The Challenge of Breast Cancer in Low- and Middle-income Countries – Implementing the Breast Health Global Initiative Guidelines

a report by

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Breast cancer is the most common cancer in women, accounting for 23% of all female cancers around the globe. There were an estimated 1.15 million cases diagnosed in 2002.[1] There is marked geographical variation in incidence rates, being highest in the developed world and lowest in the developing countries in Asia and Africa. The highest age-standardised incidence is in North America, at 99.4 per 100,000 population, while the lowest is in central Africa, at 16.5 per 100,000.[2] However, in most low- and middle-income countries (LMCs), incidence rates are increasing at a more rapid rate than in areas where incidence rates are already high. Global breast cancer incidence rates have increased by about 0.5% annually since 1990, but cancer registries in China are recording annual increases in incidence of 3–4%.[1] In a population-based cancer registry in Western Turkey in 1992, breast cancer incidence and prevalence were 24.4/100,000 and 0.3%, respectively; cervical cancer was relatively rare (age-standardised incidence rate of 5.4).[2] Breast cancer incidence has increased in Turkey, and the estimated number of breast cancer cases in 2007 was 44,253.[3] The distribution of breast cancer incidence varies significantly among different regions of Turkey due to geographical, economic, social and cultural factors. The breast cancer incidence in Western Turkey (50/100,000 in 2000) is more than two times that of Eastern Turkey (20/100,000) due to 'Westernised' lifestyles (early menarche, late menopause, first birth >30 years of age, less breast-feeding, etc.) and other factors in the last decades.[4,5]

The prognosis of those with breast cancer is good, although globally it still ranks as the leading cause of cancer mortality among women. Favourable breast cancer survival rates in developed countries have been attributed to early detection by screening and timely and effective treatment.[6] For example, women diagnosed with breast cancer between 1990 and 1992 and reported in the population-based case series from the Surveillance, Epidemiogy and End Results (SEER) programme (13,172 women) had an 89% five-year survival rate.[7] In a study from Istanbul including 1,841 breast cancer patients, the five-year survival rate was 86%.[8] In contrast, age-adjusted survival rates for breast cancer in less developed regions of Eastern Turkey average 60% and are as low as 46% in India and 32% in sub-Saharan Africa.[1,4,5]

Poorer survival in LMCs is largely due to the late presentation of the disease, which, when coupled with limited resources for diagnosis and treatment, leads to particularly poor outcomes.[6] Of the over 15,000 new cases presenting for treatment each year in Turkey, 75% have locally advanced breast cancer (LABC) at diagnosis in Eastern Turkey.[4] Compounding the problem of late diagnosis, breast cancer case fatality rates are high because LMCs typically lack major components of healthcare infrastructure and the resources necessary to implement improved methods for early detection, diagnosis, and treatment of breast cancer.[8,9] Although low-resource countries have not identified cancer as a priority healthcare issue because infectious diseases and malnutrition are the predominant public health problems, as the control of communicable diseases improves and life expectancy rises, cancer care will become an important health issue.[10]

Evidence-based guidelines outlining optimal approaches to breast cancer detection, diagnosis and treatment have been well developed and disseminated in several high-resource countries.[11–13] Optimal practice guidelines may be inappropriate to apply in LMCs for numerous reasons, including inadequate numbers of trained healthcare providers, inadequate diagnostic and treatment infrastructure and cultural, societal or religious barriers to women accessing the healthcare system. Thus, in a country with limited resources, many barriers exist between the average patient and the level of care dictated by guidelines applicable to high-resource settings. Hence, there is a need to develop clinical practice guidelines orientated towards countries with limited financial resources.[14] It was for this purpose that the Breast Health Global Initiative (BHGI) was established in 2002. The BHGI held three global summits in October 2002 (Seattle), January 2005 (Bethesda) and October 2007 (Budapest) and, using an expert consensus, developed an evidence-based approach to resource-sensitive guidelines that define comprehensive pathways for step-by-step quality improvements in healthcare delivery.
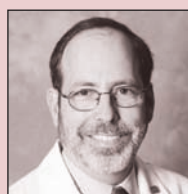
Breast Health Global Initiative Summits 2002 and 2005

The first evidence-based guidelines were developed at the 2002 BHGI Global Summit, 'International Breast Healthcare Guidelines for Countries with

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Limited Healthcare Resources', for: early detection; diagnosis; and treatment. These guidelines, published in 2003, describe healthcare disparities at different economic levels and outline principles for programmatic improvement in breast health services as applied to LMCs.[15–18]

At the 2005 BHGI global summit, the previous BHGI guidelines were updated and expanded into a flexible comprehensive framework for improving the quality of healthcare delivery based on outcomes, cost, cost-effectiveness and the use of healthcare services. The 2005 guidelines addressed: early detection and access to care;[19] diagnosis and pathology;[20] cancer treatment and allocation of resources;[21] and healthcare systems and public policy.[22] The stepwise, systematic approach to healthcare improvement outlined by the 2005 BGHI panels involved a tiered system of resource allotment defined using four levels – basic, limited, enhanced and maximal – based on the contribution of each resource toward improving clinical outcomes.

During the BHGI summits, several key points were identified or demonstrated.[23] First, early breast cancer detection improves outcome in a cost-effective fashion, assuming that treatment is available.[24] Second, the effectiveness of early detection programmes requires public education to foster active individual participation in diagnosis and treatment.[25] Third, clinical breast examination combined with diagnostic breast imaging (breast sonography with or without diagnostic mammography) can facilitate cost-effective tissue sampling techniques for cytological or histological diagnosis.[20] Fourth, breast cancer treatment with partial mastectomy and radiation requires more healthcare resources and infrastructure than mastectomy, but can be provided in a thoughtfully designed limited-resource setting.[26] Fifth, the availability and administration of systemic therapy are critical to improving the survival of breast cancer patients. Sixth, oestrogen-receptor testing allows patient selection for hormonal treatments (tamoxifen, oophorectomy), which is better for patient care and allows the proper distribution of services. Seventh, chemotherapy, which requires a substantial allocation of resources and infrastructure, is needed to treat LABC, which represents the most common clinical presentation of disease in low-resource countries. Furthermore, when chemotherapy is unavailable, patients presenting with locally advanced, hormone-receptor-negative cancers can receive only palliative therapy.[21]

Breast Health Global Initiative Summit 2007
The BHGI guidelines published in 2006[17,20–22] were re-examined, revised and extended at the third global summit held on 1–4October 2007 and hosted by the American Society of Clinical Oncology (ASCO) in Budapest, Hungary.[27] Specific attention was paid to guideline implementation in LMCs in the areas of prevention,[28] early detection,[29] diagnosis[30] and treatment,[31] and special discussion was directed at healthcare systems[32] in LMCs as the foundation through which breast healthcare and all healthcare is supported.

Prevention
Health behaviours that may reduce the risk of breast cancer include prolonged lactation, regular physical activity, weight control, avoiding excess alcohol intake, avoiding prolonged use of exogenous hormone therapy and avoiding excessive radiation.[28] These behaviours, while not proved in clinical trials to reduce risk, are likely to be beneficial. Information on them can be provided as a prevention strategy in LMCs, although the methods of information delivery and follow-up will depend on financial and personnel resources. While the magnitude of absolute

risk reduction based on risk factor management is somewhat unclear, any of these health behaviours can reduce risk of other chronic diseases, so they may be of high interest for general public health in both LMCs and high-income countries.

Early Detection
While prevention is ideal, these strategies will not eliminate breast cancer incidence in LMCs, which remains the most prominent cancer among women even in countries that lack the most common 'Westernised' breast cancer risk factors.[33] Public education is a key first step because early detection cannot be successful if the public is unaware of the problem or has adverse misconceptions about the value of early detection. Social and cultural barriers to early breast cancer detection must be considered in any context where early detection programmes are being established. Public education must include health education messages conveying the idea that breast cancer is curable in the majority of women when it is detected early, diagnosed accurately and treated correctly.

Breast cancer screening modalities include breast self-examination (BSE), clinical breast examination (CBE) and screening mammography. Screening mammography is the single modality that has been shown to improve breast cancer mortality in prospective randomised trials, but its cost is prohibitive in many settings.[34] When screening mammography is employed in LMCs, target populations and screening intervals need to be selected in a way that is judged to be optimal for the overall population and within the scope of available resources. Breast cancer carries poorer prognosis in young patients and its frequency in women below 40 years of age is 20% in Turkey and up to 30% in developing Asian countries.[4,35] Thus, screening younger women in LMCs requires more attention and resources to implement.[29]

Diagnosis
Obtaining a patient's history, specific both to the breast disease and to general health, provides important information for clinical assessment of breast disease and co-morbid disease that might influence breast cancer therapy choices.[30] Focused CBE and complete physical examination provide guidance as to the extent of disease, the presence of metastatic disease and the patient's ability to tolerate more aggressive therapeutic regimens.

Breast imaging, initially with ultrasound and, at higher resource levels, with diagnostic mammography, improves pre-operative diagnostic assessment, and also permits image-guided needle sampling of suspicious lesions. Diagnostic mammography and magnetic resonance imaging (MRI), while helpful for breast-conserving surgery, are not mandatory in LMCs when these resources are lacking.[36] Additional imaging studies (plain chest and skeletal radiography, liver ultrasound) facilitate metastatic work-up and therefore patient treatment selection. Selected laboratory studies (blood chemistry profile, complete blood counts) are required for the safe administration of cytotoxic chemotherapy, which is a basic-level resource for the treatment of node-positive, estrogen-receptor (ER)-negative, and locally advanced disease.

The choice of sampling procedures (fine-needle aspiration biopsy [FNAB], core needle biopsy, or excisional biopsy) should be based on the availability and access to cytopathologists/pathologists in each medical community and the training and experience of the available pathology specialists. FNAB is the most cost-effective diagnostic sampling procedure and has a short turnaround time, but requires specialised

expertise in reading cytology slides.[37] When available, core needle biopsy is preferable to excisional biopsy for diagnosis because it is minimally invasive and does not limit subsequent definitive surgical procedures. Sentinel lymph node (SLN) biopsy, while developed in the context of high-income countries, can actually be used by breast surgery teams in lower-income settings at low cost when the technique is restricted to the use of blue dye without radiotracer.[38] The availability of predictive tumour markers, especially ER testing, is critical to proper selection of cancer therapy when endocrine therapies are available, although quality assessment of immunohistochemical (IHC) testing is important to avoid false-negative results.

Treatment

Surgical Therapy

The ability to perform modified radical mastectomy (MRM) is the mainstay of locoregional treatment at the basic level of breast healthcare.[31] While the MRM (total mastectomy plus level I/II axillary lymph node dissection) is considered fundamental surgical training in high-income countries, surgeons from LMCs may have had less exposure to the procedure and may not be knowledgeable about the operation's proper technical execution. Breast-conserving surgery can be provided as a limited resource but requires proper breast-conserving radiation therapy planning. If this is unavailable, patients should be transferred to a higher-level facility for radiation.

Systemic Therapy

For adjuvant therapy in stage I–III breast cancer, chemotherapy becomes available at the limited level beginning with anthracyclines in stage II at the basic level.[31] The provision of endocrine therapy requires relatively few specialised resources, but ideally necessitates the knowledge of hormone receptor status to ensure treatment of patients most likely to benefit. HER2-targeted therapy is very effective in tumours that overexpress the HER2/neu oncogene, but cost largely prevents the use of this treatment in LMCs.

Tamoxifen is recommended for patients with ER-positive tumours in LMCs. Aromatase inhibitors (AIs) give better results than tamoxifen and are recommended for countries with enhanced and maximal resources, but cost constraints make tamoxifen a very reasonable alternative to AIs. Despite its benefits for disease control, no overall survival benefit has been attributed to AIs over tamoxifen. Hormonal therapy should be used after surgery for at least five years.

Radiation Therapy

Radiation therapy resources are insufficient in LMCs. There is a need to provide the necessary equipment but also to improve quality, technique and resource utilisation in an optimal and sustainable fashion. Radiation therapy can be delivered with a cobalt-60 unit or a linear accelerator (linac) along with other quality assurance tools. Although linac is considered to be the preferred therapy in most settings, telecobalt machines are a reasonable alternative in LMCs. Of note, linac requires consistent electricity for powering and water for cooling the equipment. Applying safe and effective treatment requires well-trained staff, support systems, geographical accessibility and the initiation and completion of treatment without undue delay.[26]

Management of Locally Advanced Disease

LABC and metastatic breast cancer (MBC) are the most common stages at presentation (60–80% of cases) in most LMCs.[11,39,40] The preferred initial treatment of LABC is systemic therapy; if optimal chemotherapy and evaluation are not available, primary MRM is acceptable. However, it should be recognised that without systemic therapy, surgery alone for LABC is unlikely to improve outcome. After responding to systemic therapy, most LABC patients will require an MRM followed by radiation therapy.

Inflammatory breast cancer should be initially managed with pre-operative drug therapy irrespective of resource level. Standard pre-operative therapy includes anthracycline-based chemotherapy. The addition of sequential taxane after anthracycline-based chemotherapy improves pathological responses and breast-conservation rates, but may not improve survival. The high cost and lack of clear survival benefit do not justify taxane use at limited resource levels for metastatic and inflammatory cancer. CMF combination chemotherapy is less potent than anthracycline and taxanes, but may be used in its classic schedule in LMCs because of lower costs and lesser complications. The role of pre-operative endocrine therapy remains to be better defined, but appears to be feasible and acceptable in elderly women.

Healthcare Systems

Poorer outcomes in LMCs may relate to their healthcare systems having a limited capacity for successful early detection, diagnosis and treatment of breast cancer. Impediments to better outcomes include deficits in public education and awareness, insufficient numbers of appropriately trained healthcare workers, limited access to screening/treatment facilities, inadequate supplies of necessary drugs and timeliness of treatment after diagnosis.

Public Education

Obstacles to improving cancer care arise from multiple sources, including deficits in public knowledge and awareness, social and cultural barriers, challenges in organising healthcare and insufficient resources. Early breast cancer detection improves outcome in a cost-effective fashion (assuming that treatment is available), but requires public education to foster active patient participation in diagnosis and treatment.

Professional Education and Training

The education of healthcare professionals, trusted traditional healers, governmental agencies, women and the general public about breast health and breast cancer detection, diagnosis, and treatment is central to the provision of high-quality breast cancer care.

Cancer Centre Organisation

The use of multidisciplinary teams for the management of breast cancer in general, and LABC in particular, is strongly recommended and should be available wherever breast cancer patients are treated.[41] In LMCs where some or several subspecialists are unavailable, the team approach should be adapted to include only two to four members (e.g. a surgeon, a radiologist, a pathologist and a medical and/or radiation oncologist). Every effort should be made to have local pathologists available. Patient advocates may play an important role in encouraging the set-up of multidisciplinary teams and can serve a special role in strengthening patient navigation through a given healthcare system.

Radiation Facilities

The current supply of megavoltage radiotherapy machines (cobalt-60 or linear accelerator) is only 18% of the estimated need in some parts

of the developing world.[42] Cobalt machines are cheaper and have lower quality assurance, maintenance and staffing needs.[43] They have greater simplicity with regards to mechanical and electrical components and operations, and hence are an attractive option in a low-resource setting.

Guideline Implementation

To successfully implement the BHGI guidelines in LMCs, three goals must be addressed. First, dissemination and implementation strategies need to be developed such that the guideline adoption takes place. Rather than assuming we know the optimal approaches to information transfer in LMCs, varied strategies need to be explored and studied in different LMC environments. Second, education of the public, healthcare providers and health system administrators is necessary for guideline adoption to be successful and sustained. Third, effective and affordable technology for detection, diagnosis and treatment must be achieved in target LMCs so that cancer diagnosis and treatment are correctly performed. The BHGI guidelines are designed with sensitivity to the existing diversity in the delivery of breast healthcare and recognise the economic and cultural differences in LMCs. A key characteristic of these guidelines is the concept of stratification into four resource levels, making it applicable to countries with differing resource levels. This approach is more realistic and each country should make an effort to improve its delivery of breast healthcare.[44]

Our next step is to develop methodology to translate these theoretical guidelines into practice. When guidelines are implemented, practical process metrics are needed to assess the adequacy of implementation. These two areas – implementation and evaluation – will be a formidable task in resource-poor countries that already lack the skilled manpower and infrastructure to collect data and evaluate programmatic success. The BHGI guidelines can be used to communicate programmatic needs to hospital administrations, government officials and/or healthcare ministries. The thesis of the BHGI is that these guidelines create a framework for change by defining practical pathways through which breast cancer care can be improved in an incremental and cost-effective fashion.[23] However, guidelines do not in and of themselves improve outcomes for women. Implementation is the critical step by which the value of the guidelines can be measured. The results of pilot research projects and demonstration projects need to be studied and reported, both to determine the effectiveness of the guidelines and to create evidence that will guide and facilitate guideline implementation in other settings. ■

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