BREAST HEALTH GLOBAL INITIATIVE

Breast Cancer in Limited-Resource Countries: Treatment and Allocation of Resources

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■ **Abstract:** Treating breast cancer under the constraints of significantly limited health care resources poses unique challenges that are not well addressed by existing guidelines. We present evidence-based guidelines for systematically prioritizing cancer therapies across the entire spectrum of resource levels. After consideration of factors affecting the value of a given breast cancer therapy (contribution to overall survival, disease-free survival, quality of life, and cost), we assigned each therapy to one of four incremental levels—basic, limited, enhanced, or maximal—that together map out a sequential and flexible approach for planning, establishing, and expanding breast cancer treatment services. For stage I disease, basic-level therapies are modified radical mastectomy and endocrine therapy with ovarian ablation or tamoxifen; therapies added at the limited level are breast-conserving therapy, radiation therapy, and standard-efficacy chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil [CMF], or doxorubicin and cyclophosphamide [AC], epirubicin and cyclophosphamide [EC], or 5-fluorouracil, doxorubicin, and cyclophosphamide [FAC]); at the enhanced level, taxane chemotherapy and endocrine therapy with aromatase inhibitors or luteinizing hormone–releasing hormone (LH-RH) agonists; and at the maximal level, reconstructive surgery, dose-dense chemotherapy, and growth factors. For stage II disease, the therapy allocation is the same, with the exception that standard-efficacy chemotherapy is a basic-level therapy. For locally advanced breast cancer, basic-level therapies are modified radical mastectomy, neoadjuvant chemotherapy (CMF, AC, or FAC), and endocrine therapy with ovarian ablation or tamoxifen; the therapy added at the limited level is postmastectomy radiation therapy; at the enhanced level, breast-conserving therapy, breast-conserving whole-breast radiation therapy, taxane chemotherapy, and endocrine therapy with aromatase inhibitors or LH-RH agonists; and at the maximal level, reconstructive surgery and dose-dense chemotherapy and growth factors. For metastatic or recurrent disease, basic-level therapies are total mastectomy for ipsilateral in-breast recurrence, endocrine therapy with ovarian ablation or tamoxifen, and analgesics; therapies added at the limited level are radiation therapy and CMF or anthracycline chemotherapy; at the enhanced level, chemotherapy with taxanes, capecitabine, or trastuzumab, endocrine therapy with aromatase inhibitors, and bisphosphonates; and at the maximal level, chemotherapy with vinorelbine, gemcitabine, or carboplatin, growth factors, and endocrine therapy with fulvestrant. Compared with the treatment of early breast cancer, the treatment of advanced breast cancer is more resource intensive and generally has poorer outcomes, highlighting the potential benefit of earlier detection and diagnosis, both in terms of conserving scarce resources and in terms of reducing morbidity and mortality. Use of the scheme outlined here should help ministers of health, policymakers, administrators, and institutions in limited-resource settings plan, establish, and gradually expand breast cancer treatment services for their populations. ■

Key Words: breast cancer, chemotherapy, developing countries, endocrine therapy, hormonal therapy, lumpectomy, mastectomy, surgery, treatment

Guidelines for breast cancer treatment have been developed for countries with a high level of health care resources (1–3). In the guidelines presented here, we focus on the central aspects of breast cancer treatment and resource allocation that should form the core of breast cancer treatment programs across the spectrum of settings from basic to maximal levels of medical resources. These guidelines should assist ministers of health, policymakers, administrators, and institutions in

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prioritizing resources when the available resources are limited.

METHODS

As part of the Breast Health Global Initiative (BHGI), a panel of breast cancer experts and patient advocates met in 2002 to develop evidence-based consensus recommendations for the treatment of breast cancer in countries with limited resources. The multinational panel followed a process recommended by the World Health Organization (WHO) to address international breast cancer care in countries with low-level or medium-level resources (4). After reviewing available evidence and consensus-defined breast care guidelines, the panel debated approaches for breast cancer treatment and specifically considered how this treatment may best be provided under the constraints of significantly limited resources. The results of this consensus have been previously published (5,6).

As a continuation of this effort, a multinational panel of breast cancer experts and patient advocates was convened in Bethesda, Maryland, on January 14, 2005, to update and extend the earlier evidence-based consensus guidelines. Specifically the panel was charged with developing recommendations for systematically prioritizing medical therapies across the entire spectrum of resource levels.

The cumulative work product of the 2002 and 2005 panels is the substance of this report. A detailed description of the methodology used is given elsewhere in this supplement (7). Because the treatment of breast cancer is a rapidly evolving area of medical care, these guidelines should be viewed as a work in progress and not as recommendations to be applied indefinitely.

FINDINGS AND RECOMMENDATIONS

Treatment-Related Issues

Principles of Breast Cancer Treatment The treatment of localized invasive breast cancer involves an assessment of the clinical and pathologic features of the tumor and of the health status of the patient; the application of therapy aimed at eradicating local disease in the breast, the chest wall, and the regional lymph nodes; the potential application of systemic therapy aimed at eradicating subclinical, micrometastatic disease; and the follow-up of women after treatment for evidence of recurrent disease. Relapsed or metastatic disease is, with few exceptions, incurable; treatment is aimed at controlling symptoms, with the aim of preserving quality of life and prolonging survival.

Analytic End Points The assessment of the value of treatment for breast cancer may be based on a number of different endpoints or outcomes, including survival, disease-free survival, quality of life, and cost. The recommendations of the panel are made considering all of these end points and outcomes.

Early and Accurate Diagnosis The early and accurate diagnosis of breast cancer is important for optimizing treatment. Compared with the treatment of more advanced breast cancer, the treatment of early breast cancer is less resource-intensive and generally has superior outcomes. Accurate histologic diagnosis is necessary to ensure that women with breast cancer may be given optimal treatment and that healthy women are not erroneously treated. The availability of resources to provide accurate histologic diagnosis and accurate assessment of prognostic and predictive factors, such as the presence or absence of estrogen receptors (ERs) and progesterone receptors (PRs) in a tumor, is crucial for making decisions regarding systemic therapy and for providing cost-effective breast cancer care. The following guidelines offer approaches for the early detection of breast cancer (8) and the diagnosis of breast cancer (9) when health care resources are limited.

Education Education of health care professionals, traditional healers, women, governmental agencies, and the public about breast health and about breast cancer detection, diagnosis, and treatment is central to the provision of high-quality breast cancer care (10).

Access to Breast Cancer Data The availability of cancer registries is highly desirable. Such registries assist in assessing the effectiveness of breast cancer care in the region of the registry and in identifying areas to which limited resources should be applied to optimize breast cancer care. In the absence of cancer registries, cancer incidence can be approximated using GLOBOCAN data provided by WHO (11). However, these estimated statistics cannot be used for monitoring the outcomes of interventions.

Cultural, Religious, and Social Factors Breast cancer, its diagnosis, and its treatment impact the patient, the patient's family, and society in many ways (12). Consequently, treatment considerations must respect local cultural, religious, and social factors.

Staging Systems The use of consistent, reproducible criteria for the staging of breast cancer allows for the comparison of treatments across treatment facilities, the selection of appropriate treatment for the individual patient, and the estimation of overall prognosis. The American Joint Committee on Cancer (AJCC) and the TNM

Committee of the International Union Against Cancer (UICC) have both developed TNM-based tumor staging systems that are similar and compatible (13,14). In this guideline, we use the clinical staging system for breast cancer developed by the AJCC and updated in 2002 (13,15).

Research Although progress has been made in the management of breast cancer, in no clinical situation has the treatment of the disease been optimized. In countries with limited resources, large numbers of patients with breast cancer are treated each year. Limited-resource populations differ from resource-rich populations in having disease that is more advanced at diagnosis and fewer available therapeutic options. Therefore, scientifically robust clinical trials need to be performed specifically in limited-resource countries to address questions special to these populations. In addition, the assumption that the results of studies from wealthy countries universally apply in limited-resource settings requires validation in selected key areas. Whenever possible, participation in well-designed clinical trials appropriate for the resource level of the setting and for the special clinical problems of patients with breast cancer and the regional health care system should be encouraged. These research efforts benefit both the patient and society.

Stage I and II Breast Cancer

Local Treatment. Local treatment of stage I or II disease entails modified radical mastectomy (with postmastectomy radiation therapy in some cases) or breast-conserving therapy.

Modified Radical Mastectomy Local treatment of stage I and II breast cancer normally requires treatment of the entire breast and the axillary lymph nodes with surgery, radiation therapy, or a combination of these. Modified radical mastectomy (mastectomy plus a level 1 and level 2 axillary dissection) is effective local treatment for breast cancer and uses surgical techniques that are widely available (16). This procedure is a rapid treatment and is usually associated with a short posttreatment convalescence and limited long-term complications.

Modified radical mastectomy may be performed alone or in association with reconstruction. A number of breast reconstruction techniques are available that differ greatly in the extent of surgery, complication rates, technical difficulty for the surgical team, and recovery (17). Reconstruction of the breast enhances body image, self-esteem, and psychosocial adjustment for many women, but does not impact the probability of disease recurrence or survival. Unfortunately the cost of breast reconstruction can be prohibitive in countries with limited resources, with costs depending on whether the procedure is performed using implants, myocutaneous flap reconstruction, or a combination of these.

After treatment by mastectomy and adjuvant systemic therapy, there is a substantial risk of local-regional recurrence within the first 1–2 years, particularly in the chest wall, when the ipsilateral axillary lymph nodes are involved by cancer. Postoperative radiation therapy substantially decreases the risk of local-regional recurrence and has also been shown to improve survival among patients with positive lymph nodes (16,18–20).

Breast-Conserving Therapy An alternative treatment to mastectomy is breast-conserving therapy, that is, breast-conserving surgery (a lumpectomy or a "quadrantectomy") followed by radiation therapy (16,21,22). More specifically, breast-conserving therapy entails complete excision of the tumor in the breast, surgical axillary staging, and radiation therapy to the whole breast and potentially to the regional lymph node-bearing areas. Under appropriate conditions, breast-conserving therapy allows preservation of the breast and provides survival equivalent to that of a modified radical mastectomy. The main benefit of breast-conserving surgery for many women is the preservation of body image, which greatly improves their quality of life.

Breast-conserving therapy requires high-quality breast imaging (mammography and, if available, ultrasound) to ensure that complete excision of the tumor is possible and is achieved, and surgical pathology services to ensure tumor-free margins of excision. If it is not feasible to perform detailed margin assessment because pathology services are unavailable, it may still be reasonable to provide local control with surgery and radiation, if it is possible to create wide (greater than 1.0 cm) margins, using the "quadrantectomy" skin-resecting approach.

Other requirements for breast-conserving therapy include surgical services experienced in achieving a good cosmetic result while achieving negative pathologic margins of excision, support systems to allow for the delivery of radiation therapy over a period of weeks, and the availability of radiation therapy facilities. The radiation therapy facilities should have radiation oncologists and support staff (including technologists and medical physicists), megavoltage radiation teletherapy equipment, a simulator, immobilization devices, and a planning computer. In addition, the facilities should be geographically accessible to patients and should allow treatment without long delay.

Studies evaluating the use of wide excision of the tumor alone (i.e., without radiation therapy) have demonstrated higher rates of recurrence in the local-regional area, but

major differences in survival have not been observed (21–25). However, the panel consensus is that patients who can undergo breast-conserving surgery without radiation therapy are the exceptions rather than the rule. In other words, a health care system must be able to provide radiation therapy in order to offer surgery less than modified radical mastectomy for invasive cancer.

Postmastectomy Irradiation of the Chest Wall and Regional Lymph Nodes The chest wall and regional lymph nodes represent a common site of recurrent disease after modified radical mastectomy. Risk factors for local-regional recurrences include involved axillary lymph nodes, large tumor size, positive margins of resection, and involvement of the skin or chest wall (26). In North American breast cancer treatment guidelines, postmastectomy radiation therapy is generally recommended for tumors larger than 5 cm in maximum diameter and those with four or more involved axillary lymph nodes, those with positive surgical margins on resection, and those with involvement of the skin or underlying chest wall (1,27). The use of postmastectomy chest wall radiation therapy decreases the relative risk of local-regional recurrences in all groups of patients, with the largest absolute risk reduction occurring in those with the highest risk for recurrent chest wall disease. Postmastectomy chest wall and regional lymph node irradiation with a proper technique may also improve overall survival in women with axillary lymph node-positive breast cancer (1,18–20,25,27).

There is general agreement that patients with four or more positive axillary nodes should receive radiation therapy after mastectomy, but its role among patients with one to three positive nodes remains controversial (27,28). As for breast-conserving therapy, necessary resources include the availability of radiation therapy facilities (equipment and staff), geographic accessibility, access to treatment without long delay, and support systems to allow delivery of radiation therapy over a period of weeks. Recommended doses and schedules for radiation therapy are outlined in an accompanying article (29).

Systemic Treatment After primary treatment, a large number of women with initial stage I or II breast cancer will ultimately experience a relapse of their disease and die from it. A number of factors are independently prognostic for recurrence, including the number of involved axillary lymph nodes, tumor size, tumor histologic grade, and tumor hormone receptor status (30). These factors may be used to estimate a woman's individual risk for recurrence of disease and of death from disease when given local treatment alone. These same factors may also be used to predict the relative and absolute reduction in risk of recurrence and of death from breast cancer that is achieved with the use of systemic chemotherapy or endocrine therapy (31–33). The decision-making process regarding the use of systemic therapy thus is strongly influenced by the pathologic characteristics of the tumor, especially tumor size, number of involved axillary lymph nodes, and tumor hormone receptor status. Computer-based models have been developed for estimating the risks of breast cancer relapse and death, and the benefits from adjuvant therapy in North American populations of women (34,35). The applicability of these models to other populations has not been assessed.

The availability of careful pathologic assessment, including the determination of tumor ER and PR content, is central to making decisions about systemic adjuvant therapy (36,37). The best current technology for assessing hormone receptor status is with immunohistochemical reactions performed on histologic sections prepared from paraffin-embedded breast tumor tissues that have been fixed in 10% buffered formalin. Across different populations, approximately 55% of breast tumors will stain positive for both ER and PR, 8% will stain positive for ER only, 8% will stain for PR only, and 29–39% of tumors will not stain positive for either receptor (37).

Endocrine Therapy Many breast cancers are responsive to a wide variety of endocrine therapies. Benefit from such therapies may be predicted by the presence of ER or PR in the breast cancer. The use of adjuvant endocrine therapy in women with hormone receptor-positive breast cancer substantially reduces the risk of disease recurrence and death (32). The benefit from endocrine therapy is considerable enough that in the absence of hormone receptor determination (i.e., unknown receptor status), a breast cancer should be considered receptor positive. The most widely used endocrine therapy is the selective estrogen receptor modulator (SERM) tamoxifen. The SERM toremifene is similarly efficacious (38). Evidence suggests that 5 years of tamoxifen therapy is superior to shorter durations of therapy (32). Ten years of tamoxifen therapy provided no advantage over 5 years of therapy in two studies of women with lymph node-negative breast cancer (39,40).

The benefit of chemotherapy is additive to that achieved with the use of tamoxifen (32). Therefore the use of both cytotoxic chemotherapy and tamoxifen provides benefits greater than those from either therapy alone. Tamoxifen is associated with toxicity, including hot flashes and a low risk of thromboembolic disease, endometrial carcinoma, and cataracts. In postmenopausal

women, tamoxifen appears to maintain bone mineral density. In women with hormone receptor-positive tumors, tamoxifen decreases the risk of second, contralateral breast cancers.

In postmenopausal women, the major source of estrogen is the conversion of adrenally synthesized androgen to estrogens by the aromatase enzyme. This conversion is inhibited by the use of selective aromatase inhibitors. These agents do not adequately suppress estrogen levels in women with functioning ovaries. Selective aromatase inhibitors have been evaluated in postmenopausal women in direct comparison with tamoxifen or in sequence with tamoxifen (41,42). Recent evidence from six randomized phase III trials suggests a benefit from the use of aromatase inhibitors in postmenopausal women either alone or sequentially with tamoxifen (43–47). All trials have shown improvement in disease-free-survival in favor of the incorporation of an aromatase inhibitor in the treatment of hormone receptor-positive breast cancer in postmenopausal women.

These gains achieved with aromatase inhibitors must be balanced with the substantial costs associated with these agents as well as their different toxicity profiles (48). Tamoxifen and the aromatase inhibitors are usually very well tolerated, with few patients stopping treatment due to toxicity. However, tamoxifen causes more uterine bleeding, endometrial cancer, and thromboembolism. Substantial numbers of patients who take aromatase inhibitors experience musculoskeletal symptoms, osteoporosis, and fractures.

The aromatase inhibitors should only be used in postmenopausal women with breast cancers that express ER or PR. Many related questions remain unanswered, including the optimal duration of adjuvant endocrine therapy, the ideal sequence of tamoxifen and aromatase inhibitors, and the long-term toxicity and risks of the aromatase inhibitors (49). The aromatase inhibitors should not be used in the treatment of invasive breast cancer in women with functioning ovaries.

Ovarian ablation (e.g., surgical oophorectomy or radiation ablation) or suppression (e.g., use of gonadotropin-releasing hormone or luteinizing hormone–releasing hormone [LH-RH] analogs) with or without tamoxifen is an effective endocrine therapy in the treatment of breast cancer in premenopausal women (33,50,51). Early studies of ovarian ablation or suppression in premenopausal women unselected for the hormone receptor status of their breast cancer demonstrated disease-free and overall survival equivalent to those achieved with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy (33,52). Recent studies have demonstrated that ovarian ablation plus tamoxifen may be superior to CMF chemotherapy in premenopausal women with hormone receptor-positive breast cancer (51).

Cytotoxic Chemotherapy Cytotoxic chemotherapy has an established role in the treatment of invasive breast cancer (31). It is important that this therapy not be unnecessarily delayed, nor should suboptimal doses or schedules of treatment be given (53–55). Policymakers, administrators, providers, and patients must understand that reducing the standard dosage administered or the number of courses given can compromise the benefits of this therapy and that doing so simply to reduce costs is unacceptable.

In women who have undergone local treatment for stage I or II breast cancer, cytotoxic chemotherapy reduces the annual odds of recurrence by approximately 24% (31). This therapy is beneficial to patients regardless of hormone receptor or axillary lymph node status. The magnitude of risk reduction for recurrence or death achieved with combination chemotherapy decreases with increasing age. The efficacy of cytotoxic chemotherapy in women more than 70 years of age remains uncertain. Both physicians offering this treatment and their patients should understand the degree of risk reduction it may provide (31). In general, combination chemotherapy is superior to single-agent chemotherapy. As previously noted, the benefits achieved with cytotoxic chemotherapy are additive to those achieved with tamoxifen (32).

Node-Negative Breast Cancer Many patients with node-negative breast cancer experience recurrence of their disease (13). Independent prognostic factors may be used to distinguish women who are more likely to have a recurrence; these factors include age, tumor grade, histology, and hormone receptor status (56). HER-2/*neu* status and angiolymphatic invasion have also been proposed as independent prognostic factors. Thus women with axillary node-negative disease who have a moderate risk of recurrence can experience benefit from chemotherapy. A variety of chemotherapy regimens can be used; four cycles of doxorubicin and cyclophosphamide (AC) or six cycles of CMF are widely used and appropriate regimens in this context. Women who have small, hormone receptor-positive stage I tumors or comorbid conditions and women who are elderly may derive little benefit from the addition of chemotherapy to endocrine therapy.

Node-Positive Breast Cancer The benefits of adjuvant chemotherapy in patients with node-positive breast cancer have been well established. A number of cytotoxic chemotherapy regimens are effective for treating such disease.

In unselected women, anthracycline-containing chemotherapy appears overall to be superior in efficacy to CMF chemotherapy (31). Classical (oral cyclophosphamide) CMF has proved to be equivalent to anthracycline-based chemotherapy in several clinical trials, and represents an effective and less expensive adjuvant chemotherapy regimen (57). Although the chemotherapy agents in CMF are less expensive than those in AC, CMF requires more frequent visits and intravenous administrations. Furthermore, patient compliance with the oral cyclophosphamide used in the most effective CMF regimen is not assured.

In the adjuvant setting, the addition of taxanes to anthracycline-based chemotherapy may be superior to anthracycline-based chemotherapy alone (58–60). Interpretation of the results of studies of this combined approach is confounded by the potential interaction between endocrine therapy and taxanes. At present, the routine use of taxanes for the treatment of breast cancer in the adjuvant setting is still controversial in women with hormone receptor-positive breast cancer.

Cytotoxic chemotherapy often requires intravenous administration and may be associated with serious and sometimes life-threatening complications. Such therapy must be delivered by an experienced health care team that is familiar with the management of immediate and delayed toxicities of the chemotherapy regimen. In addition, the use of cytotoxic chemotherapy requires the availability of laboratory facilities to monitor white blood cell, red blood cell, and platelet counts; the ability to monitor cardiac function (echocardiography, electrocardiography); pharmacy services to compound the drugs; antiemetics; infusion facilities to administer intravenous chemotherapy; and the availability of medical services to monitor and manage the toxicities of treatment (laboratory facilities, transfusion services for red blood cells and platelets, growth factors, hydration facilities, microbiology laboratories, broad-spectrum antibiotics, and pulmonary and cardiac support systems).

Trastuzumab Four large, multicenter, randomized trials are testing trastuzumab as an addition to the adjuvant treatment of breast cancer patients with overexpression or amplification of HER-2/*neu*. Since the panel meeting in January 2005, the initial results of three of the trials (61–63) have been presented. The first interim analysis of the fourth trial (BCIRG 006) was completed and will be presented at the European Conference on Clinical Oncology meeting in November 2005. These data were not available for analysis during the panel meeting, and in view of the high costs required for testing and treatment, recommendations concerning the use of trastuzumab will be discussed and included in a future version of this article.

Locally Advanced Breast Cancer

Locally advanced breast cancer (LABC) encompasses breast cancer with a wide range of biological behaviors. It includes cancer with the following features:

- T3 tumors: those larger than 5 cm in greatest diameter.
- T4 tumors: those with chest wall involvement, edema, or ulceration of the skin; those with satellite nodules; or inflammatory carcinoma.
- N2 nodal status: metastasis in ipsilateral axillary lymph node(s) fixed to surrounding structures or to each other, or metastasis in clinically apparent ipsilateral internal mammary lymph node(s) without axillary lymph node involvement.
- N3 nodal status: metastasis in ipsilateral internal mammary lymph node(s) with ipsilateral axillary lymph node involvement, or metastasis in ipsilateral infraclavicular or supraclavicular lymph node(s).

Locally advanced breast cancer represents 50–80% of all breast cancer cases in countries with limited resources (64,65). Approximately half of the women die of their disease within 5 years of diagnosis. The treatment of LABC is multidisciplinary, necessitates extensive staging, and requires a combined-modality treatment approach involving surgery, radiation therapy, and systemic therapy. LABC is thus an important health problem that uses substantial resources. Such resources could be used in a more effective way if these cancers were detected at an earlier stage.

The initial management of LABC requires histologic sampling (e.g., core biopsy, incisional biopsy, or skin biopsy) for confirmation of the diagnosis and for determination of hormone receptor status prior to the initiation of neoadjuvant chemotherapy.

Neoadjuvant Chemotherapy The standard approach to LABC requires initial treatment with anthracycline-based neoadjuvant (primary) chemotherapy for four to eight cycles (66,67). Anthracycline-based chemotherapy is preferred over CMF chemotherapy based on indirect evidence from studies of women with axillary node-positive breast cancer or metastatic disease. An adequate dose intensity and total dose of anthracycline should be used (54,55) and treatment should be given without long delay. CMF chemotherapy is appropriate in women who cannot receive anthracycline-containing chemotherapy because of underlying heart disease.

Patients who are treated with neoadjuvant chemotherapy need to be monitored carefully for evidence of response. Patients with LABC whose tumors respond to primary chemotherapy fare better than those with breast cancers that do not respond to primary chemotherapy. A pathologic complete response to primary chemotherapy predicts better survival (68). Patients with responding tumors should receive neoadjuvant treatment for up to eight cycles, depending upon the response of the disease and the chemotherapy regimen utilized; the threshold for anthracycline-associated cardiac toxicity should not be exceeded. Patients who do not respond after four cycles of optimally dosed anthracyclines generally receive local treatment.

In the neoadjuvant setting, the addition of a sequential taxane after anthracycline-based chemotherapy has been demonstrated to increase the rate of pathologic complete response compared with anthracycline-based chemotherapy alone (67,69,70). However, this improvement did not translate into a survival benefit in the largest of these trials (71). Therefore the role of the taxanes in primary chemotherapy for inoperable LABC remains to be defined.

Recent evidence suggests that neoadjuvant endocrine therapy may be beneficial in postmenopausal patients with hormone receptor-positive disease. Patients who are not candidates for any chemotherapy can be initially managed with endocrine therapy (an aromatase inhibitor or tamoxifen in postmenopausal women, or tamoxifen in premenopausal women) and then receive local treatment. Although all of the trials suggest a benefit in favor of aromatase inhibitors over tamoxifen, there are no long-term follow-up or survival data available. Therefore the neoadjuvant use of aromatase inhibitors in LABC remains investigational.

Local Treatment Optimal control of LABC requires, when feasible, local treatment with both surgery and radiation therapy.

Surgery After an initial course of neoadjuvant chemotherapy, the use of surgery is appropriate (1,66). Most patients with LABC will require a modified radical mastectomy, a procedure that remains the standard surgical treatment for operable locally advanced disease. The role of breast-conserving surgery in LABC is unclear and the subject of research. Selected patients may be treated with wide local excision followed by whole-breast and regional lymph node irradiation. Because the majority of patients in developing countries present with locally advanced disease, including positive lymph nodes, treatment with mastectomy without postoperative irradiation of the chest wall and regional lymph nodes would generally be insufficient in this setting.

Radiation Therapy The results of randomized trials and data extrapolated from trials involving women with node-positive disease support the use of local-regional radiation therapy in patients with LABC who are treated with mastectomy (18–20,76,77). This therapy should be delivered to the chest wall and to the supraclavicular and axillary nodes. The recommended dose of radiation is 50 Gy in 25 fractions or equivalent (29). The role of internal mammary lymph node irradiation is unclear.

In patients in whom mastectomy is not possible after neoadjuvant chemotherapy, the use of whole-breast and regional lymph node irradiation alone is appropriate. Patients who are treated with radiation therapy without surgery should be given tumoricidal doses to areas of bulk disease (60–66 Gy in 30–33 fractions or equivalent) (29,78).

Systemic Treatment after Local Treatment After local treatment, systemic treatment may entail chemotherapy and endocrine therapy.

Chemotherapy After local treatment, most patients should be treated with additional chemotherapy. A recently reported study showed a trend toward improved relapse-free and overall survival even in those patients with LABC who had a poor response to anthracycline-based neoadjuvant chemotherapy when given a non-cross-resistant regimen after surgery (79).

Endocrine Therapy The panel's recommendations for adjuvant endocrine therapy of LABC are the same as those for stage I and II breast cancer. After completion of chemotherapy, patients with LABC and hormone receptor-positive tumors should receive adjuvant endocrine therapy. The role of aromatase inhibitors in postmenopausal women with hormone receptor-positive LABC continues to be defined, although their activity should be substantial based on the results achieved with the use of adjuvant or sequential aromatase inhibitors in early stage breast cancer.

Metastatic (Stage IV) or Recurrent Breast Cancer

Patients with detectable metastatic or recurrent breast cancer have, with rare exceptions, incurable disease. The treatment of their breast cancer is based on prognostic and predictive factors and how the available therapies are expected to impact both quality of life and overall survival.

Local-Regional Treatment For patients with metastasis confined to a single site, local treatment with surgery, radiation therapy, or both is appropriate. In women who have undergone breast-conserving therapy and who experience an ipsilateral in-breast recurrence of their

disease, the use of total mastectomy is appropriate treatment. In addition, for those with disease causing or likely to cause a significant catastrophe (e.g., spinal cord compression or central nervous system metastasis), local treatment with surgery or radiation therapy is necessary. Radiotherapy can be very effective for symptomatic relief. Studies have shown, for instance, that after a very short (1–2 days) course of radiotherapy, many patients with painful metastases remain pain free for a considerable proportion of their remaining lives (80). For the majority of patients who have more than localized disease, systemic treatment is necessary.

Systemic Treatment Despite advances in primary and adjuvant therapy, metastatic breast cancer is essentially incurable with standard treatment, and the median survival of patients with metastatic breast cancer is approximately 2 years (81). Systemic treatment in most patients extends survival, but only modestly. The focus of treatment is therefore mainly palliation and improvement of quality of life. The goal is to reduce disease-related symptoms, with minimum treatment-related toxicity.

If the patient has indolent disease, no impending visceral crises, and hormone receptor-positive disease, a trial of endocrine therapy should be given (1). In patients with an impending visceral crisis or with receptor-negative disease, cytotoxic chemotherapy is preferred, as it is more likely to produce a response. Trials comparing combination chemotherapy with single-agent therapy have shown higher rates of response and longer times to first disease progression with the combination, but with greater overall toxicity and with survival that is not different from that with the use of sequential single-agent therapy. A number of active cytotoxic agents can be used, including anthracyclines, taxanes, capecitabine, vinorelbine, cyclophosphamide, methotrexate, and gemcitabine. The choice of drugs depends on financial considerations, preferences regarding the route and schedule of administration, and toxicity.

Surveillance after Treatment of Stage I, II, or III Breast Cancer

After the treatment of stage I, II, or III breast cancer, women remain at risk for the development of recurrent disease for many years. The post-treatment surveillance of women for a recurrence includes history and physical examinations at increasing time intervals in conjunction with yearly mammography evaluation and, in women taking tamoxifen, pelvic examination. The use of surveillance chest radiographs, ultrasound, computed tomography, and blood chemistries has not been demonstrated to substantially aid the diagnosis of recurrent disease, nor has it been demonstrated to enhance overall survival (82–84).

Allocation of Resources

The WHO has stated that "an initial priority, especially in developing countries, should be the development of national diagnostic and treatment guidelines to establish a minimum standard of care, and promote the rational use of existing resources and greater equity in access to treatment services" (4). Some of the therapies used in the treatment of breast cancer require sophisticated technology that is available only in settings with substantial resources, and the cost of establishing and maintaining medical facilities is high. Thus WHO has recommended that medical facilities should initially be concentrated in relatively few places in a country to optimize the use of resources. Medical facilities can be made more widely available when additional resources are available.

Countries with limited resources constitute a heterogeneous group. Important differences often exist with regard to social, economic, and health system development, not only between countries, but also between different regions of the same country. Furthermore, limited-resource countries often have large social and economic inequalities that give rise to a sharp contrast between the poor majority of the population and the wealthy minority, which enjoys a standard of living and a level of health comparable or nearly so to those in affluent countries.

To develop guidelines for breast cancer treatment, and based on WHO recommendations (4), the panel used the following scheme to stratify breast cancer therapies:

- Basic level: Core resources necessary for any breast health care system to function. Core resources can be applied in a single clinic interaction.
- Limited level: Second-tier resources to provide breast health care that improve outcome in a major way. Limited resources may involve single or multiple clinical interactions.
- Enhanced level: Third-tier resources that make some optional treatments available.
- Maximal level: Resources applied in a modern breast health care practice, typical of a country with high-level resources, that improve outcome in a minor way compared with the enhanced level.

This incremental, step-by-step allocation scheme accounts for the aforementioned disparities in a population and provides a means for better ensuring equity in access to care. It is a pragmatic approach that takes into consideration

Table 1. Therapy Overview: Modified Radical Mastectomy and Breast-Conserving Therapy

Therapy	Strengths	Weaknesses	Required resources
Modified radical mastectomy	Effective local treatment Uses surgical techniques widely available Rapid treatment Short posttreatment convalescence Limited long-term complications Radiation therapy can be avoided in some cases	Loss of body image (mutilation) Negative psychosocial impact Radiation therapy is often still necessary	Core surgical resources Trained surgeon General anesthesia Operating room Postoperative care facility Pathology[a] Postmastectomy irradiation of the chest wall and regional lymph nodes[b]
Breast-conserving therapy[c]	Equivalent survival to modified radical mastectomy Preservation of body image for the woman Improved quality of life	Slight increase in the rate of recurrence (in breast) compared with modified radical mastectomy Lower acceptance among less educated people Prolonged treatment course Requires access to a radiation therapy facility	High-quality breast imaging (mammography and, if available, ultrasound) Core surgical resources (same as for modified radical mastectomy) Pathology for margin assessment[a] Surgical services experienced in the procedure Breast-conserving whole-breast irradiation[d] Geographic accessibility Support systems that allow receipt of radiation therapy over a period of weeks

[a]See the accompanying Diagnosis and Pathology guideline in this supplement (9).
[b]See Table 2 for required resources.
[c]Breast-conserving surgery followed by radiation therapy.
[d]Required resources are the same as those for postmastectomy radiation therapy (see Table 2).

the fact that although the ultimate goal of every health care system is to offer optimal care to all patients, resource constraints may necessitate intermediate steps toward this goal.

According to the incremental nature of this scheme, each successive level assumes that all of the resources for the preceding levels are already available to all patients in the health unit (a community, a city, a region, or a country). For example, in order for the health system to be able to offer enhanced-level treatments, it should first be able to provide to all patients in the health unit with basic- and limited-level treatments. This sequential strategy should prevent substantial inequity in the use of limited resources, and it prioritizes resource utilization for the greatest benefit of the largest number of people possible.

In applying this scheme, the short-term goal is to advance to the next higher level, and the long-term goal is to advance to the maximal level. Of note, 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 one national cancer center that provides treatment at the enhanced or maximal level. How these facilities are linked nationally (e.g., for referral) will be country specific.

In developing these guidelines, the panel first reviewed the evidence on the strengths and weaknesses of each cancer therapy, and devised checklists of the resources required to deliver that therapy safely and effectively. The resulting overviews of each therapy are presented in Tables 1–4. Next, for each of four disease stages—stage I,

Table 2. Therapy Overview: Postmastectomy Radiation Therapy

Therapy	Strengths	Weaknesses	Required resources
Postmastectomy irradiation of the chest wall and regional lymph nodes	Reduces the relative risk of local-regional recurrences in all groups of women May also improve overall survival in women with axillary lymph node-positive breast cancer	Overall survival benefit still controversial Prolonged treatment course Requires access to a radiation therapy facility	Core radiation therapy equipment Megavoltage radiation equipment Treatment simulation capability Immobilization devices Treatment-planning computer system Dosimetry equipment Core radiation therapy staff or tasks Radiation oncologist Medical physicist Radiation therapy technologist/positioning Support systems that allow receipt of radiation therapy over a period of weeks

Table 3. Therapy Overview: Adjuvant Endocrine Therapy

Therapy	Strengths	Weaknesses	Required resources
Adjuvant endocrine therapy	Adjuvant endocrine therapy in women with ER- or PR-positive or unknown breast cancer substantially reduces the risks of disease recurrence and death Limited toxicity Easily administered by general practitioner or surgeon Benefits increase with increasing risk of recurrence	Optimally requires availability of ER and PR determination Benefits are limited in low-risk breast cancer Compliance varies	Pathology[a] Tumor steroid hormone receptor content Number of involved axillary lymph nodes Tumor size Tumor histologic grade Resources for management of toxicities Pharmacy/drug distribution
Specific adjuvant endocrine therapies			
Tamoxifen	Improves disease-free and overall survival in all age groups and nodal subsets and with or without chemotherapy in ER- or PR-positive or unknown disease Reduces the risk of second, contralateral breast cancers Appears to maintain bone mineral density in postmenopausal women Inexpensive Known long-term toxicity profile	Toxicity: Hot flashes Thromboembolic disease Endometrial carcinoma Cataracts	Same as for adjuvant endocrine therapy (see above); resources for management of toxicities should include gynecology
Aromatase inhibitors	In postmenopausal women with hormone receptor-positive resected breast cancer: Anastrozole is superior to tamoxifen Anastrozole or exemestane sequentially with 2–3 years of tamoxifen is superior to tamoxifen alone Extended therapy with letrozole following 4.5–6 years of tamoxifen is superior to 5 years of tamoxifen alone There is no increase in thromboembolic events or endometrial cancer	Absolute difference between aromatase inhibitors and tamoxifen alone in terms of disease-free survival is small Impact on survival is uncertain Substantially higher cost of aromatase inhibitors compared with tamoxifen alone Toxicity: increased risk of bone fracture, arthralgias	Same as for adjuvant endocrine therapy (see above)
Ovarian ablation	Effective therapy in the treatment of breast cancer in premenopausal women with ER- or PR-positive or unknown breast cancer Equivalent to CMF chemotherapy Oophorectomy plus tamoxifen may be considered an appropriate adjuvant endocrine therapy Likely to be a cost-effective strategy compared with chemotherapy alone	Long-term adverse effects of estrogen deprivation in young women High cost if LH-RH agonist used	Core surgical resources[b] Pathology: same as for adjuvant endocrine therapy (see above) Resources for management of toxicities

[a]See the accompanying Diagnosis and Pathology guideline in this supplement (9).
[b]The same as the core surgical resources for breast surgery (see Table 1).
CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; ER, estrogen receptor; LH-RH, luteinizing hormone–releasing hormone; PR, progesterone receptor.

stage II, LABC, and metastatic and recurrent breast cancer—the panel stratified therapies by level after extensive consideration and discussion of the previously described analytic endpoints. The resulting recommendations for resource allocation are presented in Tables 5–8.

For further discussion and comments on the integration of recommendations for treatment and the allocation of resources with the conclusions from other panels (Early Detection and Access to Care, Diagnosis and Pathology, and Health Care Systems and Public Policy) see the overview article (7). Selected areas are identified where disagreement exists among the panels regarding stratification levels for resources.

CONCLUSION

The treatment of breast cancer requires an integrated, multidisciplinary approach using multiple resources in a focused, disease-oriented manner. Existing evidence-based guidelines outlining optimal approaches to the treatment of breast cancer have been defined and disseminated, but do consider the multiple deficits in infrastructure and the availability of therapies in limited-resource countries. Marked heterogeneity exists among countries and also between regions of the same country with regard to social, economic, and health system development. Therefore a uniform approach for all limited-resource

Table 4. Therapy Overview: Adjuvant Cytotoxic Chemotherapy

Therapy	Strengths	Weaknesses	Required resources
Cytotoxic chemotherapy	Established role in the treatment of women with invasive breast cancer Combination chemotherapy is superior to single-agent chemotherapy	Expensive Absolute benefits decrease with increasing age Requires a chemotherapy-experienced health care team	Laboratory facilities to monitor white blood cell, red blood cell, platelet counts, and chemistry Ability to monitor cardiac function Echocardiography Electrocardiography Pharmacy services to compound the drugs Antiemetics Infusion facilities to administer intravenous chemotherapy Medical services to monitor and manage the toxicities of treatment Microbiology and general laboratory facilities Transfusion services for red blood cells and platelets Growth factors Hydration facilities Broad-spectrum antibiotics Pulmonary and cardiac support systems
Specific cytotoxic chemotherapy regimens			
Classical (oral) CMF	Equivalent to regimens of anthracycline-based chemotherapy An effective and less expensive adjuvant chemotherapy regimen	Prolonged treatment Multiple infusions Variable patient compliance	Same as for cytotoxic chemotherapy (see above)
Anthracycline-based chemotherapy (e.g., AC, EC, or FAC)	Superior overall to CMF chemotherapy in unselected patients Generally a short course of therapy	Cardiac toxicity Expensive	Same as for cytotoxic chemotherapy (see above)
Taxanes	Taxane chemotherapy sequential to anthracycline-based chemotherapy is superior to anthracycline-based chemotherapy alone	Expensive Additional toxicity when given after or with anthracycline-based chemotherapy Benefit in ER-positive disease is small	Same as for cytotoxic chemotherapy (see above)

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; ER, estrogen receptor; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide.

countries is neither practical nor realistic. We propose a stepwise, systematic approach for building national or regional breast health treatment systems by stratifying health care resources into four levels—basic, limited, enhanced, and maximal—based on the contribution of incremental resources in improving clinical outcomes.

The therapy overview checklist tables, by listing the required resources for each intervention, can help in the

Table 5. Treatment and Allocation of Resources: Stage I Breast Cancer

	Local-regional treatment		Systemic treatment (adjuvant)	
Level of resources	Surgery	Radiation therapy	Chemotherapy	Endocrine therapy
Basic	Modified radical mastectomy			Ovarian ablation Tamoxifen
Limited	Breast-conserving therapy[a]	Breast-conserving whole-breast irradiation as part of breast-conserving therapy Postmastectomy irradiation of the chest wall and regional nodes for high-risk cases	Classical CMF[b] AC, EC, or FAC[b]	
Enhanced			Taxanes	Aromatase inhibitors LH-RH agonists
Maximal	Sentinel node biopsy Reconstructive surgery		Growth factors Dose-dense chemotherapy	

[a]Breast-conserving therapy requires mammography and reporting of margin status.
[b]Requires blood chemistry profile and complete blood count (CBC) testing.
AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone–releasing hormone.

Table 6. Treatment and Allocation of Resources: Stage II Breast Cancer

	Local-regional treatment		Systemic treatment (adjuvant)	
Level of resources	Surgery	Radiation therapy	Chemotherapy	Endocrine therapy
Basic	Modified radical mastectomy	—[a]	Classical CMF[b] AC, EC, or FAC[b]	Ovarian ablation Tamoxifen
Limited	Breast-conserving therapy[c]	Breast-conserving whole-breast irradiation as part of breast-conserving therapy Postmastectomy irradiation of the chest wall and regional nodes for high-risk cases		
Enhanced			Taxanes	Aromatase inhibitors LH-RH agonists
Maximal	Sentinel node biopsy Reconstructive surgery		Growth factors Dose-dense chemotherapy	

[a]Chest wall and regional lymph node irradiation substantially decrease the risk of postmastectomy local recurrence. If available, it should be used as a basic-level resource.
[b]Requires blood chemistry profile and complete blood count (CBC) testing.
[c]Breast-conserving therapy requires mammography and reporting of margin status.
AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone–releasing hormone.

organization of breast cancer treatment units. The goal of this practical approach is to make rational use of existing resources and to ensure equity in access to treatment services.

The establishment of a "minimum standard of care" as a foundation on which to build an incremental model for improving breast cancer care is proposed. The incremental allocation of resources based on our recommendations leads to the development of a multidisciplinary breast cancer treatment system that gives priority to the most effective, resource-sensitive treatment interventions. This incremental approach facilitates the establishment of the best breast cancer treatment possible across the broad spectrum of health care resources available in diverse regions on a global scale. Thus health benefits for both women with breast cancer and society in general are optimized.

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Table 7. Treatment and Allocation of Resources: Locally Advanced Breast Cancer

	Local-regional treatment		Systemic treatment (adjuvant)	
Level of resources	Surgery	Radiation therapy	Chemotherapy	Endocrine therapy
Basic	Modified radical mastectomy		Neoadjuvant AC, FAC, or classical CMF[a]	Ovarian ablation Tamoxifen
Limited		Postmastectomy irradiation of the chest wall and regional nodes		
Enhanced	Breast-conserving therapy[b]	Breast-conserving whole-breast irradiation	Taxanes	Aromatase inhibitors LH-RH agonists
Maximal	Reconstructive surgery		Growth factors Dose-dense chemotherapy	

[a]Requires blood chemistry profile and complete blood count (CBC) testing.
[b]Breast-conserving therapy requires mammography and reporting of margin status.
AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone–releasing hormone.

Table 8. Treatment and Allocation of Resources: Metastatic (Stage IV) and Recurrent Breast Cancer

	Local-regional treatment		Systemic treatment		
Level of resources	Surgery	Radiation therapy	Chemotherapy	Endocrine therapy	Supportive and palliative therapy
Basic	Total mastectomy for ipsilateral breast tumor recurrence[a]			Ovarian ablation Tamoxifen	Nonopioid and opioid analgesics
Limited		Palliative radiation therapy	Classical CMF[b] Anthracycline monotherapy or in combination[b]		
Enhanced			Taxanes Capecitabine Trastuzumab	Aromatase inhibitors	Bisphosphonates
Maximal			Growth factors Vinorelbine Gemcitabine Carboplatin	Fulvestrant	

[a]Required resources are the same as those for modified radical mastectomy.
[b]Requires blood chemistry profile and complete blood count (CBC) testing.
CMF, cyclophosphamide, methotrexate, and 5-fluorouracil.

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