BREAST HEALTH GLOBAL INITIATIVE

Breast Cancer in Limited-Resource Countries: Diagnosis and Pathology

Roman Shyyan, MD, MSc,* Shahla Masood, MD,† Rajendra A. Badwe, MD, MBBS,‡ Kathleen M. Errico, PhD, ARNP,§ Laura Liberman, MD,¶ Vahit Ozmen, MD,# Helge Stalsberg, MD,^ Hernan Vargas, MD,€ and László Vass, MD, PhD,¢ for the Global Summit Diagnosis and Pathology Panel

**Lviv Cancer Center, Lviv, Ukraine; †University of Florida, Jacksonville, Florida; ‡Tata Memorial Hospital, Mumbai, India; §University of Washington and Seattle University, Seattle, Washington; ¶Memorial Sloan-Kettering Cancer Center, New York, New York; #Istanbul University, Istanbul, Turkey; ^University Hospital of North-Norway, Tromsø, Norway; €Harbor-UCLA Medical Center, Torrance, California; and ¢University Teaching Hospital F. FLÓR of Pest County, Budapest, Hungary*

■ **Abstract:** In 2002 the Breast Health Global Initiative (BHGI) convened a panel of breast cancer experts and patient advocates to develop consensus recommendations for diagnosing breast cancer in countries with limited resources. The panel agreed on the need for a pathologic diagnosis, based on microscopic evaluation of tissue specimens, before initiating breast cancer treatment. The panel discussed options for pathologic diagnosis (fine-needle aspiration biopsy, core needle biopsy, and surgical biopsy) and concluded that the choice among these methods should be based on available tools and expertise. Correlation of pathology, clinical, and imaging findings was emphasized. A 2005 BHGI panel reaffirmed these recommendations and additionally stratified diagnostic and pathology methods into four levels—basic, limited, enhanced, and maximal—from lowest to highest resources. The minimal requirements (basic level) include a history, clinical breast examination, tissue diagnosis, and medical record keeping. Fine-needle aspiration biopsy was recognized as the least expensive reliable method of tissue sampling, and the need for comparing its clinical usefulness with that of core needle biopsy in the limited-resource setting was emphasized. Increasing resources (limited level) may enable diagnostic breast imaging (ultrasound ± mammography), use of tests to evaluate for metastases, limited image-guided sampling, and hormone receptor testing. With more resources (enhanced level), diagnostic mammography, bone scanning, and an onsite cytologist may be possible. Mass screening mammography is introduced at the maximal-resource level. At all levels, increasing breast cancer awareness, diagnosing breast cancer at an early stage, training individuals to perform and interpret breast biopsies, and collecting statistics about breast cancer, resources, and competing priorities may improve breast cancer outcomes in countries with limited resources. Expertise in pathology was reaffirmed to be a key requirement for ensuring reliable diagnostic findings. Several approaches were again proposed for improving breast pathology, including training pathologists, establishing pathology services in centralized facilities, and organizing international pathology services. ■

Key Words: breast cancer, core needle biopsy, developing countries, diagnosis, fine-needle aspiration biopsy, imaging, mammography, surgical biopsy, triple test, ultrasound

Correct diagnosis is a prerequisite for successful cancer treatment. The diagnosis of breast cancer relies on a combination of clinical examinations, pathology tests, and imaging studies that provide the clinician with relevant prognostic and predictive information to counsel patients and initiate cancer treatment. In these guidelines, we focus on the central aspects of breast cancer diagnosis and pathology that should form the core of the breast cancer program in countries with limited resources. In addition, we expand on the previous guidelines formulated in 2003 by stratifying the recommendations explicitly into resource levels.

Address correspondence and reprint requests to: Roman Shyyan, MD, MSc, Surgical Oncology, Lviv Cancer Center, Hasheka St. 2a, 79000, Lviv, Ukraine, or e-mail: roma@txnet.com.

The Breast Journal, Volume 12 Suppl. 1, 2006 S27–S37

METHODS

An international group of breast cancer experts and advocates met at a summit in Bethesda, Maryland, on January 12–15, 2005, to reexamine consensus recommendations for breast cancer diagnosis and pathology in countries with limited resources. In the morning, summit participants gave presentations on topics related to the

diagnosis and pathology of the disease, and current approaches and barriers to delivery of these services in parts of the world where resources are markedly constrained. In the afternoon, the Diagnosis and Pathology Panel, a subgroup of conference participants, reviewed the available evidence, the Breast Health Global Initiative (BHGI) 2003 guidelines on diagnosis (1), and current international guidelines on breast cancer diagnosis; debated approaches to diagnosis and pathology under the constraints of limited resources; and drafted preliminary recommendations. The panel, representing 12 countries with resource levels spanning the spectrum, followed a process similar to that followed in the first BHGI summit (2), based on methods initiated by the World Health Organization (WHO) (3), to address cancer care in countries with low- or medium-level resources.

One of the panel's aims was to take the 2003 guidelines to the next level by making specific recommendations about resource stratification for diagnosis and pathology. The stratification scheme specifies four levels: basic, limited, enhanced, and maximal. These levels refer to the method or the set of methods (e.g., surgical biopsy, imaging) used in a health unit (e.g., a community, city, or region) and not necessarily to a country overall; the different levels were conceptualized as coexisting within the same country.

In this stratification scheme, basic-level methods are those that are absolutely required to have a breast program. Limited-level methods provide a large improvement in outcome relative to the basic level. Enhanced-level methods provide a small improvement in outcome relative to the limited level. And maximal-level methods are those recommended by existing guidelines that assume unlimited resources. These levels were conceptualized as incremental. Therefore, every successive level assumes that the health care unit already has all the methods needed for the lower level(s) and now has sufficient resources to add more methods. In this way, the scheme provides a logical, systematic framework for building diagnostic and pathology capacity.

The methods used are described in greater detail in the accompanying overview (4). The final work product of the Diagnosis and Pathology Panel is the substance of this report.

FINDINGS AND RECOMMENDATIONS

Issues Related to Diagnosis and Pathology

Goal of Diagnosis The primary goal of diagnosis in countries with limited resources, just as in countries with abundant resources, is to accurately distinguish benign from malignant breast lesions and invasive from non-invasive breast lesions, thereby permitting delivery of timely and appropriate care. The panel reaffirmed three main themes of the first summit: 1) that improving breast cancer awareness and education facilitates diagnosis of the disease at an early stage; 2) that early diagnosis is advantageous because it is lifesaving and cost effective, and requires less aggressive therapy; and 3) that collecting accurate national statistics about breast cancer (type, tumor size, stage, treatment, and outcome), available resources (personnel, equipment, and facilities), and competing priorities (health or other issues) will help to tailor these guidelines for breast cancer diagnosis and pathology to the needs of an individual country.

Definitions The panel also reaffirmed the key distinction between a clinical diagnosis and a pathology diagnosis. Clinical diagnosis refers to a diagnosis based on a combination of the history, findings on a clinical breast examination (CBE), and results of breast imaging studies (mammography and ultrasound). These findings may suggest a benign or malignant diagnosis.

Pathology diagnosis, also called tissue diagnosis, refers to a diagnosis based on the microscopic features of cells or tissues, which allow a lesion to be properly categorized pathologically. The interpretation of these microscopic findings is the definitive diagnosis (i.e., the final word).

Simplicity of the Process Simplicity in the diagnostic process is critical in limited-resource settings because patients may face numerous barriers that prevent repeated visits. To address such barriers and increase compliance, diagnostic tests and tissue sampling techniques should be used in a combination that allows establishing the pathology diagnosis and assessing the extent of the disease in one visit.

Quality of the Process Panelists emphasized that it is important not only that a diagnostic test is available but also that it is done competently so that a correct diagnosis is made and the treatment providers can be confident about the results. Specific recommendations on quality assurance and standardization of practices are provided in a later section.

Correlation of Findings Regardless of the type of tissue sampling that is performed for diagnosis, the pathology results must be correlated with all other information, including clinical findings and the findings of imaging

studies (if available), to assess for concordance. The panel reaffirmed that this so-called triple test is key for ensuring accurate diagnosis. If the clinical findings, imaging findings, or both are highly suggestive of breast cancer, but the biopsy yields benign findings, the biopsy result is considered discordant; it may be necessary to repeat the biopsy to ensure an accurate diagnosis.

Importance of the System Implementation of a breast pathology program requires more than the resources needed to perform and interpret the biopsy. This program must be integrated in a comprehensive system that addresses other facets of care. For example, there must be mechanisms in place for specimen labeling and transportation, documentation of pathology results in the patient's medical record, and communication of the results to other health care providers and the patient. Follow-up is also essential after biopsy and enables evaluation of diagnostic performance; this practice is discussed in greater detail in the section on record keeping.

Diagnostic Process

The diagnostic process entails both initial diagnosis (to establish the presence or absence of breast cancer) and, when cancer is present, staging (to determine the extent of disease) (5); the latter may include an examination to ascertain whether a patient has metastases. Knowledge of the stage of the disease is important for estimating prognosis and making choices between curative and palliative therapy. The panel again noted the importance of using the triple test for accurate initial diagnosis and agreed on the need for a judicious approach for the use of tests after diagnosis for staging.

Clinical Assessment The methods used in clinical assessment for breast cancer include a history, CBE, physical examination, and when appropriate, assessment for metastatic disease.

History Taking a medical history is the initial step in evaluating a breast complaint. Providers should obtain baseline information regarding symptoms, menopausal status, and breast cancer risk factors, and should document the findings in the patient's record. In addition to obtaining the history relevant to breast health, the panel endorsed obtaining an overall medical history to appropriately document the presence or absence of other illnesses that might affect treatment decisions.

Clinical Breast Examination CBE is a procedure whereby a health care provider examines a woman's breasts, chest wall, and axillae; it can be used as either a screening test or a diagnostic test (6). When used as a diagnostic test (i.e., in a patient with signs or symptoms of a breast problem), CBE plays a fundamental role in providing information about breast changes that may signal the presence of cancer. A breast mass, nipple discharge, or other changes in the skin, nipple, or both are frequent initial symptoms of breast cancer that require prompt attention (6,7). The panel agreed that CBE is important for confirming the presence of a dominant mass and other breast abnormalities, for documenting tumor size, and for determining the local extent of disease.

Physical Examination In patients with findings suggestive of early breast cancer, physical examination is unlikely to provide diagnostic information beyond that provided by history and CBE, although it may reveal evidence of other illnesses that may have potential implications for treatment decisions, such as malnutrition or AIDS. In patients with findings suggestive of advanced breast cancer, physical examination may provide information about the presence of metastases in the lymph nodes and distant sites, as discussed below.

Assessment of Metastatic Disease Assessment of metastatic disease in patients with primary breast cancer is a component of cancer staging. Patients with metastatic breast cancer uniformly succumb to their disease; however, survival may range from a few months to several years (8). In countries with limited resources, patients often present with disease that has already metastasized, and proper staging is valuable in planning cancer treatment.

Obtaining a medical history is the first step in the assessment of metastatic disease. Pulmonary, musculoskeletal, and abdominal symptoms may raise clinical suspicion for metastatic disease and prompt a diagnostic examination. Physical examination may reveal lymphadenopathy, hepatomegaly, or bone tenderness that likewise suggests metastatic disease.

Laboratory measurement of the serum alkaline phosphatase level as a method of screening for bone and liver metastases has been suggested. However, elevated alkaline phosphatase levels have high false-positive and false-negative rates. Thus, this test is not a good predictor of bone or liver metastases in patients with breast cancer (9) and cannot be recommended.

A number of studies have evaluated the role of bone scanning, chest radiography, and liver ultrasonography in breast cancer staging at the time of diagnosis. Overall the yield for these imaging studies is low and stage dependent. The prevalence of metastases detected by imaging techniques is near zero in patients with stage I or II breast cancer (0.5%), but dramatically increases in patients with

stage III disease (8–40%) (10). In a study of patients with stage III disease, the findings of bone scan, chest radiograph, and liver ultrasound were positive for metastases in 14%, 7%, and 6% of cases, respectively (11). An additional important consideration is the occurrence of false-positive results in tests with a low yield. Such results cause additional testing at a significantly increased cost and unnecessarily subject patients to anxiety, discomfort, and less frequently, morbidity.

Therefore, the panel recommends a judicious approach to laboratory and imaging studies to assess metastatic disease, regardless of the level of resources available. Extensive, routine laboratory and imaging studies are not justifiable in patients with early breast cancer in the absence of symptoms or physical findings. In contrast, in patients with T4 or N1–2 breast cancer, bone scanning, chest radiography, and liver ultrasonography have a higher yield and are indicated when resources permit. The panel recommends their introduction at the limited-resource level (chest radiograph and liver ultrasound) and enhanced-resource level (bone scan).

Breast Imaging The breast imaging modalities used in diagnosing breast lesions include diagnostic mammography and diagnostic ultrasound.

Diagnostic Mammography Diagnostic mammography is complementary to physical examination in evaluating women with signs and symptoms of breast cancer, and provides a more accurate assessment of the extent of disease in women known to have cancer (12). It also provides additional information about the contralateral breast because a small but significant percentage (3–5%) of women with breast cancer will have synchronous or metachronous cancer in the other breast (13).

Diagnostic mammography requires trained personnel, equipment, facilities, reporting, and follow-up systems, and establishing and maintaining a high-quality diagnostic mammography program is relatively costly (14). Moreover, this imaging cannot replace the need for a pathology diagnosis in women with signs or symptoms of breast cancer. The panel identified the following factors influencing the decision to introduce diagnostic mammography: 1) the availability of the equipment and skilled personnel, 2) the cost of film for mammography, 3) the predominant size of lesions at presentation (e.g., palpable versus nonpalpable disease), 4) the patient population being assessed (e.g., younger women, who have dense breasts and who may be more likely to have cysts, versus older women), and 5) alternatives for establishing the diagnosis (e.g., aspiration to establish that a mass is a cyst). In addition, in countries with limited resources, few women are able to undergo breast-conserving therapy because of the typically advanced stage of cancer at presentation and because this therapy is resource intensive (15). In this context, the benefit of determining the extent of cancer within the breast seems low when compared with the cost of a diagnostic mammography program.

The panel concluded that the introduction of diagnostic mammography can be recommended at the limited level of resources. If mastectomy is the only available surgical treatment for breast cancer, diagnostic mammography is not essential; however, if breast conservation is offered, diagnostic mammography is necessary to determine if there is cancer elsewhere in the same quadrant (multifocal disease) or in different quadrants (multicentric disease).

Approaches to treating breast cancer hinge on the stage at the time of diagnosis because treatment for locally advanced breast cancer differs from that for early stage breast cancer (15). Mammography can help distinguish early stage from late-stage cancer, although this benefit varies depending on the patient and the cancer.

Diagnostic Ultrasound Breast ultrasound can be used as a screening test (when performed in asymptomatic women, with the goal of identifying otherwise occult breast cancer) or as a diagnostic test (when performed in women with abnormalities on physical examination, mammography, or both). For women who have a palpable breast lump or a focal symptom, ultrasound can play an important role in further evaluation of the clinical findings. In this group of women, ultrasound has three important contributions: distinguishing simple cysts from solid masses (16), providing an estimation of the likelihood of malignancy in a solid mass (17), and guiding tissue sampling for a pathology diagnosis (18,19).

Ultrasound, like mammography, can help determine the extent of cancer within the breast, which again is important when breast-conserving therapy can be offered to women. Ultrasound is more widely available than mammography in countries with limited resources and is particularly useful in women with palpable lesions, as noted above. In addition, this modality can also help assess the status of the axilla, can guide a minimally invasive (needle) biopsy in the axilla, and can allow examination of the liver to detect metastatic disease. The panel therefore recommends introduction of diagnostic ultrasound at the limited-resource level.

Pathology Diagnosis The diagnosis of breast cancer carries prognostic and therapeutic implications that are life changing for a woman. The panel strongly and uniformly recommends that all women suspected of having breast cancer have an accurate pathology diagnosis that confirms

the presence of the disease before beginning definitive treatment. This includes women who have clinical findings strongly suggestive of cancer. A pathology diagnosis should not be bypassed, even when health care resources are very limited, because a misdiagnosis of breast cancer can lead to erroneous treatment of women without breast cancer, which is harmful to the woman and wasteful of treatment resources.

The most basic function of pathology in breast care is the formulation of timely and accurate diagnosis. It can be achieved by the use of appropriate biopsy (tissue sampling) techniques, optimal tissue processing, and competent interpretation of gross and microscopic pathology findings. A successful pathology service requires timely and accurate comprehensive reporting, as well as archiving of slides, tissue blocks, and reports with accurate patient and specimen identification.

A variety of methods are available for sampling a breast lesion to determine if it is cancer, and they have comparable accuracy if properly performed. Two general groups of methods are reliable for obtaining a pathology diagnosis: minimally invasive biopsy, also called percutaneous or needle biopsy (i.e., fine-needle aspiration biopsy [FNAB] and core needle biopsy), and surgical biopsy (i.e., incisional biopsy and excisional biopsy).

The panel reaffirmed that the choice among these methods in the limited-resource setting will be influenced by factors such as availability of the necessary equipment and expertise (1). Regardless of the method used, procedures should be performed by appropriately trained staff and with sterile technique to minimize the risk of infectious complications. In addition, single-use equipment should be disposed of after use, and multiuse equipment should be properly sterilized between uses.

Minimally Invasive Biopsy Minimally invasive biopsy has advantages over surgical breast biopsy. The former is less invasive, less expensive, does not cause scarring or deformity, and can be performed in a clinic, obviating the need for an operating room (20). For women with early stage breast cancer, minimally invasive biopsy can convert what would otherwise have been two operations (surgical biopsy for diagnosis, followed by definitive surgery for treatment) into one operation (a single definitive surgery after needle biopsy); for women with locally advanced or metastatic breast cancer, it can provide a pathology diagnosis, enabling initiation of treatment (21).

Minimally invasive biopsy techniques differ with respect to two parameters: the needle used (fine needle versus core needle) and the method used to guide needle placement (palpation versus imaging). For most palpable lumps, the needle can be placed under the guidance of palpation; for other lesions, the needle may be placed with image guidance (discussed below).

Fine-needle aspiration biopsy involves removal of cellular specimens with a small (22- or 25-gauge) needle (22). Advantages of FNAB include that it is the least invasive and least expensive breast biopsy method. Disadvantages include the need for personnel trained in obtaining and interpreting breast cytology specimens; small sample size, and difficulty in interpreting atypical and indeterminate lesions, as well as a moderately high frequency of insufficient samples. The frequency of insufficient samples, reported in as many as one-third of palpable (23) and nonpalpable (24) lesions, can be minimized by obtaining multiple (e.g., five or more) specimens and by having a cytologist onsite to review them, when feasible (22).

Fine-needle aspiration biopsy is the most cost-effective approach to biopsy if properly performed (25–27) and if a quality cytopathology service is available. Provisions can be made to refer the pathology interpretation of the FNAB samples to other regional consultants in specialized centers. In countries with limited resources, the panel recommends introduction of FNAB at the basic level, provided the accompanying requirement for a quality cytopathology service is also met.

Core needle biopsy is also commonly used to obtain tissue samples from breast lesions, particularly nonpalpable and image-detected abnormalities (28). In this procedure, tissue specimens are removed with a cutting needle (usually 14-gauge) and automated gun. Obtaining multiple (e.g., three to five) specimens maximizes the chance of definitive diagnosis. However, as for FNAB, the success of this procedure depends on appropriate patient selection, the availability of experienced pathologists, and correlation of the pathology findings with the clinical and imaging information. Core needle biopsy has limitations similar to those of FNAB with respect to small sample size and difficulty in interpreting atypical and indeterminate lesions (29). Given this modality's higher cost and limited availability in many countries, the panel recommends its introduction at the limted-resource level.

Of note, the value and cost-effectiveness of FNAB versus core needle biopsy has never been formally studied in a limited-resource setting, and panelists therefore cited the need for a well-designed study to compare the utility of the two methods. Such a study would evaluate the feasibility of using minimally invasive procedures to provide tissue diagnosis in limited-resource settings and measure the effectiveness of local health care providers' training in the performance of these procedures.

Surgical Biopsy Surgical biopsy is the traditional method for obtaining a pathology diagnosis of breast lesions, and it is considered the gold standard. Surgical biopsy provides tissue for histologic diagnosis and takes advantage of techniques and pathology expertise currently available in most countries. The disadvantages of this method include its invasive nature and substantial cost when performed in an operating room. However, costs are reduced if it is performed in the outpatient setting (30).

In countries with limited resources, a majority of women with breast cancer have large primary tumors at the time they seek medical care (17). A surgical biopsy under local anesthesia is more expensive, time-consuming, and traumatic than minimally invasive biopsy, but provides the greatest amount of histologic information. The panel concluded that this procedure should be introduced at the basic-resource level, provided a country also meets the pathology requirements for that level.

Record Keeping*

All Global Summit panels identified the need for a system of record keeping in countries with limited resources to document the clinical stage of the breast cancer and clinical outcomes, among other information.

Medical Records Permanent, quality medical records are essential for documenting diagnostic findings, treatments given, and patient outcomes, and for communicating this information to other health care providers. In addition, well-kept medical records are useful for generally assessing the prevailing patterns of breast cancer presentation and care, which can be helpful for planning resource allocation and monitoring changes as additional resources are applied. The panel agreed that medical records should be available at the basic-resource level.

In terms of diagnosis and pathology, the medical record should document the patient's name and unique medical record number, dates, clinical findings, imaging findings, types of biopsies performed (including needle used, whether guidance was used, and number of samples obtained), pathologic findings reported according to the pathologic TNM (pTNM) system, whether a cytologist was onsite during the procedure (for FNAB), and the patient's outcome (clinical, imaging, and surgical pathology information, when available). The panel endorsed the use of the clinical TNM (cTNM) staging system (31) and, because tumor size substantially affects prognosis (32) and a given T stage applies to a wide range of sizes, the panel also encourages documentation of tumor size. Quality pathology reports, discussed below, should become part of the medical record.

Follow-Up In addition to its obvious benefits in terms of continuity of care and support for patients, follow-up is essential for assessing and improving diagnostic performance, as previously noted. The frequency of insufficient samples with a diagnostic method should be documented at the time of the procedure and the outcome data collected during follow-up should be analyzed to assess a given method's true-negative, false-negative, true-positive, and false-positive rates. This follow-up information should help to optimize biopsy procedures based on outcome data. The panel recommends that some form of follow-up be in place at the basic-resource level, recognizing that the method and frequency of follow-up will vary by setting.

Pathology Report Elaboration of the pathology or cytology report is the responsibility of the pathologist, but requires close collaboration with surgeons and radiologists. Accurate pathologic diagnosis starts with the clinician, who provides relevant historical and physical examination information. The need for the triple test to minimize errors in diagnosis is particularly important when minimally invasive biopsy (FNAB or core needle biopsy) is used (33).

Prognostic and predictive parameters are useful to guide treatment because there is significant variability in the natural history of breast cancer (34). Predictive factors, in contrast, are clinical, pathologic, and biologic characteristics that are used to estimate the likelihood of response to a particular type of therapy (35). Features such as tumor size, lymph node status, histopathologic type, and tumor grade should be universally documented because of their limited cost and important prognostic significance (36–41). Conceptually, these features are useful in providing patients an estimate of prognosis, which facilitates their education, involvement in their therapy, and respect for their autonomy.

In the limited-resource setting, assessment of the expression of estrogen receptors, progesterone receptors, or both is recommended only if hormonal therapy such as tamoxifen, aromatase inhibitors, or surgical or medical ovarian ablation is possible. The panel recommends introduction of this assessment at the limited level, although some panelists favored introducing it at the basic level instead.

*The recommendations of this panel were integrated with those of the Health Care Systems and Public Policy panel and are presented in the matrix guideline Table 1 from that panel's consensus statement (43).

Measurement of HER-2/*neu* is problematic because the cost of immunohistochemical analysis, fluorescence in situ hybridization, and trastuzumab therapy is prohibitively expensive in the limited-resource setting; therefore the panel recommends introducing this test only at the maximal-resource level. Such important pathologic pieces of information as the status of the microscopic margin of resection and the status of the sentinel node are recommended at the limited level and maximal level, respectively, where resources also allow breast conservation and sentinel lymph node biopsy.

Registries Whereas medical records provide critical information about breast health and breast care for individual patients, registries provide such information for the populations they cover. Depending on their coverage, registries may be resource intensive. The panel therefore recommends introduction of local, regional, and national registries at the limited, enhanced, and maximal levels, respectively.

Quality Assurance and Standardization

Because treatment decisions and estimations of prognosis are based on the results of diagnostic and pathology tests, these tests must be done at a level that ensures that the information they provide is reliable and useful. Therefore the panel recommends consideration of formal quality assurance procedures whereby diagnostic findings are recorded and the accuracy of these findings is monitored over time. Such procedures help identify areas for improvement. Standardization of pathology procedures and reports is important for better characterizing breast lesions and improving communication among health care providers. A pathology service should provide not only diagnostic information, but also prognostic and predictive information, whenever possible.

Diagnostic capacity is critical to the success of a comprehensive breast health care program in countries with limited resources. This central role of diagnosis highlights the importance of training health care providers in pathology and its subspecialties (e.g., cytopathology) (42). The availability of pathologists with expertise in breast pathology differs around the globe. Approaches for improving breast pathology include training pathologists, establishing pathology services in centralized facilities, and organizing international pathology services. Panelists expressed opposing viewpoints about the advisability of training nonpathologist health care providers (such as nurses) to perform preliminary steps in diagnostic procedures, such as obtaining aspirates for FNAB.

Stratification of Diagnostic and Pathology Methods

The panel's consensus guidelines for stratification of diagnostic and pathology methods by level of resources are summarized in Table 1, and the requirements for competent performance of each of these methods are shown in Table 2

Table 1. Resource Allocation for Diagnosis and Pathology

Level of resources	Clinical	Pathology	Imaging and laboratory tests
Basic	History Physical examination Clinical breast examination Surgical biopsy Fine-needle aspiration biopsy	Interpretation of biopsies Cytology or pathology report describing tumor size, lymph node status, histologic type, tumor grade	
Limited	Core needle biopsy Image-guided sampling (ultrasonographic ± mammographic)	Determination and reporting of ER and PR status Determination and reporting of margin status	Diagnostic breast ultrasound ± diagnostic mammography Plain chest radiography Liver ultrasound Blood chemistry profile/CBC
Enhanced	Preoperative needle localization under mammographic or ultrasound guidance	Onsite cytopathologist	Diagnostic mammography Bone scan
Maximal	Stereotactic biopsy Sentinel node biopsy	HER-2/*neu* status IHC staining of sentinel nodes for cytokeratin to detect micrometastases	CT scanning, PET scan, MIBI scan, breast MRI

CBC, complete blood count; CT, computed tomography; ER, estrogen receptor; IHC, immunohistochemistry; MIBI, 99mTc-sestamibi; MRI, magnetic resonance imaging; PET, positron emission tomography; PR, progesterone receptor.

Table 2. Resource Requirements for Specific Diagnostic, Pathology, and Related Methods

Method	Trained personnel[a]	Equipment	Facility	Data collection
Clinical assessment				
History	❑ Perform (MD, NP)	None	❑ Clinic	❑ Medical record
CBE	❑ Perform (MD, NP)	None	❑ Clinic	❑ Medical record
Pathology diagnosis				
FNAB	❑ Perform (MD) ❑ Interpret (cytologist)	❑ Needles and syringes ❑ Slides ❑ Fixative ❑ Cytology fluid ❑ Labels ❑ Light microscope	❑ Clinic ❑ Cytology lab	❑ Cytology report
Core needle biopsy	❑ Perform (MD) ❑ Interpret (pathologist)	❑ Automated gun ❑ Needles ❑ Formalin ❑ Slides ❑ Labels ❑ Stains ❑ Light microscope ❑ Microtome	❑ Clinic ❑ Pathology lab	❑ Pathology report
Surgical biopsy	❑ Perform (surgeon) ❑ Interpret (pathologist)	❑ Surgical equipment ❑ Microtome ❑ Formalin ❑ Paraffin for embedding ❑ Slides ❑ Labels	❑ Clinic or operating room	❑ Pathology report
IHC	❑ Perform (pathologist, technologist)	❑ Resources for surgical biopsy (see above) ❑ IHC stains	❑ Pathology lab	❑ Pathology report
Transport	❑ Messenger	❑ Transportation ❑ Containers	None	❑ Tracking system
Diagnostic imaging				
Mammography	❑ Perform and QA (technologist) ❑ Interpret (radiologist)	❑ Mammography machine ❑ Film ❑ Light box	❑ Clinic	❑ Breast imaging report
US	❑ Perform and QA (technologist) ❑ Interpret (radiologist)	❑ US machine	❑ Clinic	❑ Breast imaging report
Image-guided biopsy	❑ Technical assistance (technologist) ❑ Perform (radiologist)	❑ US or mammography machine ❑ Resources for FNAB or core (see above) ❑ Localizing grids ❑ Wires and/or blue dye[b]	❑ Clinic	❑ Medical record
Reporting[c]	❑ Reporter (e.g., MD, NP) or transcriptionist	❑ Pen and paper, typewriter, or computer	❑ Office	❑ Medical record
Follow-up and QA[d]	❑ Record keeper	❑ Recording: pen and paper, typewriter, or computer ❑ Communication: computer, phone, fax, or mail	❑ Clinic	❑ Data sorted by patient and procedure

CBE, clinical breast examination; FNAB, fine-needle aspiration biopsy; IHC, immunohistochemistry; MD, medical doctor (physician); NP, nurse practitioner; QA, quality assurance; US, ultrasound.
[a]The personnel used for this purpose at the maximal-resource level are listed in parentheses. Depending on available resources and expertise in the limited-resource setting, other individuals may be trained to fill some of the functions listed here.
[b]Needed for preparative localization of the tumor if the breast-conserving surgery is planned.
[c]Essential for all aspects of breast diagnosis.
[d]Essential for all aspects of breast diagnosis. The collection and recording of follow-up data are essential for individual patient care as well as for assessment of the performance of different diagnostic procedures. Data should be sorted by the individual patient as well as by the procedure.

in a checklist format. The personnel suggested in the latter table refer to those generally used in countries with a maximal-resource level; the panel agreed that creative use of existing personnel, cross-training individuals to perform different tasks, and development of incentives to attract and maintain trained personnel may be useful for meeting personnel requirements in the limited-resource setting.

Although there was generally agreement as to the diagnostic and pathology methods that were feasible in countries with limited resources, there was some debate within and between panels regarding the level at which specific methods should be introduced. The panel noted that the resource level applied in a given health unit will depend on factors such as available personnel, equipment, and facilities; the needs of the population served; and competing health care priorities. Such health system considerations are discussed in an accompanying guideline (43).

Basic Level Minimal diagnostic and pathology requirements include the ability to take a history, perform CBE and physical examination, make a pathology diagnosis of breast cancer by interpreting the specimens obtained by surgical biopsy or FNAB, determine clinical and pathologic stage, and record this information in the medical record. The panel emphasized that even at the basic level, the availability of accurate information regarding breast cancer size and stage at presentation, and breast cancer treatment and outcome is invaluable to determine the next steps required to decrease breast cancer mortality.

Limited Level At the limited level, characterized by increasing but still constrained resources, the panel recommends that diagnostic breast imaging with ultrasound or mammography be available. Core needle biopsy, as a minimally invasive method for obtaining histological diagnosis, can be performed on palpable masses at low cost, and can provide tissue for immunohistochemical staining to determine hormone receptor status prior to surgical intervention. At the high end of limited resources, the panel also suggests introducing image-guided needle sampling. Panelists agreed that ultrasound guidance for needle biopsy has the advantages of lower cost and multipurpose use of the equipment; in contrast, stereotactic guidance was considered to require a higher (maximal) level of resources. The accompanying guidelines addressing treatment recommend breast-conserving surgery at the limited-resource level (44); if breast conservation is offered, diagnostic breast imaging is essential. Although the panel uniformly agreed about the importance of assessing hormone receptor status, which in the context of limited resources is practical only if hormonal therapy is available, it disagreed as to whether such assessments should be introduced at the basic or limited level. Also at the limited level, the health unit may have the capability for determining and reporting the margin status and better assessment for metastatic disease with plain chest radiography, liver ultrasound, and blood chemistry profile/complete blood count.

Enhanced Level At the enhanced level, the level at which breast conservation is available (44), the panel recommends introduction of core needle biopsy with mammographic or ultrasound guidance and preoperative needle localization under mammographic or ultrasound guidance. Improved pathology services may involve the presence of an onsite cytopathologist. Higher-level resources should also allow the use of more sophisticated methods of metastatic examination, such as bone scanning.

Maximal Level The panel's main focus was on developing guidelines for diagnosis and pathology in countries with less than maximal resources. However, maximal resources make available additional diagnostic and related methods that can further improve outcomes in patients with breast cancer, including (but not limited to) stereotactic biopsy, sentinel node biopsy, determination of HER-2/*neu* status, use of immunohistochemical staining to detect micrometastases, and advanced imaging studies. Panelists agreed that although resource constraints may limit the methods that can be applied in the short term, the maximal level should be the goal for the long term.

PANELISTS

Roman Shyyan, MD (panel cochair), Lviv Cancer Center, Lviv, Ukraine; Shahla Masood, MD (panel cochair), University of Florida, Jacksonville, Florida; Justus Apffelstaedt, MD, FCC(S), MBA, University of Stellenbosch, Tygerberg, South Africa; Rajendra Badwe, MD, MBBS, Tata Memorial Hospital, Mumbai, India; Arturo Beltran-Ortega, MD, National Cancer Institute-Mexico, Mexico City, Mexico; Louis Chow, MD, University of Hong Kong Medical Center, Hong Kong; Kathleen Errico, PhD, ARNP, University of Washington, and Seattle University, Seattle, Washington; Laura Liberman, MD, Memorial Sloan-Kettering Cancer Center, New York, New York; Riccardo Masetti, MD, Catholic University of Rome, Rome, Italy; Vahit Özmen, MD, Istanbul University, Istanbul, Turkey; Paola Pisani, PhD, International Agency for Research on Cancer, Lyon, France; Rengaswamy Sankaranarayanan, MBBS, MD, International Agency for Research on Cancer, Lyon, France; Helge Stalsberg, MD, University Hospital of North-Norway, Tromsø, Norway; Hernan Vargas, MD, Harbor-UCLA Medical Center, Torrance, California; László Vass, MD, PhD, University Teaching Hospital F. FLÓR of Pest County, Budapest, Hungary.

Acknowledgments

Financial support for this work is described elsewhere in this supplement (4,45). The Diagnosis and Pathology Panel wishes to acknowledge the participation of the following individuals in the discussions leading to the generation of these guidelines: Ute-Susann Albert, MD, MIAC, Philips-University of Marburg, Marburg, Germany; Benjamin O. Anderson, MD, University of Washington, Seattle, Washington; Zeba Aziz, MD, Allama Iqbal Medical College, Lahore, Pakistan; Susan Braun, Susan G. Komen Breast Cancer Foundation, Dallas, Texas; Maira Caleffi, MD, PhD, Breast Center at Hospital Moinhos de Vento em Porto Alegre, and Breast Institute of Rio Grande do Sul, Porto Alegre, RS, Brazil; Oladapo Campbell, MD, University College Hospital, Ibadan, Nigeria; Robert W. Carlson, MD, Stanford University Medical Center, Stanford, California; Margaret Fitch, MD, Toronto Sunnybrook Regional Cancer Center, and Supportive Care, Cancer Care Ontario, Toronto, Ontario, Canada; Gabriel Hortobagyi, MD, University of Texas MD Anderson Cancer Center, Houston, Texas; Julio Ibarra, MD, Long Beach Memorial Medical Center and Orange Coast Memorial Medical Center, Long Beach, California; Raimund Jakesz, MD, Vienna Medical University, Vienna, Austria; Ranjit Kaur, Reach to Recovery International, Petaling Jaya, Malaysia; Richard Love, MD, Ohio State University Comprehensive Cancer Center Columbus, Ohio; Mary Onyango, Kenya Breast Health Programme, Nairobi, Kenya; Tatiana Soldak, MD, CitiHope International and Belarusian Breast Cancer Screening and Early Diagnosis Project, Andes, NY; Cheng-Har Yip, MD, University Malaya Medical Center, Kuala Lumpur, Malaysia.

REFERENCES

1. Vargas HI, Anderson BO, Chopra R, *et al.* Diagnosis of breast cancer in countries with limited resources. *Breast J* 2003;9(suppl. 2):S60–66.

2. Anderson BO, Braun S, Carlson RW, *et al.* Overview of breast health guidelines for countries with limited resources. *Breast J* 2003;9(suppl. 2):S42–50.

3. World Health Organization. Executive summary. In: *National Cancer Control Programmes: Policies and Managerial Guidelines*. Geneva. Switzerland: World Health Organization, 2002:i–xxiv.

4. Anderson BO, Shyyan R, Eniu AE, *et al.* Breast cancer in limited-resource countries: an overview of the Breast Health Global Initiative 2005 guidelines. *Breast J* 2006;12(suppl. 1):S3–15.

5. Sobin LH, Wittekind C, eds. *TNM Classification of Malignant Tumours*, 6th ed. New York: John Wiley & Sons, 2002.

6. Morrow M. Physical examination of the breast. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. *Diseases of the Breast*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2004:29–32.

7. Margolesse RG, Fisher B, Hortobagyi GN, *et al.* Neoplasms of the breast. In: Bast RC Jr, Kufe DW, Pollock RE, *et al.*, eds. *Holland-Frei Cancer Medicine*, 5th ed. Hamilton, Ontario, Canada: BC Decker, 2000:1735–822.

8. Insa A, Lluch A, Prosper F, Marugan I, Martinez-Agullo A, Garcia-Conde J. Prognostic factors predicting survival from first recurrence in patients with metastatic breast cancer: analysis of 439 patients. *Breast Cancer Res Treat* 1999;56:67–78.

9. Brar HS, Sisley JF, Johnson RH. Value of preoperative bone and liver scans and alkaline phosphatase in the evaluation of breast cancer patients. *Am J Surg* 1993;165:221–23.

10. Myers RE, Johnston M, Pritchard K, Levine M, Oliver T, Breast Cancer Disease Site Group of the Cancer Care Ontario Practice Guidelines Initiative. Baseline staging tests in primary breast cancer: a practice guideline. *CMAJ* 2001;164:1439–44.

11. Puglisi F, Follador A, Minisini AM, *et al.* Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications. *Ann Oncol* 2005;16:263–66.

12. Winchester DP, Cox JD. Standards for breast-conservation treatment. *CA Cancer J Clin* 1992;42:134–62.

13. Egan RL. Bilateral breast carcinoma: role of mammography. *Cancer* 1976;38:931–38.

14. Olivotto IA, Kan L, Mates D, King S. Screening mammography program of British Columbia: pattern of use and health care system costs. *CMAJ* 1999;160:337–41.

15. Carlson RW, Anderson BO, Chopra R, *et al.* Treatment of breast cancer in countries with limited resources. *Breast J* 2003;9(suppl. 2):S67–74.

16. Jokich PM, Monticciolo DL, Adler YT. Breast ultrasonography. *Radiol Clin North Am* 1992;30:993–1009.

17. Stavros AT, Thickman D, Rapp DL, *et al.* Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. *Radiology* 1995;196:123–34.

18. Smith DN, Rosenfield Darling ML, Meyer JE, *et al.* The utility of ultrasonographically guided large-core needle biopsy: results from 500 consecutive breast biopsies. *J Ultrasound Med* 2001;20:43–49.

19. Liberman L, Ernberg LA, Heerdt A, *et al.* Palpable breast masses: is there a role for percutaneous imaging-guided core biopsy? *AJR Am J Roentgenol* 2000;175:779–87.

20. Liberman L. Percutaneous image-guided core breast biopsy: state of the art at the millennium. *AJR Am J Roentgenol* 2000;174:1191–99.

21. Liberman L, Goodstine SL, Dershaw DD, *et al.* One operation after percutaneous diagnosis of nonpalpable breast cancer: frequency and associated factors. *AJR Am J Roentgenol* 2002;178:673–79.

22. Vargas HI, Masood S. Implementation of a minimally invasive breast biopsy program in countries with limited resources. *Breast J* 2003;9(suppl. 2):S81–85.

23. Chaiwun B, Settakorn J, Ya-In C, Wisedmongkol W, Rangdaeng S, Thorner P. Effectiveness of fine-needle aspiration cytology of the breast: analysis of 2,375 cases from northern Thailand. *Diagn Cytopathol* 2002;26:201–5.

24. Pisano ED, Fajardo LL, Caudry DJ, *et al.* Fine-needle aspiration biopsy of nonpalpable breast lesions in a multicenter clinical trial: results from the Radiologic Diagnostic Oncology Group V. *Radiology* 2001;219:785–92.

25. Logan-Young W, Dawson AE, Wilbur DC, *et al.* The cost-effectiveness of fine-needle aspiration cytology and 14-gauge core needle biopsy compared with open surgical biopsy in the diagnosis of breast carcinoma. *Cancer* 1998;82:1867–73.

26. Rimm D, Stastny J, Rimm E, Ayer S, Frable W. Comparison of the costs of fine-needle aspiration and open surgical biopsy as methods for obtaining a pathologic diagnosis. *Cancer* 1997;81:51–56.

27. Lannin DR, Silverman JF, Walker C, Pories WJ. Cost-effectiveness of fine needle biopsy of the breast. *Ann Surg* 1986;203:474–80.

28. Meunier M, Clough K. Fine needle aspiration cytology versus percutaneous biopsy of nonpalpable breast lesions. *Eur J Radiol* 2002;42:10–16.

29. Hoda SA, Rosen PP. Practical considerations in the pathologic diagnosis of needle core biopsies of breast. *Am J Clin Pathol* 2002;118:101–8.

30. Vargas HI, Agbunag RV, Khalkhali I. State of the art of minimally invasive breast biopsy: principles and practice. *Breast Cancer* 2000;7:1–10.

31. Breast. In: Green F, Page D, Fleming I, *et al.*, eds. *AJCC Cancer Staging Manual*, 6th ed. New York: Springer, 2002:221–40.

32. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status and survival in 24,740 breast cancer cases. *Cancer* 1989;63:181–87.

33. Vargas HI, Vargas MP, Gonzalez KD, *et al.* Diagnosis of palpable breast masses: ultrasound-guided large core biopsy in a multidisciplinary setting. *Am Surg* 2004;70:867–71.

34. Contesso G, Mouriesse H, Friedman S, *et al.* The importance of histologic grade in long-term prognosis of breast cancer: a study of 1010 patients uniformly treated at the Institute Gustave-Roussy. *J Clin Oncol* 1987;5:1378–86.

35. Allred DC, Harvey HM, Berardo MD, *et al.* Prognostic and predictive factors in breast cancer by immunohistochemical analysis. *Mod Pathol* 1998;11:155–68.

36. Wolberg WH, Street WN, Mangasarian OL. Importance of nuclear morphology in breast cancer prognosis. *Clin Cancer Res* 1999;5:3542–48.

37. Quiet CA, Ferguson DJ, Weichselbaum RR, Hellman S. Natural history of node positive breast cancer: the curability of small cancers with a limited number of positive nodes. *J Clin Oncol* 1996;14:3105–11.

38. Page DL, Jensen RA, Simpson JF. Routinely available indicators of prognosis in breast cancer. *Br Cancer Res Treat* 1998;51:195–208.

39. Elston CW, Ellis JO. Pathological prognostic factors in breast cancer: experience from a long study with long-term follow-up. *Histopathology* 1991;19:403–10.

40. Veronese SM, Gambacorta M, Gottardi O, *et al.* Proliferation index as a prognostic marker in breast cancer. *Cancer* 1993;71:3926–31.

41. Pinder S, Ellis IO, O'Rourke S, *et al.* Pathological prognostic factors in breast cancer. Vascular invasion: relationship with recurrence and survival in a large series with long-term follow-up. *Histopathology* 1994;24:41–47.

42. Masood S. The expanding role of pathologists in the diagnosis and management of breast cancer: worldwide excellence in breast pathology program. *Breast J* 2003;9(suppl. 2):94–97.

43. Anderson BO, Yip CH, Ramsey SD, *et al.* Breast cancer in limited-resource countries: health care systems and public policy. *Breast J* 2006;12(suppl. 1):S54–69.

44. Eniu AE, Carlson RW, Aziz Z, *et al.* Breast cancer in limited-resource countries: treatment and allocation of resources. *Breast J* 2006;12(suppl. 1):S38–53.

45. Financial acknowledgments. *Breast J* 2006;12(suppl. 1):S121.