right to access to health care, but that considerable challenges exist in implementing breast health care programmes when resources are limited. Second, it was assumed that all women have the right to education about breast cancer, but that it must be culturally appropriate, and targeted and tailored to specific populations in need[21].

Breast cancer outcomes in LMIC correlate with the degree to which 1) cancers are detected at early stages, 2) newly detected cancers can be diagnosed correctly, and 3) appropriately selected multimodality treatment can be provided properly in a timely fashion. In LMC, the majority of women have advanced or metastatic breast cancer at the time of diagnosis. Based upon evidence-based review and consensus discussion, BHGI made four core observations[13]:

➤ Because advanced breast cancer has the poorest survival and is the most resource-intensive to treat, efforts aimed at early detection can reduce the stage at diagnosis, potentially improving the odds of survival and cure, and enabling simpler and more cost-effective treatment;

➤ There is a need to build programmes that are specific to each country's unique situation;

➤ The development of cancer centres can be a cost-effective way to deliver breast cancer care to some women when it is not yet possible to deliver such care to women nationwide;

➤ Collecting data on breast cancer is imperative for deciding how best to apply resources and for measuring progress.

BHGI created and developed a stepwise, systematic approach for breast programme development based on resource stratification. A tiered system of resource allotment was defined using four levels – basic, limited, enhanced, and maximal – based on the contribution of each resource towards improving clinical outcomes (Table 1). Based on these principles, BHGI invited international experts to review and develop resource-stratified guideline tables for early detection, diagnosis, treatment, and health care systems[15]. In each area, a prioritization scheme was developed that considered both limitations in resources and corresponding stage of disease at diagnosis to consider how systematic improvements can be developed in each area such as breast cancer early detection (Table 2). During this analysis, a number of key points were identified and/or demonstrated:

➤ Early breast cancer detection improves outcome in a cost effective fashion assuming treatment is available.

➤ The effectiveness of early detection programmes requires public education to foster active patient participation in diagnosis and treatment.

➤ Clinical breast examination combined with diagnostic breast imaging (breast ultrasound with or without diagnostic mammography) can facilitate cost-effective tissue sampling techniques for cytological or histological diagnosis;

➤ Breast conserving therapy with partial mastectomy and radiation requires more health care resources and infrastructure than mastectomy, but can be provided in a thoughtfully designed limited-resource setting;

➤ The availability and administration of systemic therapy are critical to improving breast cancer survival;

➤ Estrogen receptor testing allows patient selection for hormonal treatments (tamoxifen, oophorectomy) which is both better for patient care and allows proper distribution of services;

➤ Chemotherapy, which requires some allocation of resources and infrastructure, is needed to treat node-positive, locally advanced breast cancers, which represent the most common clinical presentation of disease in low-resource countries;

➤ When chemotherapy is unavailable, patients presenting with locally advanced, hormone receptor negative cancers can only receive palliative therapy.

Guideline implementation

The BHGI Guidelines can be used to communicate programmatic needs to hospital administrators, government officials and/or health care ministries. It is the thesis of BHGI that these works create a framework for change, by defining practical pathways through which breast cancer care can be improved in an incremental and cost-effective fashion[14]. However, guidelines do not in-and-of themselves improve outcomes for women. Implementation is the critical step by which the value of the guidelines may be measured. Pilot research and demonstration projects are needed both to determine the effectiveness of the guidelines, and to create evidence that will promote similar guideline implementation in other regions with similar resource constraints.

BHGI examined common patterns in health care delivery in low-[22] and middle-[23] resource settings to determine what health system and patient-related barriers are contributing to late-stage presentation and assess what strategies[24] can be applied to improve outcomes in an incremental fashion without exceeding realistic capacity within that system[16]. As countries progress to higher economic status, the rate of late presentation is expected to decrease, and diagnostic and treatment resources are expected to improve. Health care systems in LMIC share many challenges including national or regional data collection, programme infrastructure and

Table 1: Resource level descriptions used for guideline development	
Level	**Description of resource level**
Basic	Core resources or fundamental services absolutely necessary for any breast health care system to function; basic-level services are typically applied in a single clinical interaction.
Limited	Second-tier resources or services that are intended to produce major improvements in outcome, such as increased survival, and are attainable with limited financial means and modest infrastructure; limited-level services may involve single or multiple clinical interactions.
Enhanced	Third-tier resources or services that are optional but important; enhanced-level resources should produce further improvements in outcome and increase the number and quality of therapeutic options and patient choice.
Maximal	High-level resources or services that may be used in some high-resource countries, and/or may be recommended by breast care guidelines that do not adapt to resource constraints but that nonetheless should be considered lower priority than those resources or services listed 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.

Table 2: BHGI guideline table for early detection resource allocation for breast cancer[17]			
Level of resource	**Public education and awareness**	**Detection methods**	**Evaluation goal**
Basic	Development of culturally sensitive, linguistically appropriate local education programmes for target populations to teach value of early detection, breast cancer risk factors and breast health awareness (education + self-examination).	Clinical history and CBE.	Breast health awareness regarding value of early detection in improving breast cancer outcome.
Limited	Culturally and linguistically appropriate targeted outreach/education encouraging CBE for age groups at higher risk administered at district/provincial level using health care providers in the field.	Diagnostic breast US +/- diagnostic mammography in women with positive CBE. Mammographic screening of target group*.	Downsizing of symptomatic disease.
Enhanced	Regional awareness programmes regarding breast health linked to general health and women's health programmes.	Mammographic screening every 2 years in women ages 50–69*. Consider mammographic screening every 12–18 monthsin women ages 40–49*.	Downsizing and/or downstaging of asymptomatic disease in women highest yield target groups.
Maximal	National awareness campaigns regarding breast health using media.	Consider annual mammographic screening in women aged 40 and older. Other imaging technologies as appropriate for high-risk groups.	Downsizing and/or downstaging of asymptomatic disease in women in all risk groups.

capacity (including appropriate equipment and drug acquisitions, and professional training and accreditation), the need for qualitative and quantitative research to support decision-making, and strategies to improve patient access and compliance as well as public, health care professional, and policy-maker awareness that breast cancer is a cost-effective, treatable disease. The biggest challenges identified for low-income countries were little community awareness that breast cancer is treatable, inadequate advanced pathology services for diagnosis and staging, and fragmented treatment options, especially for the administration of radiotherapy and the full range of systemic treatments[22]. The biggest challenges identified for middle-resource countries were the establishment and maintenance of data registries, the coordination of multidisciplinary centres of excellence with broad outreach programmes to provide community access to cancer diagnosis and treatment, and the resource-appropriate prioritization of breast cancer control programmes within the framework of existing, functional health care systems[23].

Next steps

The resource stratified guideline approach appears to be a key first step in determining how cancer care can best be administered in the setting of limited resources. In their 2007 report, Cancer Control Opportunities in Low- and Middle-Income Countries, the US Institute of Medicine (IOM)

provides a detailed summary of BHGI methodology, which the editors identify as a model approach for developing resource-sensitive guidelines that could be applied to other cancers or chronic diseases for which effective treatments are available.[25] BHGI analyses suggested that to better assess breast cancer burden in poorly studied populations, countries require accurate statistics regarding cancer incidence and mortality so that chronic diseases taking the greatest toll can be identified and targeted[24]. To better identify health care system strengths and weaknesses, countries require reasonable indicators of true health system quality and capacity. Using qualitative and quantitative research methods, countries should formulate cancer control strategies to identify both system inefficiencies and patient barriers. Patient navigation programmes linked to public advocacy efforts feed and strengthen functional early detection and treatment programmes. Cost-effectiveness research and implementation science are tools that can guide and expand successful pilot programmes. ●

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Dr Anderson created and chairs the Breast Health Global Initiative (BHGI), which developed and studies implementation of resource-sensitive, culturally appropriate guidelines for breast cancer early detection, diagnosis and treatment in low- and middle-income countries (LMIC). As private sector advisor on the US delegation to the 58th World Health Assembly in Geneva, Dr Anderson contributed to the first WHO Cancer Prevention and Control Resolution passed in 2005, which reinforces comprehensive cancer policies and strategies for LMICs. Honouring his commitment to women's health throughout the world and his dedicated efforts to improve their quality of care, Dr Anderson was awarded the 2011 Partners in Progress Award by the American Society of Clinical Oncology (ASCO). Most recently, Dr Anderson was elected to the Board of Directors of the Union for International Cancer Control (UICC).

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