



ADVANCES IN BREAST CANCER SCREENING AND DIAGNOSIS

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ABSTRACT

Breast cancer is the most common form of cancer in American women and the second leading cause of death. In the continuing battle against this disease, surgeons and radiologists are constantly refining techniques to find the disease early, stage it accurately, and develop evidence-based treatment plans tailored to the individual patient with the intention of preserving the patient's breast and quality of life. This article is a review of recently developed strategies for diagnosing breast cancer, identifying hard-to-reach tumors, minimizing tissue sampling errors, and making an accurate diagnosis, so that the resulting plan of contemporary treatment will include all options and procedures.

This is the first in a series of articles about breast cancer. Future articles will delve into the latest advances in treatment options and other aspects of care for patients with breast cancer.

INTRODUCTION

One out of every seven women in a doctor's care will develop breast cancer, and about 20% of these women will die of the disease.¹ Gone are the days when the only screening program for most women was their own ability to feel a lump in the breast. Also gone are the days when the only treatment option was a radical mastectomy. Since the 1990s, there has been a burgeoning of screening and diagnostic strategies for breast specialists that allow us to find some of the smallest nonpalpable lesions deep in breast tissue, and have dramatically improved our ability to make an accurate diagnosis. Some of these strategies are updated versions of old standards, like mammography. Others involve new applications of standard technology, such as using imaging techniques and increasing the use of ultrasound and the addition of MRI for accurate diagnosis. These strategies allow both preoperative counseling and planning, and dramatically decrease the need for excisional biopsies.

This is a review of state-of-the-art techniques for the screening and diagnosis of breast cancer. The indications—and limitations—of these strategies are presented, and those that are promising but still under investigation will be distinguished from those that are ready for use in the office, the radiology suite, or the OR.

PART I: SCREENING

The breast self examination (BSE) remains the gatekeeper to breast cancer detection, with patients finding the most tumors that result in a diagnosis.² In younger women, a lump found on BSE is more likely to be benign. This does not make the BSE any less important in this age group, however, because breast cancers are diagnosed in women as young as their 20's. A regular BSE gives younger women a chance to "get to know what normal is," so they can recognize changes in their breasts quickly and report them to you promptly.

The American Cancer Society (ACS) strongly recommends that we continue to encourage all women to examine their breasts on a regular basis. A clinical breast exam should be conducted at least once a year for women older than 40 years and at least once every 2 years for younger women. The office exam provides an excellent opportunity to teach your patients how to do a BSE or to check their technique. The earlier a woman learns how to do the BSE, the better. At Lancaster General, group classes in BSE or one-to-one tutorials are offered through the Breast Center. Mothers can teach BSE to their daughters when they reach puberty, so that young women will make BSE part of their personal hygienic routine.

MAMMOGRAPHY

Mammography, complemented by the breast exam, has served as the pillar of breast cancer screening for about 3 decades.³ Currently, screening mammography primarily serves 2 purposes: (1) to find lesions while they're

still small; and (2) to localize lesions for a subsequent stereotactic biopsy (discussed later). Lesions found on a screening mammogram are evaluated by a radiologist and determined to be either probably benign, or malignant.

Recommendations for Mammography Screening

The ACS recommends a baseline mammogram at age 35 years followed by annual or bi-annual mammography for all women beginning at age 40.⁴ Regular mammograms are also recommended for women younger than 40 years who have a family history of breast cancer in a first degree relative. This is especially true if the family history includes premenopausal breast cancer, or an established *BRCA1* or *BRCA2* gene mutation. Ultrasound in alternating years can be useful for screening high risk younger patients who have dense breasts.

Mammography: The Technology

Both film and digital mammography are now available. For *film mammography*, which has been available since the 1960s, the breast is exposed to very low-energy x-rays, which scatter throughout breast tissue while emitting photons that are absorbed onto an image receptor to form a conventional latent image. These images are then archived on a recording device. Film mammography provides very good spatial resolution and contrast, and thus is useful for finding nonpalpable pathology and identifying subtle differences among the various types of soft tissue in the breast. Film storage is a problem, however, and if the film is damaged or inadequate, the study must be repeated.

The overall sensitivity of film mammography is about 85%, and it varies with the expertise of the user. It is frequently combined with a computer-aided detection (CAD) program to improve its sensitivity and to reduce reader variability. CAD converts x-ray films into digitized images that are displayed on a (small) computer monitor after having been analyzed with software that seeks patterns suggesting malignancy. CAD is used after the radiologist has already made an initial assessment, thereby serving as a radiological "re-review" of suspicious areas to reduce the risk of missing any abnormalities. Although CAD is most commonly used for screening purposes, radiologists with limited breast mammography experience often find it beneficial in making a diagnosis.

Digital mammography (also known as *full-field digital mammography*) was developed to overcome some of the

limitations of film mammography by segregating the methods of image capture, display, and archiving, so that each component of the imaging process can be manipulated separately for maximum effect.⁵ A digital image is created when a digital detector captures photons either *indirectly*—using a scintillator to absorb x-rays and emit scintillated light, which is detected by photodiodes—or *directly*, using a photoconductor to capture x-rays and transform them directly into a digital signal. Digital mammography offers 3 key advantages over film: (1) the images, which are stored electronically, can be transmitted over long distances, allowing clinicians in geographically remote areas to consult with distant specialists; (2) the radiologist can manipulate the images to focus on 3-dimensional images of discrete areas of the breast; and (3) the images are not easily degraded, which simplifies storage. Lancaster General Hospital will convert to digital mammography soon.

The DMIST trial⁶ (Digital Mammographic Imaging Screening Trial) compared film versus digital mammography in almost 50,000 women. The trial's report in the *New England Journal of Medicine* concluded that "digital mammography was significantly better than conventional film mammography at detecting breast cancer in young women, premenopausal and perimenopausal women, and women with dense breasts." They added that despite the added cost (1.5 – 4x the cost of film mammography in the DMIST trial, which concluded in 2003), they believe "the significant improvement in accuracy in specific subgroups of women justifies the use of digital mammography in those groups." Since that trial was completed in 2003, improved understanding of the role of *BRCA-1* and *BRCA-2* genes in putting young women at high risk for developing breast cancer suggests that they too might benefit from digital mammography.

ULTRASOUND

Ultrasound, often referred to as "the stethoscope of the breast specialist," is most often used for diagnosis of a mass that has already been located by palpation. Ultrasound can usually identify masses as cystic or solid, and can recognize characteristics of solid masses that are strongly suggestive of malignancy. Sonography is particularly important in young women, whose breast tissue tends to be dense and thus more likely to cause a falsely negative mammogram.⁷

The Technology

Sonography takes advantage of the fact that controlled sound waves reflected off body tissues provide information not only about the distance of the tissue from the sound source, but about its size, shape, and internal consistency (e.g., fluid vs. solid). A transducer is used to transmit high-frequency sound waves into the body, and to record the character and strength of reflected waves to produce a real-time, dynamic image of the target tissue on a computer monitor. Still frames can be generated to allow the radiologist to evaluate and document the appearance of lesions and suspicious areas in the breast.

Ultrasound is very operator dependent. The complexity of breast ultrasound is compounded by the necessity to correlate sonographic findings with the mammogram, so the sonographer should also be experienced in mammography. An operator who is not familiar with breast tissue may fail to position the transducer properly and miss areas in which occult lesions are most likely to be found. Repeat targeted ultrasound is indicated if the physician has a strong clinical suspicion.

Application

The USFDA has not yet approved ultrasound for breast cancer screening, so its two major applications are: (1) to distinguish lesions found on a mammogram as malignant or benign; and (2) to guide core biopsies, whether performed in the Radiology Department or the surgeon's office. It does not do well in detecting microcalcifications in the breast, which are much better visualized by mammography.

MAGNETIC RESONANCE IMAGING

Contrast-enhanced MRI captures 3-dimensional images and detects lesions hidden in dense tissue, making it suitable for finding tumors that mammography misses.⁸ It has excellent sensitivity for invasive malignancy, and high grade Ductal Carcinoma In Situ (DCIS). MRI often misses low grade DCIS, but is particularly helpful for diagnosing multifocal DCIS in patients with in situ calcifications, and detecting other malignant lesions that can not be seen on a mammogram.

How an MRI Detects Cancer

MRI detects cancer by evaluating patterns of enhancement in the breast. Tumors, whether benign or malignant, grow their own blood supply ("tumor angiogenesis");

since blood vessels of benign and malignant lesions tend to differ in both organization and permeability, they enhance in different ways under MRI. Additionally, dynamic scanning allows the radiologist to see how a lesion enhances over time.

In addition to the pattern of enhancement, the shape of a lesion is important in determining whether it is benign or malignant. Computer systems such as DynaCAD make it easier to evaluate MRI images by generating contrast enhancement curves and producing 3-dimensional images of the area containing the lesion (J. Kegel, MD personal communication, June 2006).

Indications

The American Society of Breast Surgeons has identified 5 indications for breast MRI:

1. To localize primary occult lesions in patients with axillary metastases.
2. To determine the extent of tumor involvement in the ipsilateral breast and evaluate the contralateral breast in patients with proven cancer.
3. To monitor the response to neoadjuvant chemotherapy.
4. To screen patients with *BRCA1* or *BRCA2* mutations.
5. To rule out cancer in patients who have an indeterminate physical examination, mammography, or ultrasound.

High-risk Screening

MRI is recommended for women younger than 40 years who have an elevated risk for breast cancer because they harbor a *BRCA1* or *BRCA2* mutation or have several first degree relatives who have had breast cancer. The *BRCA1* and *BRCA2* mutations are found with increased frequency (2.3%) in individuals of Ashkenazi (Eastern European Jewish) descent, as well as in natives of Norway, the Netherlands and Iceland.^{9,10} These mutations are thought to interfere with the repair of double-strand breaks in DNA by blocking a nucleotide excision repair pathway that is activated by lesions that distort the helix (e.g., oxidative stress). The altered *BRCA1* gene product is also believed to affect patterns of growth and differentiation in breast epithelial cells, thereby increasing the risk of oncogenesis. LGH works closely with screening programs of the University of Pennsylvania and Hershey Medical Center to refer appropriate patients for genetic screening. Unfortunately, insurance coverage for the \$3,000 cost of genetic screening is often denied.

PART II: DIAGNOSIS**INTRODUCTION**

The key to an accurate diagnosis is an adequate amount of relevant tissue for cytological analysis. Before the 1990s, a suspicious lesion was often excised completely for histological examination. In an early attempt to reduce the size of the biopsy, technology first swung to the opposite extreme by developing fine needle aspiration biopsy (FNAB), in which thin (25-gauge) needles were inserted and an area was sampled under the guidance of either palpation or ultrasound. FNAB reduced scarring and the trauma of a biopsy, but often failed to obtain enough tissue for an unequivocal diagnosis.

Biopsy techniques have evolved over the last two decades, with development of hollow needles that are just wide enough to obtain an adequate sample size, and are guided by advanced imaging techniques to minimize tissue sampling errors. The following section discusses these minimally invasive needle biopsy procedures, which have virtually replaced excisional biopsy.^{11,12,13}

Core Needle Biopsy

Core needle biopsy is used under ultrasound, mammographic, or MR guidance to remove solid cylinders of tissue, using a relatively wide (10- to 14-gauge) hollow needle attached to a tissue sampling device. The device may be spring-loaded or vacuum suction assisted, or it may employ a cryo-assisted core gun.

Spring-loaded devices operate almost like a gun. A notched needle is mounted onto a spring-loaded device and "shot" into the target tissue, where a small cylinder of tissue is cut out and collected in the notch. When used to diagnose *in situ* and invasive cancers, this technique very rarely produces false-negative results. Preop diagnosis by core biopsy reduces re-lumpectomy rates and most importantly preserves the surgeon's ability to perform sentinel lymph node biopsy (SLNB) for axillary LN staging.

Vacuum-assisted biopsy—c.g., the Mammotome probe (Biophys, Irvine, Calif)—is one of the most accurate methods of determining the histology of microcalcifications by taking multiple core samples in an area.

The cryo-assisted rotational device (Sanarus, Cassi) uses a freezing process that minimizes bleeding and trauma.

No matter which technique is used, the core biopsy site is marked, typically with a titanium clip. If the results of core biopsy are benign, the clip serves as a marker on subsequent mammograms. If the biopsy results are malignant, the clip serves as a marker for mammographic or ultrasound guided needle localization on the day of surgery. A specimen x-ray is typically obtained at the time of surgery to confirm that the tissue removed contains the lesion/microcalcifications and clip. In some rare cases, the core biopsy does not produce a definitive diagnosis and an excisional biopsy is necessary.

Stereotactic Needle Biopsy

Stereotactic needle biopsy is predominantly used to obtain a histologic diagnosis of microcalcifications, but it can also be used to biopsy areas with architectural distortion and masses which can not be seen sonographically. X-rays taken from two different angles provide stereo images of the biopsy path, which then create a 3-dimensional image of the area of interest and improve the accuracy of needle placement.¹ The images are taken with the patient lying prone on a specially constructed table that allows the breast to hang down through an opening. The radiologist or surgeon and x-ray technologist sit below the table and take several pairs of images. Key coordinates are then identified on a computer monitor, and small core tissue samples are removed by vacuum assisted needle biopsy.

This useful technique does have some limitations, and other techniques are sometimes substituted. The necessary positioning is not suitable for patients with severe neck or back problems, patients who weigh more than the table can accommodate (approximately 250 lbs), and those who are extremely anxious (though pre-procedure sedation with Valium is very helpful).

Percutaneous Excisional Biopsy

Devices are available that excise small lesions entirely. Currently, these are not used at LGH because current core techniques are accurate and very small benign lesions can be left *in situ* and followed with radiology studies.

SUMMARY

State-of-the-art options for screening and diagnosis have improved our ability to detect and diagnose breast cancer early, but the BSE and mammogram remain the mainstays for detection of breast cancer. Mammography, particularly with computer-aided detection, can now produce

images detailed enough for diagnostic purposes, and digital mammography allows transmission of 3-dimensional images over long distances. These advances mean that we are close to removing major logistical barriers to access to screening and care for breast cancer.

MRI has an increasingly important role in breast imaging, especially in high risk patients, and those with an indeterminate physical exam, mammogram, or ultrasound. It is particularly useful in the search for occult disease, and to see if a recognized tumor is more extensive than seen on mammography. Ultrasound is an essential complement to

breast imaging, particularly when a lump is palpable, or in young women whose breasts appear dense on mammography. Breast biopsy techniques have improved dramatically over the past two decades, and image guided core biopsy techniques have essentially eliminated the need for excisional biopsy to obtain a diagnosis. Ultrasound is the mainstay of guidance for core biopsies.

Ultrasound and MRI now help provide the information needed to develop treatment plans that are exquisitely tailored to each patient, and dramatically increase the chances of saving every woman's breast, as well as her life.

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