Sonography is suitable for breast imaging not only because of its nonionizing-radiation, but also its cost-effectiveness and availability. The recently developed high-resolution scanners can provide much finer detail concerning the anatomical information of the breast parenchyma. Better diagnostic results can be therefore achieved. As high-resolution ultrasound US has become more popular for evaluation of breast symptoms and for complementary study of unsatisfactory or equivocal X-ray mammography XRM©, more cancers are being detected before they become clinically palpable. In this review, we briefly describe the techniques, instrumentation, US features, and common pitfalls in the detection of nonpalpable breast cancer.

**Patient Positioning and Breast Survey Techniques**

The patient is placed supine with the ipsilateral arm comfortably elevated to help spread out the breast and allow better evaluation of the axillary region. If the breast is large or pendulous, slight rotation of the chest to the contralateral side permits optimal scanning of the evenly distributed breast tissue surrounding the centrally located nipple. An abundance of acoustic couplant gel and a light touch by the operator are needed. For a large glandular breast, however, more compression with the transducer may be required to obtain better penetration.

To ensure a better orientation of a breast lesion and better communication with the surgeon, the breast is examined by a radial fashion surrounding the nipple. The location of a lesion is labeled according to the o’clock position and the distance from the nipple e.g., 12:00/2 cm©. Evaluation of a focal lesion with dynamic study graded compression should be routinely done to demonstrate the tumor and assess its margin and compressibility. The anteroposterior AP and lateral L dimensions should be recorded for reference of AP/L ratio. The scanner should be optimally set to fit the condition of individual patient.
Instrumentation
High-frequency linear electronically focused 7-13-MHz probes are preferred. The state-of-the-art scanners may have dynamic focusing or multifrequency capability, and provide good axial and lateral resolutions in both near and far fields. Some lesions may be located in the very superficial region e.g., within 1 cm and can be obscured in part by the near field artifact. A stand-off pad or a large amount of gel used as a stand off may greatly improve the near-field image quality. The more recent broadband technology enhances the spatial and contrast resolution significantly, and also permits a better penetration to the deeper structures.

US Features of Nonpalpable Cancer
Breast lesions may be clinically nonpalpable due to its small size, relatively soft in consistency, flat in distribution, obscured in the background of dense glandular tissue, hiding in a large breast, or deep in location. The most common nonpalpable cancers are small infiltrative carcinomas, carcinoma in situ CIS, i.e., intraductal carcinomas, comedo carcinomas and lobular CIS, colloid mucinous carcinomas, and medullary carcinomas. Except for sonographically typical malignant tumors, US features of nonpalpable cancers are not specific. Color Doppler US may be helpful in the differentiation between benign and malignant lesions in some nonpalpable nodules. When the US findings mandate histologic documentation, US-guided fine needle aspiration cytology FNAC or biopsy may provide important histological information. US-guided wire localization may localize the lesion precisely and guarantee an accurate removal.

Small Infiltrative Ductal Carcinomas
An infiltrative ductal carcinoma, if less than 1.1 cm, can be physically nonpalpable. The US findings of a small infiltrative ductal carcinoma typically include marked hypoechoogenicity, angular margins, distal acoustic shadowing, microcalcifications within the tumor territory, and an anteroposterior AP dimension equal to or greater than the lateral L dimension AP/L ratio 1. These features do not differ from those of larger carcinomas. However, smaller lesions e.g., 4-6 mm in size may have a relatively smooth boundary, distal acoustic shadows are infrequently seen.
**Carcinoma in Situ (CIS)**

The main types of CIS are intraductal carcinoma ductal CIS, DICS, lobular CIS LCIS, and Paget’s disease of the nipple. In DCIS, the tumor presents as a cluster of thick-walled ducts which are filled with large pleomorphic tumor cells, with a high mitotic rate. Necrosis is always present in the center of the lesion. When these ducts are compressed, necrotic debris can be squeezed out as in comedo, and hence resulted the name comedo carcinoma. Microcalcifications are frequently seen in the necrotic areas. US diagnosis of CIS is difficult because most CIS’s are small and infrequently form soft tissue masses. The mass in CIS, if present, is not as distinct as is found in infiltrative ductal carcinoma. However, sonographically distinct mass in CIS is occasionally seen in association with concentric fibrosis and infiltration of mononuclear inflammatory cells or fibrocystic disease. Microcalcifications without distinct mass effect can be demonstrated in some cases, particularly in comedocarcinomas. Architectural changes is infrequent in CIS. Intraductal papillary carcinomas and occasionally other forms of carcinomas may have attained a size sufficient to be detected on US as a dilated echogenic duct or a distinct echogenic nodule within a dilated duct. Tumor spread along the ductal system may extend into the lactiferous sinuses and collecting ducts and may be followed by tumor cell infiltration of the nipple epidermis, representing Paget’s disease. However, US detection of the underlying in situ ductal carcinoma in the area adjacent to the nipple is extremely difficult.

**Colloid Carcinoma**

Colloid carcinoma, also known as mucinous, mucoid, or gelatinous carcinoma, is usually a well-circumscribed tumor composed of extracellular pools of mucinous material and nests or cords of tumor cells. Most colloid carcinomas appear with well-circumscribed margins, lobulated contours and relatively higher echogenicity as compared with the much more common infiltrative ductal carcinomas. They are hard in consistency. However, colloid carcinomas may be flat or cord-like in shape and therefore not palpable physically.

**Medullary Carcinoma**
Medullary carcinomas are relatively soft tumors. Although they are usually large on presentation, relatively small tumors may be detected during routine breast US survey. A larger medullary carcinoma shows the US features indistinguishable from a circumscribed ductal carcinoma. Small lesions are homogeneous in echotexture. They have well-defined and usually smooth margins, and usually lack an infiltrative appearance. Small medullary carcinomas are rounded in shape with a high AP/L ratio.

**US Detection of Nonpalpable Cancer**

In a study with combined screening XRM and US examinations of 5242 patients during a period of 4 years, we disclosed 41 patients 0.78% with nonpalpable breast cancers. Among these 41 patients, US detected 24 tumors 59%. US presentations include nodular lesions without demonstrable calcifications 16 cases or 67%, clustered microcalcifications 5 cases or 21%, microcalcifications in a small nodule < 0.7 cm; 2 cases or 8%, and microcalcifications in dilated ducts 1 case or 4%. The 16 nonpalpable cancers presented as noncalcified nodules ranged in size from 0.4-1.1 cm. Suggestive signs of malignancy were present in only 3 out of 16 on XRM, and 5 out of 16 on US. XRM demonstrated 32 cancers 78%, 25 were presented as microcalcifications with or without nodules 2 and 23, respectively and 7 as noncalcified nodules. With combination of these two modalities, a higher accuracy can be achieved.

**Common Pitfalls in US Detection of Nonpalpable Cancer**

Pitfalls in performing or interpreting the examination or fundamental limitations of the instruments and sound physics may influence the detectability of tumors. The following are common pitfalls caused by improper performance: inadequate penetration of breast tissue, subareolar lesion obscured by the nipple, superficial lesion hidden in the near field artifact. Limitations of the instrument include failure to detect lesions in the fatty breast, failure to detect small or intraductal cancer or malignant microcalcifications, failure to demonstrate small tumors in dilated ducts.
Further Reading

TN STAGING OF BREAST CANCER USING ULTRASONOGRAPHY

Jeong Mi Park, M.D.
Department of Diagnostic Radiology, Asan Medical Center, Seoul, Korea

Important prognostic factors in breast cancer are the size of the tumor, status of axillary lymphadenopathy, pathologic staging after primary therapy and presence or absence of Estrogen receptor (ER) and/or progesterone receptor (PR) activity (1). Staging of the disease is especially important in patients who are candidates for breast-conserving treatment. Two or more gross tumors in separate quadrants or tumor location beneath the nipple are contraindications to breast-conserving treatment (2).

Radiologists must do an important role in evaluating the stage of the disease by using mammography, ultrasonography, MR or other modalities. Among these, ultrasonography could provide the most convenient and also very effective role. Ultrasonographic evaluation of the breast includes axillary areas and staging must include items below;

a. For ipsilateral breast; Size and location of the primary tumor, multifocality or multicentricity, involvement of nipple or skin.
b. For contralateral breast; Bilaterality of the tumor
c. For axillary area; Status of lymphadenopathy

Anatomically, axillary nodes are divided into apical or subclavicular nodes, axillary vein nodes, interpectoral (Rotter) node, scapular nodes, central nodes, external mammary nodes, paramammary nodes. Otherwise, more simplified classification is dividing it into three levels; Level I is defined as lateral to the pectoralis minor muscle, Level II is behind the muscle, Level III is medial to the muscle and synonymous with “infraclavicular area”. Interpectoral nodes (Rotter’s nodes) are located between the pectoralis major muscle and the pectoralis minor muscle and can be included in level II (3). Metastsis to axillary nodes are generally progressed in a predictable way from level I...
to level III which is the basis for the idea of sentinel node, however, skip metastasis could occur in which nodes in high levels are involved earlier than nodes in low levels. Boova et al (4) reported 3.5 % rate of skip metastasis, therefore, all levels of nodes must be included in routine ultrasonographic examination.

References
MAMMOGRAPHIC AND ULTRASONOGRAPHIC DIAGNOSIS OF EARLY BREAST CANCER

Hye-Young Choi, M.D.
Department of Diagnostic Radiology, Ewha Womans University, Korea

Introduction

Definition of early-stage breast cancers is DCIS, or invasive, but 1cm or smaller in diameter and without evidence of axillary lymph node involvement. Initially Gallagher and Martin defined the term minimal breast cancer to mean LCIS, DCIS, or invasive carcinoma that was no larger than 0.5cm in diameter. The definition of minimal cancer was altered in the BCDDP to include tumors up to 1cm in diameter, thus confusing its use. Because confused terminology makes it difficult to evaluate data, general terms such as minimal breast cancer should be discarded and replaced by more accurate descriptions that include size, tumor grade, lymphatic and vascular involvement, the proximity of the cancer to the excised tissue margin, and nodal status. Each of these appears to provide prognostic information, and to ensure that populations being compared are indeed comparable, these factors should be controlled. As noted tumor size is significant for its prognostic value. In the Swedish Two County Trial of mammography screening, Tabar et al. found that women with invasive cancers <1cm had excellent survival and that when tumors were this small, histologic grade did not effect survival and they all did uniformly well.

Earlier detection, unfortunately, does not mean that a cancer is early in its development and does not guarantee a favorable result. There is also a variation in the metastatic potential of breast cancers. In addition, there are most certainly varying host responses to breast cancers that have not yet begun to be understood. Even the most exacting screening program will not save all women. The mortality reduction that can be expected on the basis of the HIP and Swedish data is 25% to 50%. Nevertheless, screening provides an opportunity to reduce breast cancer deaths that is worthy of vigorous pursuit.

Breast cancer is not a single disease process. It has numerous variations. Pathologic review of the tissues using light microscopy remains the most accurate diagnosis test. The breast cancer begins in the epithelial lining of the duct. The cells of the intralobular terminal duct are likely those responsible for most proliferation, and it is these cells that are believed to be susceptible to malignant transformation. Cancer cells that remain confined within the duct (Ductal carcinoma in situ, DCIS) can not cause death. Breast cancer becomes lethal only when it develops the capability of breaking out of the duct and
invading into the surrounding tissue (Invasive ductal carcinoma, IDC), gaining access to the blood and lymphatic systems through which it can spread to other organs, and grow and destroy their functions.

**Origins of Breast Cancer**

There are two theories about origin of breast cancer, **continuum and dual theories**. The continuum theory suggest that intraductal carcinoma proliferates for a variable length of time confined within the duct, which ultimately one or more cells develop the ability to penetrate the basement membrane, and their clones invade the surrounding stroma, gaining access to the vascular and lymphatic networks and permitting metastatic spread. Dual theory argue that a significant number of nonlethal cancers develop in the breast that will never affect the left of woman. Invasive, potentially lethal cancer is interpreted as a separate distinct lesion that also develops in the epithelium but rapidly invades and metastasizes before it can be detected.

Ohuchi et al demonstrated that DCIS can spread up and down the duct network and remain in situ, whereas invasive cancer can be found associated with a part of the process. This finding would support the continuum theory. Their data suggest that one of the already genetically unstable cells in the DCIS developed an invasive clone and that this clone proliferated while the remaining in situ cells, unable to invade, continued to proliferate and spread up and down the ducts. This observation explains how DCIS and invasive breast cancer can be found in the same lesion.

Invasive cancer develops from a single cell. It is the clones of this cell that form the initial tumor. Once a cell is genetically abnormal, the likelihood of additional changes increases. The development of additional clones with different characteristics is the probable explanation for the frequent cellular heterogeneity of cancers. Eventually, the most aggressive clone likely predominates. In situ cancer is not found within many invasive cancers for various reasons. It is possible that there are some cancers in which the first malignnt cell, or one of the early in situ cells, develops all of the necessary ability to invade and even metastasize. Thus, some cancers may never go through any significant in situ stage. In other cancers, it is likely that just as the invasive cancer invades and destroys normal tissue, it also destroys any in situ tumor as well, and when diagnosed, only invasive cancer is found.

**Multifocal breast cancer** should be defined as multiple foci of cancer associated with on duct network, whereas **multicentric breast cancer** involves foci that are in separate lobes or segments. Multifocality is the result of cancer originating from a single cell whose
clones spread up and down the duct, with the subsequent development of invasive clones forming independently at various locations. Multicentricity requires the independent transformation of two separate cells. Multifocality is fairly common; multicentricity is fairly unusual.

Screening is an attempt to detect breast cancer early, by the time a tumor is clinically apparent (at approximately 1 cm in diameter) it has probably been growing for 5 to 10 years because the average doubling time of breast cancer is approximately 100 to 180 days. The mammographic detection of breast cancer that is not yet clinically evident appears to advance the time of detection by 1 to 2 years in younger women and up to 4 years for older women. Thus, early detection is a relative term. The size of the tumor in the breast is only important as it relates to the development of metastases.

**Prognostic Factors of Breast Cancers**

The major significant factors are the size of the tumor, its histologic type and grade, the presence or absence of hormone receptors (estrogen), the status of axillary nodes, and the presence or absence of distant metastatic disease.

In the Breast Cancer Detection Demonstration Project (BCDDP), the percentage of women with positive axillary nodes increased with the size of the tumor. None of the women had positive nodes when the cancer was in situ, and if the invasive cancer was <0.3cm, only 4% had positive lymph nodes. This increased to 10% for tumors between 0.3cm and 1cm, 22% for tumors 1 to 2cm, 32% for tumors 2 to 3 cm, 44% for tumors 4 to 5 cm, and 50% for tumors 5 cm or more. Rosen et al demonstrated a significant survival difference for node-negative invasive cancers <1cm relative to those between 1 and 2cm. If the tumor was <1cm and the nodes were negative, 20% of the women had recurrence by 20 years and died. If the tumor was 1 to 2 cm, deaths rose to 30%. The Swedish Two County Trial showed that if invasive cancers are <1cm, the patients all do so well that histologic grade has no influence on survival. Histologic grade worsened with tumor size. Tabar found that the grade of the tumor appears to change as it increases in size. This may reflect progressive genetic changes as tumors age with the selection of more aggressive clones. Hensen et al found that women whose tumors were classified stage I, grade 1 had a 99% 5-year survival and a 95% 10-year survival rate. Even if their lymph nodes contained tumor, if their tumors were <2cm and the histologic grade was 1, their 5-year survival was 99%. The prognosis for breast cancers are strongly associated with the presence or absence of metastatic disease in the axillary lymph nodes at the time of diagnosis. For example, for tumors <2cm, the 5-year survival rate diminishes from 96% in women who have no nodal
involvement to 87% in women with one to three positive nodes to 66% for women with four or more involved lymph nodes. In BCDDP, women with cancers >1cm in diameter had a 29% positive nodes whereas only 14% of women whose cancers were <1cm had positive nodes. About hormone receptor, the presence of estrogen receptors in significant quantity is associated with a better prognosis and suggests a greater response from hormone manipulation, such as the use of tamoxifen to block the effects of estrogen.

**Ductal Carcinoma**

Ninety percent of breast cancers have cellular features that are similar to ductal epithelium and are classified as ductal cancers. When in situ (remaining confined to the duct), they are called **intraductal carcinoma**, or more commonly, **DCIS**. When the cells have breached the basement membrane surrounding the duct and invaded the surrounding tissues they are termed **invasive or infiltrating ductal carcinoma**.

DCIS, left without definitive treatment, will progress to invasive cancer in at least 30% to 50% of women. A study conducted by the National Surgical Adjuvant Breast Project (NSABP), a large multicenter collaborative group, found that women with DCIS treated with excision alone had a 23% recurrence rate by 3 years, whereas those treated with excision and radiation had the recurrence reduced to 9%. The significance of DCIS is the fact that DCIS is not a uniform process. Pathologists have started to agree that there are distinct subtypes of intraductal cancer. They do not agree on the classification, but many see a difference based on cell morphology and the architecture of the aggregated cells. Large cell tumors appear to have a different natural history than small cell cancers. Solid growth are distinguished from those forming cribriform spaces. Many tumors have areas of necrosis while others have micropapillary growths. Lagios found that poorly differentiated DCIS, particularly of the comedo (large cell) type appears to recur early, within 5 years, often with invasion. Micropapillary or cribriform types progressed at a slower rate.

**Mammographic Findings of Early Cancer**

Mammography is unchallenged as a screening test for detecting early-stage breast cancer. No their imaging technique approaches its ability to find small cancers. Mammographic criteria, however, are frequently insufficient to make the diagnosis of malignancy. Most breast cancers are radiographically very dense for their volume, but as with all signs, this is not a uniform characteristic, and some cancers are relatively low in x-ray attenuation. Round or oval lesions with smooth, sharply defined margins are usually benign, but some cancers appear smoothly marginated. Despite a lack of specificity for particular lesions,
criteria have evolved that should alert the radiologist to the possibility of malignancy. Most of these signs are not definitive because they overlap significantly and are often exhibited by benign processes. Although mammography frequently cannot be relied on to differentiate benign from malignant lesion, when certain morphologic criteria are present it is extremely accurate.

- Possibility of Malignancy
  1. Neodensity
     A new density on a mammogram should be viewed with suspicion, and unless the new density can be directly linked to the use of hormones, diagnostic evaluation is usually indicated.
  2. Spiculated lesion
     The spiculations represent fibrosis that is probably related to the generalized desmoplastic response that many cancers elicit in the surrounding tissue.
  3. Calcifications
     Fine, linear, irregular branching calcifications are practically always due to malignancy.
  4. Ill-defined margins
     Ill definition of the margins of a lesion is a common, though nonspecific, characteristic that suggests a malignant process.
  5. Lesions with a microlobulated margin
     Many well-circumscribed lesions within the breast have a degree of lobulation. the more lobulated the lesion, the more likely it is to be malignant. When the lobulations are multiple and measure only several millimeters or smaller, the degree of suspicion should increase.
  6. Architectural Distortion
     This distortion of the architecture may be the only visible evidence of malignant process.
  7. Clustered Microcalcifications
     Mammography is the only technique capable of detecting the clustered microcalcifications that frequently herald the presence of an early-stage breast cancer. The definition of clustered microcalcifications varies. The data suggest that five or more calcification, each <0.5mm in diameter isolated in a small volume of the breast, and projected within a 1-cc volume on the mammogram, warrant careful assessment.

1) Significance of the Number of Calcifications
   That five microcalcifications are a threshold for biopsy is not absolute. Calcium begins
to be deposited at some point in time, and a single deposit may form within a cancer. However, all groups of calcifications containing fewer than five particles are benign. Egan et al. found that 84% of cancers due to their associated calcifications contained >10 calcifications; they found no cancer when fewer than five calcifications were present. Most of the radiopaque deposits that are called calcifications contain calcium in the form of calcium hydroxyapatite and tricalcium phosphate, but by Galkins and associates has suggested that microcalcifications may also contain an array of heavy metals and may not be exclusively composed of calcium derivatives. The majority of cancer-associated calcifications develop in intraductal malignancy. Many tumor-related calcifications are formed in necrotic cellular debris. This is most apparent when there is comedonecrosis in DCIS. The cells are usually poorly differentiated with high nuclear grade and a great deal of central necrosis. Other calcifications may be secondary to cellular secretions of crystalline material. The latter are likely the etiology of calcifications found in the cribriform spaces of the better differentiated types of DCIS.

2) Size, Shape, and Distribution of Calcifications

The particles are usually <0.5mm in diameter. Egan and coworkers evaluated 468 lesions composed of calcifications without an associated mass. Among these, 353 were benign and 115 were malignant. They found no cancers when all the calcifications were >2mm. Because the calcifications associated with breast cancer almost always form in the intraductal portion of the tumor, some have suggested that there is a polarity to their distribution that is somewhat triangular and aimed in the general directions of the nipple. Malignant microcalcifications tend to be extremely heterogeneous in shape and very small. Intraductal carcinoma generally produces irregular, fine, linear calcifications that are interrupted in a "dot-and-dash" pattern and may branch.

3) Predicting Histology

DCIS can be divided into lesions that have poorly differentiated features, those with intermediate or moderate differentiation, and others that can be classified as well differentiated. These classifications are based on cellular features as well as pattern of growth. These features include the nuclear grade, the architectural relationship of the cells, and the presence or absence of necrosis. The nuclear morphology in the cells is a primary prognostic indicator.

Mammographic Findings of DCIS

Noninvasive breast cancer, or carcinoma in situ, is defined as breast carcinoma limited to the ducts(ductal carcinoma in situ, or DCIS) or lobules(lobular carcinoma in situ, or
LCIS) with no extension beyond the basement membrane into the surrounding stroma. With the increased use of screening mammography and the improvement in mammographic technology, more cases of noninvasive breast cancer are currently being detected than ever before. The percentage of mammography-guided biopsies of occult lesions that represent DCIS ranges as high as 20-40%. On mammogram, DCIS most often manifests as one or more clusters of irregular shaped calcifications. The calcifications in DCIS are typically either branching, irregular, pleomorphic casts of the ducts or more focal, irregular, granular-type deposits. Stomper and Connolly analyzed 66 consecutive cases of DCIS that appeared on mammograms with microcalcifications. They noted that the comedo subtype was more likely to be associated with linear calcifications than the noncomedo subtypes, and noncomedo subtypes were more likely to be associated with granular calcifications. Although DCIS most often manifests as calcifications on mammogram, other less common manifestations are also seen. Ikeda and Andersson examined atypical forms of DCIS. In their series of 190 patients, 73 women did not have microcalcifications associated with DCIS. Of these, 30 had negative mammograms, 15 had circumscribed masses, and 12 had various nodular patterns. Seven of the 15 circumscribed masses represented intracystic papillary carcinoma, a subtype of DCIS. The patients had asymmetry(1), dilated retroareolar ducts(2), and ill-defined mass(2), focal architectural distortion(4), a subareolar mass(3), and a developing density(4). In a series of 100 consecutive cases of clinically occult DCIS, Stomper et al noted that 72 manifested as calcifications, 10 as soft tissue abnormalities, and 12 as both calcifications and soft tissue masses, and six were found by the pathologist as an incidental finding. Compared with women older than 50 years, women younger than 50 years with DCIS were more likely to have breast calcifications and less likely to have soft-tissue masses. One of Swedish trial reported that microcalcifications were the most frequent findings on the mammogram in detecting in situ carcinomas(76%). Casting-type calcifications(23.2%) are most often associated with high nuclear grade/poorly differentiated in situ carcinoma, while the powdery, cotton ball-like calcifications(13.6%) represented low nuclear grade/well-differentiated cases. The majority of the calcifications cases were crushed stone-like(39.3%) and represented all grades. The remaining 24% of all in situ carcinomas were demonstrated by asymmetric density with architectural distortion(10.1%) or by finding solitary or multiple circular/oval masses(7.6%) or by performing galactography(6%). This shows that demonstrating as many in situ carcinoma cases as possible requires not only meticulous workup with mammographic examination, but also the use of ultrasound and galactography. The size of the DCIS is important with respect to multicentricity and occult
invasion. In the series of Lagios et al, four of 29(14%) lesions smaller than 25 mm were multicentric and none had foci of occult invasion; of DCIS lesions larger than 5cm, 13 of 13(100%) were multicentric and nine of 13(69%) had foci of occult invasion. Similarly, Dershaw et al noted in their series of 54 cases of DCIS that all 22 cases of lesions larger than 25mm were associated with multicentric disease. The question also arises of whether one can differentiate DCIS form infiltrating carcinoma at mammography. Hermann et al examined 193 consecutive women with nonpalpable breast carcinoma: 102 had DCIS, and 91 had infiltrating carcinoma. Of the 112 women(58%) with microcalcification, 84(75%) had DCIS and 28(25%) had infiltrating carcinoma. Of the 69(36%) with a mass, 60(87%) had infiltrating carcinoma. Of the 12(6%) with microcalcifications and a mass, nine(75%) had infiltrating carcinoma. Thus, calcifications were more likely to be associated with DCIS.

Ultrasound Findings of Breast Cancer
The ultrasound appearance of breast cancer can be similar to that of virtually any benign lesion found in the breast. Breast cancer is always hypoechoic. It is generally irregularly marginated with heterogeneous internal echoes, and there are frequently areas that produce acoustic shadowing. Thirty-five percent of the time the classic appearance of an irregularly shaped anterior margin with dense posterior shadowing is seen. Twenty-five percent of cancers of the breast may exhibit well-defined margins with a lobulated contour. These may mimic the appearance of a fibroadenoma. Frequently the diagnosis of cancer is strongly suggested when the margins of the lesion appear to merge with or "invade" the surrounding tissue. On occasion, a cancer can be extremely well defined with subtle low-amplitude internal echoes. The ultrasound may appear similar to that of a fibroadenoma and rarely has the anechoic appearance of a cyst and even 12% demonstrated retrotumoral acoustic enhancement. The overlap between benign and malignant characteristics has been confirmed by other investigators.

Ultrasound and the Future
Whole breast systems were developed to permit evaluation of the entire breast by sonography, and the criteria that had been derived were applied to these systems. However, the hoped-for sharp demarcation between benign and malignant characteristics began to blur. In a series reported by Jackson and colleagues 144 masses were interpreted on sonography as fibroadenomas. Among the 59 that underwent excisional biopsy, four proved to be cancer. Not only is ultrasound unable to differentiate benign from malignant
solid masses with sufficient accuracy to avoid biopsy, but other studies have also 
demonstrated sonography's inability to detect breast cancer in women who have negative 
mammography and physical examination. Sickles and associates studied 1000 women 
using whole-breast ultrasound and were able to detect only 58% of the 64 biopsy-proven 
cancers. In this study, ultrasound detected only 48% of cancers that had not yet spread to 
the axillary nodes. Of the 12 cancers <1cm, sonography failed to detect 92%. But, 
preceding studies are fairly old, more recent data, noted in Ultrasound for Screening, 
suggest that newer technology may increase ultrasound's ability to detect cancer. 
Ultrasound screening needs to be reassessed in large, prospective, blinded studies. 
Furthermore, ultrasound should not be used to routinely scan women who have negative 
physical examinations and mammography because it will only raise suspicions and will not 
detect cancers. This is likely to change as more studies are properly performed to 
reevaluate ultrasound for screening. Ultrasound should also not be relied on to differentiate 
benign from malignant solid lesions in a diagnostic setting.

References
1. Carter CL, et al. SEER data: Relation of tumor size, lymphnode status and survival in 
391,439-442,
3. Ketcham AS, Moffat FL. Vexed surgeons, perplexed patients and breast cancers which 
may not be cancer. Cancer 1990;65:387-393
5. Rosen PP. Axillary lymph node metastasis in patients with occult noninvasive breast 
6. Rosner D, Bedwan RN, Vana J, Baker HW, Murphy GP. Noninvasive breast carcinoma: 
results of a national survey by the American College of Surgeons. Ann Surg 
1980;192:139-147
7. Page DL, Dupont WD, Rogers LW, Landenberger M. Intraductal carcinoma of the breast: 
follow-up study after biopsy only. Cancer 1982;49:751-758
8. Rosen PP, Braun DW, Kinne DW. The clinical significance of pre-invasive breast 
carcinoma. Cancer 1980;46:919-925
9. Stomper PC, Connolly JL, Meyer JE, Harris JR. Clinical occult DCIS detected with 
mammography: analysis of 100 cases with radiographic pathologic correlation. 
Radiology 1989;172:235-241


EARLY CANCER DETECTION FOR FEMALE RELATIVES OF BREAST CANCER CASES: COMPARISONS BETWEEN CLINICAL BREAST EXAMINATION, MAMMOGRAPHY AND BREAST ULTRASOUND

San-Kan Lee¹, Tain Lee¹, Tse-Jia Liu²
Department of Radiology¹, Department of Surgery²
Taichung Veterans General Hospital, Taichung, Taiwan

Breast cancer is the fourth leading cause of cancer deaths among women in the Taiwan. In 1997, the estimated mortality rate of breast cancer was 10.20 per 100,000 women,¹ and the incidence is increasing from 5.94 per 100,000 women in 1979 to 11.60 in 1986 and 18.42 in 1994.² Early detection of breast cancer can be performed by screening mammography and has demonstrated a reduction of breast-cancer mortality in Western countries.³ However, the application of mass screening in our country might be costly, due to lower frequency of breast cancer. Screening of high-risk group is an alternative choice, which will be cost-effective and beneficial for the women in demanding. A family history of breast cancer is a major risk factor.⁴,⁵ We defined a high-risk group for breast cancer by recruiting female relatives of breast cancer cases for screening.

This is a joint study from a program entitled the Taiwan Multicenter Cancer Screening (TAMCAS) for breast cancer launched by the Department of Health in Taiwan since 1994. Subjects who met the criteria of the high-risk group were invited to screening between 1994 and 1998. The screening is aimed at female relatives (including mother, daughter, sisters, grandmother) of breast-cancer cases. Since 1994, relatives aged over 35 years have been invited to annual screening by a combination of physical examination, mammography and ultrasound (US). Aspiration cytology or biopsy was applied for further confirmation of those with positive results of the 3 screening methods.

The mammograms were obtained from a dedicated x-ray mammography with screen-film combination technique. We routinely took medio-lateral bolique and cranio-caudal
views on each screening. A high-resolution scanner with a 7.5-10 MHz transducer was applied for the US study. A color Doppler US was added for further evaluation when a solid lesion was detected. Up to December 31, 1998, a total of 249 women with family history of breast cancer have been recruited and received their first screening. Among the 249, only 118 attended the second screening and total number is 367.

Forty-eight screenings had final cytological or histological diagnosis and 43 of them were benign and 5 were malignancy. The malignant diagnoses included 3 infiltrating ductal carcinoma, 1 intraductal with medullary carcinoma, and 1 case of adenocarcinoma diagnosed by aspiration cytology only. In these 48 screenings, physical examination detected 14, mammography detected 15 and US detected 42 of them. The results of this high-risk screening project are listed on Table I and the efficacy of the screening methods is listed as Table II.

Table I. Results of High-risk Breast-cancer Screening

<table>
<thead>
<tr>
<th>Year</th>
<th>Screening cases</th>
<th>Physical examination +</th>
<th>Mamography +</th>
<th>US Any examination +</th>
<th>Malignancy</th>
<th>Benign</th>
<th>Cancer + predictive value</th>
<th>Screening rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>98</td>
<td>7</td>
<td>11</td>
<td>33</td>
<td>37</td>
<td>3</td>
<td>18</td>
<td>8.1</td>
</tr>
<tr>
<td>1996</td>
<td>63</td>
<td>5</td>
<td>4</td>
<td>17</td>
<td>17</td>
<td>1</td>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>1997</td>
<td>115</td>
<td>7</td>
<td>6</td>
<td>41</td>
<td>45</td>
<td>0</td>
<td>16</td>
<td>0.0</td>
</tr>
<tr>
<td>1998</td>
<td>91</td>
<td>5</td>
<td>1</td>
<td>21</td>
<td>23</td>
<td>1</td>
<td>6</td>
<td>4.3</td>
</tr>
<tr>
<td>Total</td>
<td>367</td>
<td>24</td>
<td>22</td>
<td>112</td>
<td>122</td>
<td>5</td>
<td>43</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Symbol: + = positive

Table II. Diagnostic accuracy of the screening methods (cut-point at malignant lesion)

<table>
<thead>
<tr>
<th>Screening method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>+ predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>0.2</td>
<td>1.00</td>
<td>0.92</td>
<td>1.00</td>
</tr>
<tr>
<td>Mamography</td>
<td>0.6</td>
<td>1.00</td>
<td>0.96</td>
<td>1.00</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>0.8</td>
<td>1.00</td>
<td>0.98</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Four prevalent breast cancers and 1 incident screen-detected case were found in this study. The four mastectomy patients showed stage II on 3 and stage III on 1 of them. Color Doppler US was performed on 30 benign lesions and all of the malignant tumors. Only 23% of the benign lesions presented with Doppler flow and 80% of malignant tumors show flow signals within the tumor.
Mammography is good for screening purposes and is effective in reducing mortality from breast cancer for women aged above 40 year.\textsuperscript{3,4} US is sensitive in detecting the breast lesions and confirming the cystic component. Breast sonography is not useful for screening for breast cancer in any age group, but it is an indispensable adjunct to mammography and their findings should be interpreted together.\textsuperscript{6} A routine US examination of clinical/mammographic abnormalities is recommended.\textsuperscript{7} In this study, the sensitivity of mammography is lower than that of the Western report\textsuperscript{7,8} which might be attributed the dense breast parenchymal pattern of the Chinese women, and the higher sensitivity of US was speculated to be due to the same reason. Color Doppler US is advantageous in differentiating the breast mass\textsuperscript{9} and could be considered as an adjunct to the breast examination. A triple assessment -- the combination of clinical examination, imaging (mammography or/and US) and fine needle aspiration cytology -- is sensitive in screening the breast cancer.\textsuperscript{8} Our results of combined physical examination, mammography, US and aspiration cytology or biopsy also support this finding. For screening of high-risk breast cancer cases, we recommend the application of this combined method.

Grant sponsor: Department of Health (DOH), Taiwan, R.O.C.

References
FALSE NEGATIVE DIAGNOSIS OF BREAST CANCER AT ULTRASOUND

Boo-Kyung Han, M.D.
Samsung Medical Center, Sungkyunkwan University, Korea

Previously, breast sonography has been used to assess whether a palpable mass is cystic or solid. The advance of sonographic equipment led to expanded indications; the differentiation of a benign from a malignant solid breast mass and the assessment of nonpalpable masses identified by mammography. The differentiation of a benign from a malignant solid breast mass is particularly important regarding nonpalpable masses because palpable solid masses are often removed regardless of their imaging characteristics. Therefore, recently, the use of breast sonography is increasing rapidly in the majority of breast clinics. Several kinds of diagnostic criteria are applied. Representative ones almost include shape, border, boundary echo, internal echo, posterior echo, lateral shadowing, and depth/width ratio and so on.

In the latest publication, Stavros et al. (1) reported a 99.5% negative predictive value for cancer in solid breast nodules with benign sonographic characteristics. The benign characteristics are as follows; absent malignant findings, intense hyperechogenicity, ellipsoid shape, gentle bi- or trilobulations, and thin, echogenic pseudocapsule. The malignant characteristics are spiculation, taller than wider, angular margins, marked hypoechogenicity, shadowing, calcification, duct extension, branch pattern, and microlobulation. Nevertheless, sonographically false-negative cases for breast cancer are inevitable because of overlap of sonographic characteristics between benign and malignant nodules and difficulty in comprehensive analysis of the characteristics.

I will present the sonograms of breast cancer, which were interpreted as benign lesion or normal. The analysis of these false negative cases of breast cancer at ultrasound will be helpful for more accurate diagnosis of breast lesions.

We have 26 patients with breast cancer whose breast sonography was interpreted as benign or normal among 226 cancer patients who underwent sonograms preoperatively. Since we usually do sonography after mammography and fine-needle aspiration, the cases showing definitively or suspiciously malignant masses on mammography or cytology were not included and thus fourteen of 26 cancers were nonpalpable. We excluded the cases with carcinoma in situ, which is known to often have negative sonographic results. Experienced radiologists performed whole breast sonography, and if clinically or mammographically suspicious area was present, sonography was more focused on the suspicious area. We stored the data included even subtle abnormality as possible in entire
breasts with hard copy (n = 10) or PACS (n = 16). The operator read it including the impression about benignity or malignancy immediately after the examination.

We retrospectively reviewed the sonographic appearances with emphasis on the presence or absence of malignant characteristics of the lesion in the case interpreted as benign and the presence of lesion in the case interpreted as negative. If the new lesion at follow-up sonography replaced a subtle abnormality seen at initial sonography at the similar distance from the nipple and at the similar depth in the same quadrant, we regarded it as a subclinical cancerous lesion and included in false negative cases of breast cancer.

● Interpreted as benign
   Of twenty-three malignant solid nodules interpreted as benign, eighteen revealed equivocal findings and five showed none of the malignant characteristics by retrospective review.

1. Solid nodules with equivocal findings (n = 18)
   Minimal microlobulation (n = 9) and ellipsoid but slightly tall shape (n = 6) were most common equivocal findings. Moderately hypoechogenic internal echo (n = 3), partially ill-defined border (n = 2) and focal posterior shadowing (n = 2) were also observed. Nine nonpalpable nodules with equivocal findings underwent US-guided core needle biopsy with 14- or 18-gauge needle. Core biopsy was performed for clinical concern; contralateral breast cancer (n = 4), axillary lymph node (n = 1) or systemic (n = 1) metastasis. In two patients, sonographic mass was incidentally detected at different site during evaluation of self-palpable mass, which was appeared sonographically as normal. Eight but one were correctly diagnosed as malignancy. One was diagnosed by mastectomy performed because of axillary lymph node metastasis from unknown primary site.

2. Solid nodules without malignant characteristics (n = 5)
   Five solid nodules without malignant characteristics showed ellipsoid shape and thin echogenic pseudocapsule. Three nonpalpable nodules were followed up and six months to two years later, growing but still nonpalpable nodules were diagnosed as malignancy by the aid of US-guided core needle biopsy. One patient had serous nipple discharge, another had family history of breast cancer, and in the other patient, the problem was sonographically detected mass only.

● Interpreted as normal
   There were three breast cancer patients whose sonograms were normal. All the masses were nonpalpable. Two underwent modified radical mastectomy because of axillary lymph node metastasis from unknown primary site. In one patient, MR imaging just prior to
operation and specimen sonography showed a spiculated mass. Retrospective review of initial sonography a month ago detected a smaller spiculated mass at the same area, which had been ignored due to uncertainty. In the other patient, 0.3-cm invasive ductal cancer was discovered only pathologically and we could not find occult breast lesion at initial sonography despite retrograde review. In one patient with negative sonogram, sonogram was repeated for unchanged suspicious mammographic abnormality, and a malignant mass was detected only when doing in oblique plane to avoid nipple shadowing. The lesion was confirmed pathologically by US-guided core biopsy. We speculated that the reason for missing was lack of oblique scan.

Of course, Retrospective analysis of sonograms might be regarded as awkward and meaningless. As you know, Sonography is a real-time imaging and is operator-dependent. Nevertheless, I think that this presentation will give a lesson to many radiologists and clinician interested in breast imaging. Even small benign-appearing nodules, with any specific clinical concerns such as metastasis of unknown primary site, contralateral breast cancer, family history of breast cancer, or nipple discharge have to be managed by US-guided core biopsy or follow-up, depending on sonographic appearances and clinical background. In the cases of metastasis of unknown primary site, we can help to decide a proper therapeutic approach earlier by finding primary malignancy and obtaining histologic specimen. In the cases of screening in specific condition, we can make an opportunity for conservative surgery by early detection. Actually, if neither core biopsy nor follow-up was performed, many nodules, especially nonpalpable ones would be almost missed and would have been detected sufficiently late that treatment effectiveness might have been diminished. If the size of nodule is larger than 4 mm, US-guided core needle biopsy is possible and should be considered.

Our goal in breast imaging is that maximizes the detection of cancer with the least cost in a short period. Since mammographic or clinical evaluation can be unsatisfactory, the role of sonography in screening has been investigated as an adjunctive tool. In these days, breast sonography is being highlighted with the advent of newer sonographic machines and probes. We rely heavily on sonographic appearances in deciding whether to recommend follow-up or surgery for probably benign or inconclusive lesion by palpation and mammography. In women with radiologically dense breasts, furthermore, breast sonography is often used for a primary screening or to distinguish a true mass from a vague palpatory lesion. We performed breast sonography for screening in many cases included in this study. Interest in screening sonography recently arises also in the American College of Radiology (2) and Kolb et al reported screening sonography can depict small, early-stage, otherwise occult cancers and increase overall cancer detection by 17% (3).
However, Hall expressed strong objection to sonographic breast screening even for the scan of remainder of the ipsilateral, or occasionally both breasts when performing breast sonography for a known palpable or impalpable mass (2). We have a positive opinion for screening sonography, since five nonpalpable cancers with benign characteristics were detected during sonographic examination for vague palpable lesions at other site.

The application of many known sonographic characteristics makes the differentiation a malignant from a benign mass possible but the overlap still exists. Strict application is difficult practically because some masses have equivocal findings; ellipsoid but slightly tall shape; minimal microlobulation; moderately to markedly hypoechoic; partial, ill-defined border; focal, thick boundary echo; focal posterior shadowing. According to our result, the analysis for microlobulation and depth/width ratio needs to be more generous.

We think that our findings, which showed many overlapped characteristics of benign and malignant solid nodules, are not contrary to the recent trial for differentiation them by Stavros et al (1). They suggested that follow-up of a solid but sonographically benign breast mass is a reasonable alternative to biopsy. Our recommendation is that, at first, we have to make an effort to distinguish a malignant nodule from a benign-appearing solid nodule, by cautious and thorough analysis. And then, even with mild suspicion, the use of core biopsy, not surgical biopsy, needs to be justified and encouraged. For that reason, breast sonography should be performed by a motivated physician who can also evaluate the mammogram and who specialized in breast imaging. Also, the vigorous use of US-guided aspiration or core needle biopsy and regular follow-up will help us not to miss a malignant mass at subclinical state.

In summary, despite many overlapped features, the appropriate use of breast sonography with core biopsy to differentiate a benign from a malignant solid nodule will be beneficial for finding more cancers in treatable size and stage.

References