BREAST CANCER INITIATIVE 2.5
Making breast health a global priority

DIAGNOSIS

Clinical Assessment, Diagnostic Imaging and Staging

Knowledge Summary

UICC global cancer control
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Clinical Assessment, Diagnostic Imaging and Staging

INTRODUCTION

A clinical assessment of breast complaints is a crucial first step in breast cancer diagnosis. Diagnosis requires an efficient referral process and timely coordination of services that include: 1) initial presentation for evaluation of a breast complaint, to include a medical history and a clinical breast exam (CBE); 2) imaging studies; 3) biopsy of suspicious lesions; 4) pathology (histology/cytology) studies and 5) return visit to review the results of diagnostic studies and to discuss a treatment plan. A lack of coordination of care and poor patient access to care can cause delays in definitive diagnosis and initiation of treatment, with the potential to negatively influence outcomes.

The accurate and timely diagnosis of breast cancer is essential to improving patient outcomes. Patient delays in seeking medical care for a breast complaint and system delays in breast cancer diagnosis, all contribute to late initiation of treatment and affect quality of care and outcomes. The number of patient visits before a definitive diagnosis has been identified as a barrier to quality care and patient adherence to recommended procedures. The number of patient visits may be reduced by providing diagnostic biopsy services at primary care sites and removing unnecessary or duplicative referral steps.

Most small breast masses are not cancer. Training primary care professionals in clinical assessment of breast cancer can contribute to the diagnosis of disease at an earlier stage. A clinical assessment should include a cancer risk assessment, complete medical history, review of signs and symptoms of breast cancer and clinical breast exam (see *Early Detection: Breast Health Awareness and Clinical Breast Exam*).

Breast findings suspicious for cancer require referral for tissue biopsy for definitive diagnosis and imaging studies to determine the stage of cancer. An efficient, clearly outlined and well-functioning referral system that minimizes barriers and costs, as well as unnecessary and repeated visits and evaluations/duplication of tests for diagnosis, will help reduce the number of women who are lost to follow up. Data on breast cancer stage at presentation should be collected in a regional or national cancer registry and can be used to assess disease burden and evaluate efforts to improve early diagnosis. Quality improvement measures that are useful in evaluating breast care programs include: time from presentation of a suspicious mass to diagnosis, time from a definitive diagnosis to treatment and percentage of patients completing recommended treatment.

Centralized services may improve costs and quality of care, but potential delays in communicating diagnostic information from a centralized facility to the primary care provider and patient must be addressed. Centralized services must be balanced with patient access to care issues, such as the time required to travel for care and the availability and cost of transportation. Centralized pathology services can be used only if timely diagnostic reports can be provided to the primary care provider.

KEY SUMMARY

Diagnostic services for breast cancer

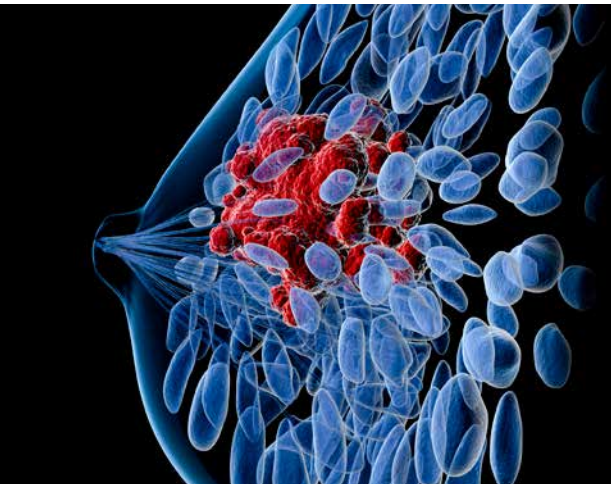
- Clinical assessment of breast complaints is a crucial first step in breast cancer diagnosis.
- Patient access to imaging services to confirm suspicion of breast cancer is essential.
- Breast cancer characterization and staging is a critical component of diagnosis and treatment planning.
- An efficient, clearly outlined and well-functioning referral system that minimizes costs, repeated visits and duplication of tests for diagnosis will help reduce the number of women who are lost to follow up.
- Benign findings are more common than malignant findings; therefore, removal of the breast should never be used as a diagnostic method.
- Timely reporting of breast diagnostic tests to the appropriate provider and patient is critical to improving outcomes.

Health systems and coordination of care

- Establish resource-appropriate guidelines and protocols regarding diagnostic biopsies, staging exams and reports.
- Increase health professional expertise at all levels of health care in breast cancer diagnosis, including signs and symptoms, clinical assessment, timely referral for biopsies and diagnostic imaging and pathology services.
- Improve existing diagnostic capacity to provide timely pathologic diagnosis of suspicious breast findings.
- Consider specialized or centralized facilities for efficiency of resource utilization while assuring patient access to care.
- Ensure patients are educated about the multistep process required to diagnose breast cancer.
- Report cancer data to the local and national cancer registry.

Resource-stratified pathways across the continuum of care

- Follow a resource-stratified pathway in developing breast cancer assessment, diagnosis and staging programs to allow for coordinated, incremental program improvement across the continuum of care. A 'pathway' is a progression of resource investment, program development and quality improvements.
- Program design and improvements should be based on outcome goals, identified barriers and needs and available resources.



POINTS FOR POLICYMAKERS:

OVERVIEW

Preplanning

- Identify data sources to estimate disease incidence, burden and stage distribution.
- Identify data on time from presentation of a suspicious breast concern to definitive diagnosis and time from referral for imaging and pathology studies to report generation.
- Identify who will lead the process as well as other stakeholders and key decision makers.

Planning Step 1: Where are we now?

Investigate and assess

- Evaluate existing diagnostic and staging practices and training programs.
- Assess workforce capacity, quality of services and available resources.
- Review and assess referral processes to optimize the health system for timely diagnosis and coordination of care.
- Evaluate patient access and barriers to accessing diagnostic services (structural, sociocultural, personal, financial).

Planning Step 2: Where do we want to be?

Set objectives and priorities

- Identify gaps and introduce policies, training and services to reduce barriers to providing a timely and accurate histopathologic diagnosis.
- Set objectives that advance the breast cancer diagnosis process.
- Optimize the system for timely breast cancer diagnosis. Breast cancer diagnosis requires coordination of care that includes clinical assessment, imaging studies, biopsy capabilities and pathology services with timely report generation.
- Assess the feasibility of interventions.

Planning Step 3: How do we get there?

Implement and evaluate

- Partner with and engage appropriate stakeholders.
- Follow a resource-stratified approach for breast cancer diagnosis that considers available resources and equitable access to services for all women.
- Implement quality assurance measures and monitor process metrics.

WHAT WE KNOW

Diagnostic studies

Breast ultrasound: Breast ultrasound is usually available in low-resource settings and can be a valuable adjunct when distinguishing benign from malignant masses. Ultrasound can help distinguish cysts from solid masses and can be used to identify enlarged lymph nodes. Ultrasound can also be used to guide biopsy techniques, inform surgical management and potentially identify additional lesions in the same breast or opposite breast.

Mammography: Diagnostic mammography is performed for patients who present with breast concerns suspicious for breast cancer after CBE or screening mammography. In diagnostic mammography, additional views are obtained to detect suspicious areas that may warrant biopsy. Diagnostic mammography can be used to evaluate the extent of disease in the affected breast and evaluate the opposite breast.

Any finding suspicious for cancer on CBE should be biopsied regardless of mammogram findings because imaging tests may be falsely negative. Biopsy and pathology studies should occur after imaging studies because swelling or bleeding from the biopsy procedure will interfere with imaging studies.

Breast magnetic resonance imaging: The appropriate use of breast magnetic resonance imaging (MRI), which is resource intensive and associated with high costs, is still being investigated. Studies suggest that breast MRI may have high sensitivity and low specificity in the evaluation of breast lesions, with more accurate estimates of tumor size, but the routine use of breast MRI is unlikely to result in fewer positive margins, lower rates of reoperation or reduced local recurrence rates and may increase the likelihood of unilateral and contralateral mastectomy (without evidence of impact on survival). Breast MRI is not currently recommended for diagnosis in limited resource settings (see *Diagnosis*).

Fine needle aspiration: In some settings, fine needle aspiration (FNA) with cytology analysis may identify women at the primary point of care who need to be referred immediately for definitive diagnosis and treatment. If a triple diagnosis exam (CBE, ultrasound or mammogram and FNA biopsy) approach reveals any findings of concern, the next diagnostic step is a tissue-based biopsy (core needle, incisional or excisional) and imaging studies for staging as appropriate.

Additional laboratory tests: Once a tissue diagnosis of cancer is confirmed, additional laboratory tests may determine if cancer has spread beyond the breast and lymph nodes and will determine the function of organs that may be affected by systemic cancer therapy. Liver function tests and serum alkaline phosphatase are often considered if there is a suspicion of metastatic disease, although the sensitivity and specificity of these tests are limited. Candidates for chemotherapy or hormonal therapy should have a complete blood count and liver and renal function tests, in addition to having menopausal status evaluated. If menopausal status is unknown, serum estradiol or follicle-stimulating hormone level tests can be informative if available. There is no routine indication for assessing tumor markers, (CA 15-3, CA 27-29 and CEA) as part of the initial diagnostic work up for breast cancer or in management of early stage disease.

Disease staging

Breast cancer characterization and staging is a critical component of diagnosis and is required for treatment planning. There are standardized systems for describing a breast tumor: 1) invasive or noninvasive; 2) size; 3) lymph nodes involvement (if so, how many); 4) whether cancer cells have spread to other areas of the body. A commonly used system is the Union for International Cancer Control–American Joint Commission on Cancer (UICC-AJCC) TNM system, which includes metrics of clinical stage (results of physical exam, biopsy and imaging tests) and pathologic stage (clinical staging information plus biopsy and laboratory findings). In the TNM system, T refers to the size and characteristics of the tumor, N refers to the extent of lymph node involvement and M refers to the degree of distant metastasis. The size and characteristics of a tumor can be assessed by CBE, biopsy and imaging. The extent of lymph node involvement can be assessed by CBE, biopsy and imaging. The degree of metastatic disease can be informed by physical exam, biopsy and imaging. The actual stage of disease, (Stage I-IV) is determined by a combination of different T, N and M characteristics.

Staging axillary lymph nodes: Normal axillary lymph nodes are generally not felt on clinical examination, although axillary adenopathy (i.e., swollen lymph nodes) can sometimes be felt. Axillary adenopathy can be caused by cancer, but there are other causes as well (e.g., an immune response to infection or injury). A biopsy and pathologic confirmation is required to determine whether axillary adenopathy is caused by cancer. Surgical staging of the axillary nodes can be performed by removal and examination of the lymph nodes in the level 1 and 2 of the axilla (the lower level of lymph nodes under the arm). When resources are available, biopsy of the sentinel lymph node (SLN) (the lymph node identified as the first lymph node likely to contain cancer cells shed from a primary tumor, as identified by the accumulation of a blue dye and/or radiotracers) is preferred because it is associated with fewer side effects than traditional axillary dissection procedures. No survival advantage has been found with traditional axillary lymph node dissection when compared with SLNB (see Table 1).

Imaging for metastatic disease

Imaging to detect cancer spread to distant sites is not recommended for tumors less than 5 cm in diameter unless there are clinical or laboratory findings consistent with metastatic disease (e.g., bone pain, shortness of breath, liver function abnormalities) or four or more positive axillary lymph nodes. Patients with tumors that are fixed to the chest wall, the skin or have signs of inflammatory breast cancer (breast edema and peau d'orange) have an increased risk of distant metastasis.

Therefore, imaging studies of distant sites are recommended. Imaging modalities used to detect distant metastases should be obtained based on clinical findings and/or laboratory tests and can include a bone scan, liver ultrasound and chest radiograph, or a Computerized Tomography (CT scan) of the chest and abdomen.

Chest x-ray for lung metastases: Low-cost plain film chest radiography can be used with few side effects and low cost. Diagnostic chest computed tomography (CT) is considered as an alternative to chest radiography in resource appropriate settings.

Bone scan for skeletal metastases: In high-resource settings, bone imaging is often recommended for asymptomatic stage II breast cancers with four or more positive axillary lymph nodes or stage III breast cancers. Symptomatic patients (localized bone pain) or patients with an elevated alkaline phosphatase test require imaging of the bones. Bone scans have a high false negative rate (10–15%) and a high false positive rate (10–30%). Plain X-ray films can detect bone lesions that are large enough to place a woman at increased risk of fracture. In resource appropriate settings, CT scans with bone imaging or MRI can be considered if the clinical concern remains high (see Table 1).

Liver ultrasound, abdominal CT scan or MRI: Liver ultrasound has minimal side effects and low costs but may be falsely negative or positive. An abdominal CT or MRI can be used instead of a liver ultrasound depending on the resources available and clinical suspicion.

FDG PET/CT: Fluorodeoxyglucose-positron emission tomography (FDG PET)/CT may be used in high-resource settings in situations in which standard imaging (e.g., chest/abdomen/pelvis CT, bone scan) is equivocal or suspicious in patients with stage IIIA-IV disease. FDG PET/CT comes at a higher cost, higher false negative and false positive rates, and has not been shown to improve outcomes.

WHAT WORKS

Coordination of care: A complex health system requires a strong primary care network, an efficient referral process, accurate diagnosis and staging capacity and accessible and time-sensitive treatment with built-in quality control and process metrics, guided by evidence and consensus recommendations. Each health facility in a country may have different levels of resources and thus different modalities available. Improvement in services should be done in a step wise manner along a resource-stratified pathway, coordinated with other facilities in the region.

Cancer registries: Understanding the burden of breast cancer requires knowing incidence and the stage of disease at presentation. Requiring breast cancer data to be routinely reported to cancer registries provides valuable information to assess needs and monitor progress.

Clinical guidelines: Resource-stratified guidelines can help health systems implement basic services and incrementally improve services across the continuum of care as more resources become available. Development and dissemination of evidenced-based clinical guidelines can help ensure appropriate utilization of resources. Advances in diagnostic studies (imaging and pathology) and advances in treatment strategies require health systems to effectively match diagnosis and staging protocols to the burden of disease and the available treatment services. If targeted therapy for HER2-positive cancers is not available, testing for HER2 status would not be a high priority. Similarly, targeted therapy for HER2-positive cancers should not be administered without proper HER2 testing. Resource-neutral guidelines are available and can be adapted to local systems. Examples include guidelines developed by the National Institute for Clinical Excellence (NICE), the British Association of Surgical Oncology (BASO), the European Society of Medical Oncology (ESMO), Cancer Care Ontario (CCO) and the National Comprehensive Cancer Network (NCCN-USA).

Health professional training: Training health professionals in breast anatomy, signs and symptom of breast cancer, CBE, breast counseling and risk assessment (see *Early Detection: Breast Health Awareness and Clinical Breast Exam*), as well as in best practices in biopsy techniques and pathology review and reports (see *Diagnosis: Clinical Assessment, Diagnostic Imaging and Staging*), is essential. Health professionals and patients should understand and have equal access to the multistep diagnosis and referral process. Assessments of medical training programs and continuing medical education programs can help keep health care professionals up-to-date on advances in detection and treatment.

Monitoring the breast program: Data on time from presentation to diagnosis, time from diagnosis to treatment and compliance to treatment recommendations can help inform health systems about resource allocation priorities for breast cancer program improvements (see *Planning Comprehensive Breast Cancer Programs: Call to Action*). Employing standardized diagnostic and staging procedures may help avoid unnecessary studies and optimize resource utilization and minimize costs.

POINTS FOR POLICYMAKERS:

PLANNING STEP 1: WHERE ARE WE NOW?

Investigate and assess

Assess the need for diagnostic services

- The incidence of breast cancer will inform the demand for diagnostic services.

Assess current diagnostic and staging capacity

- Assess the availability and quality of diagnostic services.
- Assess pathology resources for tissue diagnosis and staging of cancer.

Assess health system capacity

- Review the efficacy and efficiency of the existing referral process. Analyze available data on time from presentation of a suspicious breast concern to definitive diagnosis and time from referral for imaging and pathology studies to report generation to identify health system and patient barriers to care.
- Assess provider knowledge of early detection (including clinical breast exam) and diagnosis procedures.
- Assess human resources capacity as well as qualifications and training of personnel responsible for diagnosing, staging and testing hormone receptor status.
- Evaluate existing training programs and continuing education for diagnosis and staging of breast cancer.

Assess barriers to diagnosis

- Identify structural barriers to diagnosis (e.g., lack of trained expertise, location of services, lack of adequate referral network, equipment shortages, etc.).
- Identify sociocultural, personal and financial factors that may affect a woman's willingness and ability to present for clinical evaluation and adhere to the multiple steps required for diagnosis (e.g., lack of awareness, fear, stigma, cost, etc.).

Assess monitoring and evaluation capacity

- Assess existing quality assurance programs to ensure adequate standards are being followed. Health systems should monitor time from diagnosis to treatment as a quality metric.
- Assess the collection of accurate data regarding breast cancer diagnosis and staging and the process of reporting cancer diagnosis information to cancer registries.

PLANNING STEP 2: WHERE DO WE WANT TO BE?

Set objectives and priorities

Identify community and health system partnerships

- Identify sites where women are most likely to present for initial breast evaluation and focus health professional training programs on clinical assessment strategies in those areas.
- Identify partners (institutions or organizations) that may provide patient education or navigation.
- Consider the need for additional awareness and educational programs for health care providers, community health workers and the lay population.

Identify gaps in current health system

- Use data on time from presentation of a suspicious breast concern to definitive diagnosis and time from referral for imaging and pathology studies to report generation to identify health system and patient barriers to care.
- Identify local and regional needs in diagnostic services, such as performance of CBE, imaging capability, diagnostic biopsy procedures and pathology services.

Set achievable objectives

- Objectives include strategies to ensure equitable access to efficient and accurate diagnosis and staging for all women with a suspicious breast finding.
- Develop evidenced-based national breast cancer diagnosis guidelines.
- Balance local needs (including patient access to care) and expertise with the advantages of centralized services
- Address gaps in referral networks to ensure diagnostic follow up for all breast health complaints (WHO Package of Essential Noncommunicable [PEN] disease interventions for primary care in low-resource settings referral model).
- Report and document clinical findings (contribute data to regional and national cancer registries).
- Include quality standards, monitoring and evaluation in new diagnostic services programs.

Set priorities and determine feasibility of interventions

- Assess the feasibility of new programs by using demonstration or pilot projects with measurable outcomes.
- Follow a resource-stratified pathway for program development that identifies available resources across the continuum of care.

PLANNING STEP 3: HOW DO WE GET THERE?

Implement and evaluate

Establish financial support and partnerships

- Consider regional improvement projects that involve community stakeholders and partners.
- Consider the financial feasibility of scaling up diagnostic capacity in imaging and pathology services. Centralizing services may reduce overall health system costs and improve quality but must be implemented without decreasing patient access to care.

Launch, disseminate and implement

- Implement program improvements to overcome identified gaps and barriers to diagnosis (i.e., transportation, understanding of the multistep diagnosis process or fear of the diagnosis or treatment process).
- Introduce or expand educational programs for health professionals and patients that outline appropriate diagnostic procedures for staging studies to avoid inappropriate use.
- Strengthen and clarify the system for referrals and follow up care to all health professionals and patients to avoid duplication of procedures. Coordination of a multistep diagnostic process for breast cancer requires a strong referral network and timely communication between service providers.
- Increase capacity to accurately and efficiently diagnose and stage patients with breast cancer.

Monitor and evaluate

- Develop process metrics to evaluate quality of care delivery, using a resource-stratified approach (see Table 1). Process metrics may include percentage of patients referred for diagnostic biopsy that undergo this procedure; percentage of patients diagnosed with a benign versus malignant tumor; percentage of nondiagnostic biopsies; percentage of reports that mention histology, grade, extent of tumor, ER, PR, HER2 status and number of lymph nodes examined and number involved with tumor.

CONCLUSION

Accurate and timely diagnosis and staging of breast cancer and quick referral for treatment is a priority goal for all breast cancer control programs. Clinical and pathologic staging can help determine treatment decisions, as can more advanced pathology testing, such as estrogen receptor (ER), progesterone receptor (PR) and HER2 testing.

Understanding breast cancer incidence, tumor stage at presentation, as well as time from diagnosis to treatment will help inform program improvements and resource allocations that can contribute to diagnosing breast cancer at an earlier, more curable stage. Shifting stage at diagnosis from late stage to early stage should be a program priority because early stage breast cancer are less costly to diagnose and treat and more likely to result in cure after treatment. Using a resource-stratified approach can ensure patients receive the best available care across the continuum of services (see Table 1).

Table 1: Diagnosis resource allocation and process metrics

Level of resources	Basic	Limited	Enhanced	Maximal
Clinical	History Physical examination Clinical Breast Exam (CBE) Tissue sampling for cancer diagnosis (cytologic or histologic) prior to initiation of treatment	Ultrasound-guided FNAB of sonographically suspicious axillary nodes Sentinel lymph node (SLN) biopsy with blue dye	Image-guided breast sampling Preoperative needle localization under mammography and/or ultrasound guidance SLN biopsy using radiotracer	
Imaging and lab tests	*	Diagnostic breast ultrasound Plain chest and skeletal radiography Liver ultrasound Blood chemistry profile* Complete blood count (CBC)*	Diagnostic mammography Specimen radiography Bone scan, CT scan Cardiac function monitoring	PET scan, MIBI scan, breast MRI, BRCA1/2 testing Mammographic double reading
Pathology	Pathology diagnosis obtained for every breast lesion by an available sampling procedure Pathology report containing appropriate diagnostic and prognostic/predictive information to include tumor size, lymph node status, histologic type and tumor grade Process to establish hormone receptor status possibly including empiric assessment of response to therapy Determination and reporting of TNM stage	Determination of ER status by IHC Determination of margin status, DCIS content, presence of LVI Frozen section or touch prep SLN analysis	Measurement of HER2 overexpression or gene amplification Determination of PR status by IHC	IHC staining of sentinel nodes for cytokeratin to detect micrometastases Pathology double reading Gene profiling
Process metrics	No. of Patients with tissue diagnosis/no. of patients with suspicious mass	% Patients with biopsy-proven cancer diagnosis who have documented TNM stage	% Patients with biopsy-proven cancer diagnosis who have documented HER2 status	Process metrics determined based upon standards of care in high-income countries

Source: *Eniu A, Carlson RW, El Saghir NS, et al. Breast Health Global Initiative Treatment Panel. Guideline implementation for breast healthcare in low- and middle-income countries: treatment resource allocation. Cancer. 2008 Oct 15;113(8 Suppl):2269-81.*

*Systemic chemotherapy requires blood chemistry profile and CBC testing for safety. When chemotherapy is available at the basic level, these tests also should be provided. ER testing by IHC is preferred for establishing hormone receptor status and is cost effective when tamoxifen is available. When tamoxifen is available at the basic level, IHC testing of ER status also should be provided.

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