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Breast Cancer

# Local and Regional Staging of Invasive Breast Cancer With Sonography: 25 Years of Practice at MD Anderson Cancer Center

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*Disclosures of potential conflicts of interest may be found at the end of this article.*

**Key Words.** Breast cancer • Ultrasonography • Local and regional staging • Lymph node metastases • Ultrasound-guided needle biopsy

**Learning Objectives**

Outline the uses of sonography in staging local and regional breast cancer.

Describe advantages of using sonography in staging local and regional breast cancer.



## ABSTRACT

At The University of Texas MD Anderson Cancer Center, we have used sonography (US) extensively for more than 2 decades to refine the local and regional staging of invasive breast cancer. Although magnetic resonance imaging is superior to all other imaging modalities in the measurement of the primary tumor and detection of additional foci of malignancy, in our experience US has shown sufficient accuracy in clinical practice to stage most invasive breast cancers. The exceptions are ill-defined tumors such as invasive lobular cancers and tumors in breasts containing extensive diffuse benign disease. An advantage of US is that multifocality or multicentricity can be confirmed via US-guided fine-needle aspiration within 15 minutes and the information shared immediately with the patient and the breast surgeon or medical oncologist. US has also proved indispensable in the evaluation of lymphatic spread because it can evaluate more nodal basins (e.g., the supraclavicular fossa and low neck) than magnetic resonance imaging can and because it can guide needle biopsy to confirm the status of any indeterminate node (including internal mammary nodes) within minutes. ***The Oncologist*** 2014;19:5–15

**Implications for Practice:** Sonography (US) is used routinely to characterize breast masses and is the standard imaging technique to guide needle biopsies. However, an underused application of US with US-guided fine-needle or core-needle biopsy is the local and regional staging of breast cancer. US is remarkably effective in the detection and diagnosis of multifocal or multicentric disease and in the detection and confirmation via US-guided fine-needle aspiration biopsy of clinically occult lymphatic spread—both of which have a potentially dramatic impact on the patient's staging and management. This critical information is obtained at a limited cost and often during the patient's first visit.

## INTRODUCTION

Sonography (US) is widely accepted as the best adjunct to mammography in the diagnostic workup of breast masses and as the best guidance technique for percutaneous needle biopsy of many such masses, but US is rarely used in the local or regional staging of breast cancer. Instead, many institutions use magnetic resonance imaging (MRI) for local and regional staging. Most US studies of the breast performed in the United States are targeted examinations of a palpable mass or abnormal mammographic finding. Although a growing number of institutions now routinely include the axilla in the US examination of a patient with newly diagnosed breast cancer, very few centers include the other nodal basins.

At The University of Texas MD Anderson Cancer Center, we have been using US in the local and regional staging of recently diagnosed invasive breast cancer for the past 25 years [1]. This article describes the techniques we use and the potential pitfalls in US for local and regional staging of breast cancer. It has to be remembered that breast US has a very high detection rate for masses but fails to adequately visualize microcalcifications that are not associated with a mass. Therefore, US is used for staging invasive breast cancer, not ductal carcinoma in situ, which is by definition confined to the breast and is usually revealed by clusters of isolated microcalcifications detected on mammograms and rarely by a mass.

## US INSTRUMENTATION

### Transducers

The same linear-array transducers as those used for diagnostic breast US are used for staging US. Some manufacturers provide

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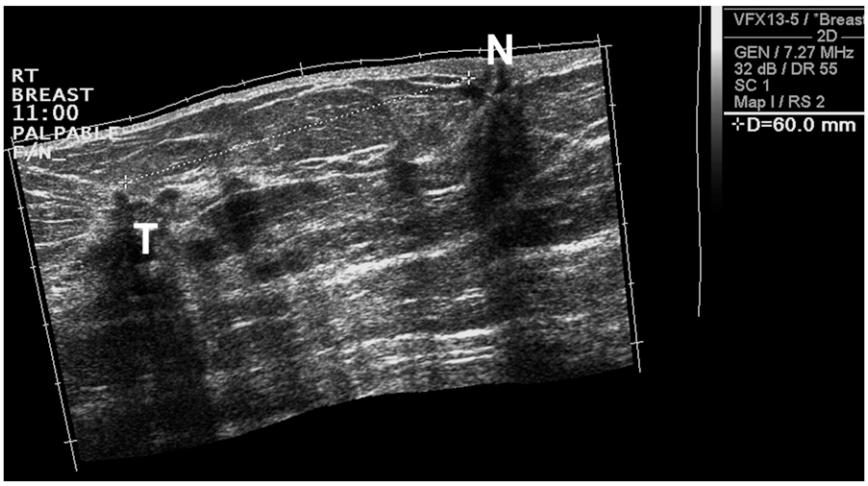


**Figure 1**. Extended-field-of-view sonogram along the 11 o'clock radius passing through the nipple and the tumor. The distance from the tumor to the nipple is 6 cm.

Abbreviations: N, nipple; T, tumor.

probes with a longer footprint of 5–6 cm for breast US. These probes allow more rapid scanning of the breast than narrower probes but may be too large to effectively image the axilla and the supraclavicular fossa in some patients. Recent technological advances in US equipment include very high-frequency and multiarray transducers as well as matrix broadband transducers. These transducers provide exquisite spatial and contrast resolution that allows the detection of breast carcinomas and lymph node metastases as small as a few millimeters. All modern transducers use a wide band of frequencies, and they should be operated at the highest clinically appropriate frequency to yield the highest spatial resolution. However, there is a trade-off between US frequency and beam penetration, and no high-frequency probe can image deeper than 4 cm (even less for many state-of-the-art machines). This limitation should be kept in mind when evaluating large breasts or lesions, as the operator may have to switch to a lower-frequency probe to achieve better penetration and a wider field of view.

## Extended Field of View

The extended-field-of-view technology now available on most high-end and midlevel scanners allows the operator to stretch the standard sonogram and build a static picture with a much wider field of view than the one available with standard real-time US transducers [2]. One major advantage of this technology, which can obtain sonograms of large sections of or even the entire breast, is the ability to scan through a lesion and the nipple to measure the distance between the two. This distance provides the optimal correlation with the lesion's location on mammograms [3]. At MD Anderson Cancer Center, the distance from the nipple of any focal lesion detected in the breast is routinely measured using extended-field-of-view imaging (Fig. 1).

## Trapezoidal Field of View

With some high-end scanners, the operator can steer the beam electronically and expand the rectangular field of view of the linear-array transducer into a trapezoidal one. This expansion of the field of view may be useful to visualize in its entirety (and therefore measure precisely) a lesion that the regular rectangular field of view of the probe cannot encompass.

## Gray-Scale US Enhancing Software

In an attempt to improve the quality of gray-scale US images, equipment manufacturers have developed software enhancement techniques. These are often advertised as enabling improved US detection of breast cancer, but most claims are not supported by nonindustry-sponsored, independent, well-designed clinical trials.

### *Real-Time Compound Scanning*

One such software enhancement technique is real-time compound scanning, which combines in real time the echoes obtained from multiple lines of sight at various angles of insonation. The expectation was that those crisscrossing beams would provide a better delineation of the margins of lesions, especially the lateral margins. However, in our experience at MD Anderson, the significant blurring associated with this technique has a negative effect on image quality, removing helpful diagnostic artifacts such as sound enhancement and shadowing and thereby resulting in diagnostic errors [4].

### *Speckle Reduction*

Speckle reduction imaging is a new technique in US designed to reduce artifacts and improve image quality. However, speckle reduction has not been shown to improve the differentiation between benign and malignant masses [5].

### *Tissue Harmonic Imaging*

Tissue harmonic imaging slightly increases spatial resolution and contrast [6]. Although this has proved beneficial in clearing spurious echoes from the lumen of cysts and making minute cysts appear more convincingly like true cysts, in our experience, tissue harmonic imaging provides no substantial benefit in the US evaluation of malignant breast and nodal masses. In fact, the boost in contrast compared with conventional gray-scale US may make areas of shadowing normally cast by Cooper's ligaments and other fibrous areas in dense breasts appear like invasive lobular carcinomas. We recommend that tissue harmonic imaging and spatial compounding be used on occasion but not as default settings of the scanner. Also, it is important to ensure that

these settings have been turned off after use so that the next technologist using the scanner will not be confused.

### Three-Dimensional and Automated Breast US

The theoretical benefit of three-dimensional (3D) US scanning is that it permits the reconstruction of sonograms that are otherwise impossible to obtain, especially coronal images. The major limitations are the time taken to render the 3D images and, more importantly, the need to navigate through multiple additional, possibly oblique scan planes, with the risk of becoming disoriented.

A recent iteration of 3D US is whole-breast US scanning using an automated scanner, also known as automated breast US (ABUS). For decades, researchers have struggled to develop an ABUS scanner, with notorious failures. The latest equipment uses a single very long, high-frequency (14–16 MHz) linear-array transducer housed in a large pad that is placed on top of the breast. The transducer scans over the breast for a few seconds, acquiring the breast volume dataset. The reconstructed and intercorrelated sagittal, transverse, and coronal views of a given area or lesion are displayed on the monitor of a workstation.

Advantages of ABUS include fast, automatic volume acquisition and reconstruction of coronal views. Correlation with mammograms, although improved compared with standard US, remains limited, however, owing to the differences in breast positioning between US and mammography. A major limitation of ABUS is that the device cannot scan the entire breast (especially if the breast is large), so more than one volume acquisition is needed to ensure that the entire breast has been scanned. But the most significant disadvantage is the lack of real-time imaging and therefore the inability of the operator to clear an area affected by an artifact (such as the shadowing from a prominent Cooper's ligament), to improve the visualization of a subtle finding by using a different position of the probe or scan plane, to apply dynamic maneuvers such as graded compression with the probe, and to guide a needle biopsy. In addition, the device has no Doppler capability and cannot be used for proper scanning of the axilla and other regional nodal basins.

### Elastography

The goal of elastography is to provide information about the stiffness (or elasticity) of tissues [7]. Elastography has recently become a very popular topic in the US community, although it has been available with MRI for many years. US elastographic techniques rely on the compression of tissues (strain technique) or on the generation of shear waves and the measurement of their velocity through tissues (shear-wave technique). With both techniques, the stiffness of a lesion is represented on a gray-scale or color map in quasi-real time, usually in a side-by-side comparison with conventional gray-scale sonograms.

Unfortunately, the current commercially available scanners capable of elastography are affected by lack of intraobserver reliability, making it not uncommon to obtain a different result on repeat elastographic testing a few seconds later. In addition, the spatial resolution of the elastographic maps does not allow evaluation of the subcentimeter solid lesions that are routinely detected by conventional US. To add to the confusion, the color scales used on elastographic maps vary among manufacturers, with some machines representing hard tissue in red and soft in blue, whereas other scanners do the opposite. However, the major issue with elastography is that there are very few evidence-based nonindustry-sponsored studies reporting any clinically relevant superiority over standard gray-scale US. In fact, a sensitivity of 82% in the diagnosis of breast cancer has been reported for elastography, versus 94% for conventional gray-scale US [8]. Furthermore, even if the technology of elastography worked flawlessly, the huge overlap in firmness between benign and malignant lesions gives this technology no practical place in the differential diagnosis of solid breast masses. Even the newest techniques, which quantify the elastic modulus with shear-wave elastography, will not overcome this problem. Thus, relying on elastography to avoid a biopsy, as has been suggested by some investigators [9], would be as dangerous as relying on palpation alone in the case of a palpable mass [10]. In addition, a research study at MD Anderson showed that strain elastography was not superior to gray-scale US in the diagnosis of axillary nodal metastases (unpublished data). We do not use elastography of the breast at our institution.

### Power Doppler US

Power Doppler US (PDUS) is used to demonstrate hypervascularity associated with inflammatory conditions (e.g., mastitis, cellulitis, abscess) and, more importantly, to map tumor-associated neovascularity (supplemental online Fig. 1). Because it is much more sensitive than color Doppler US (CDUS) in the depiction of slow and low-volume flow and because knowing the direction of flow is not needed in the two above-mentioned applications, PDUS should always be preferred over CDUS in breast US.

A simple yet powerful application of PDUS is to differentiate between a rounded, markedly hypoechoic tumor and an inspissated cyst with low-level internal echoes. The detection of even the smallest vessel within a lesion automatically excludes a cyst (or any other fluid collection) and confirms a neoplasm [11]. This simple yet useful application of PDUS is still underused, especially when searching for small additional foci of malignancy in fibrocystic breasts.

A simple yet powerful application of PDUS is to differentiate between a rounded, markedly hypoechoic tumor and an inspissated cyst with low-level internal echoes. The detection of even the smallest vessel within a lesion automatically excludes a cyst (or any other fluid collection) and confirms a neoplasm.

When searching for minimal intralesional flow signals, however, sonographers must be aware of the risk of obliterating small vessels with excessive pressure on the probe and therefore missing the opportunity of confirming a solid mass.

Over the past 2 decades, the sensitivity of PDUS has dramatically increased, allowing not only the detection of the mere presence of Doppler signals within a neoplasm or enlarged lymph node but also the detailed mapping of normal versus disturbed vascularity, which helps differentiate between benign and malignant masses or nodes.

## Local Staging

Local staging of a newly diagnosed breast cancer includes the measurement of its longest diameter to determine its T category in the TNM staging system and determination of whether the cancer is unifocal or multifocal/multicentric.

### Tumor Measurement

It has long been established that US is superior to mammography in measuring the actual size of breast cancers in dense breasts [12]. However, the accuracy of the measurement depends on the sharpness of demarcation of the boundaries, the contrast between the tumor and surrounding tissues, and the shape of the mass (Fig. 2). In addition, operator experience can affect the accuracy of the placement of the calipers for measurement. Nevertheless, in the majority of cases, US is capable of giving the clinician a precise idea of the T stage of malignant masses, especially when dealing with tumors whose size is close to 2 cm (the cutoff for T1) [13].

When a mass is poorly defined on US, identification and subsequent measurement may not be possible. For example, invasive lobular carcinoma often appears as flat areas of fibrosis and shadowing with little or no circumscribed mass (supplemental online Fig. 2). In such cases, MRI is required for appropriate local staging.

### Uni- versus Multifocality/Multicentricity

In the absence of limiting technical factors, US can detect additional malignant foci that would make the disease multifocal (with two or more foci of cancer within the same breast quadrant and less than 5 cm apart) (Fig. 3) or multicentric (with two or more foci of cancer in different quadrants or more than 5 cm apart) (supplemental online Fig. 3) and change the patient's management by precluding breast-conserving surgery in case of multicentric disease. This application of US requires a meticulous examination of the whole breast, which may take up to 20 minutes, especially if additional lesions are detected. Not only must each additional lesion be measured, but its location in the breast must also be documented precisely using its clock position and distance from the nipple, along with its distance from and position relative to the primary tumor. These distances can be easily measured with the extended-field-of-view scanning technique (Fig. 3). The direct measurement of the distance between the primary tumor and any additional focus of disease is usually more readily obtained with US than MRI.

When additional foci of disease have been detected, those that qualify the cancer as multifocal or multicentric must be confirmed by a tissue diagnosis. Although the standard for the biopsy of the primary tumor is a core biopsy to determine invasiveness and to provide enough tissue for all necessary markers to be tested, additional foci can be diagnosed using US-guided fine-needle aspiration (FNA) (supplemental online Fig. 3). FNA can render a diagnosis within 15 minutes compared with at least 48 hours for core biopsy [14].

Following the needle biopsy of both the primary tumor and additional foci, metallic tissue markers are deployed within the lesions to tag them for proper mammographic and/or US preoperative localization as well as to aid the pathologist in identifying the lesions in the pathological specimen. The placement of such markers is of utmost importance in patients who are going to receive neoadjuvant therapy, because the lesions may respond completely and disappear [15].

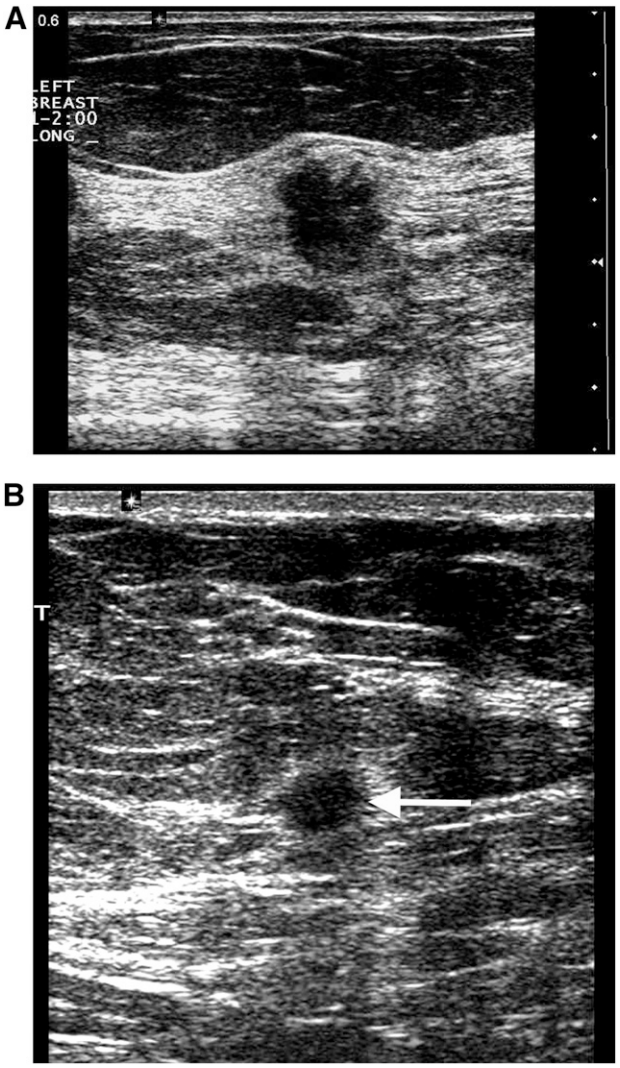


**Figure 2**. Measurement of a primary breast tumor (T category). **(A):** Sonogram shows a small (1-cm) T1 tumor. The tumor is markedly hypoechoic, and its margins are well demarcated from the adjacent echogenic tissues. This makes measurement of the tumor easy and reliable. **(B):** Measurement of a minute (0.5-cm) round cancer (arrow) is easy because of the contrast between the hypoechoic tumor and the surrounding tissues.

### US versus MRI for Local Staging

At many facilities, breast cancer is routinely staged with MRI instead of US. However, there has been a long-standing debate as to which patients (other than those with invasive lobular carcinoma) should have a preoperative staging MRI examination, as the cost effectiveness of preoperative staging MRI is unknown [16–19]. Also, not every patient with breast cancer has access to MRI for staging.

MRI has been reported to be more accurate than US in delineating the exact margins of breast cancer, although with a substantial risk of overestimating size [20, 21]. MRI also delineates ductal carcinoma in situ much better than US. Because of its exquisite sensitivity in demonstrating invasive as well as noninvasive cancer, MRI is superior to US in determining



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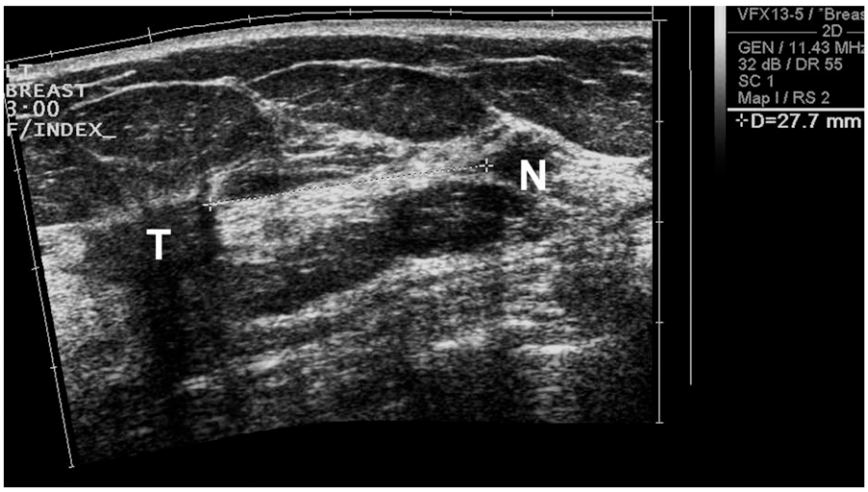


**Figure 3**. Multifocal cancer. Extended-field-of-view sonogram shows the distance (approximately 3 cm) between the primary tumor and a second smaller malignant nodule.

Abbreviations: N, second malignant nodule; T, primary tumor.

multifocality or multicentricity. However, because of the risk that false-positive findings may lead to unnecessary mastectomy, additional MRI-detected foci of suspected malignancy should be confirmed pathologically, which may be a problem in case of multiple lesions and if the equipment (and expertise) for MRI-guided biopsy is not available. Because real-time US-guided biopsy is more accurate, faster, and less traumatic than MRI-guided biopsy, US is often used after MRI (the so-called second-look US) in an attempt to confirm and biopsy additional malignant foci detected by MRI that may affect local staging [22].

At MD Anderson, we use US for local staging because in the vast majority of cases a meticulous examination of the entire breast along with US-guided needle biopsies yields the information needed by the oncologist, that is, the size of the primary, the presence or absence of multifocality or multicentricity, and the presence or absence of lymph node metastases (see below), including pathological confirmations, at a fraction of the cost of MRI and within less than 1 hour. The patient sees the oncologist immediately after the US appointment and knows the day of her first visit what her diagnosis is. The patient will return for a second visit a few days later to make a decision about treatment.

## Regional Staging

US is more sensitive than physical examination in the detection of axillary nodal metastases. It can visualize high axillary, infraclavicular, and internal mammary (IM) lymphadenopathy that cannot be assessed with palpation or mammography. US, however—like all other morphological imaging modalities—cannot detect nodal metastases that are smaller than 0.4–0.5 cm.

For the past 25 years at MD Anderson, we have included the ipsilateral axilla (including the infraclavicular [level III axillary] nodes) and the IM chains in the US examination of the breast in patients who are suspected of having or have been diagnosed with breast cancer [1]. If suspicious nodes are found in the axilla, the examination is extended to include the supraclavicular fossa and the low neck.

Examination of the nodal basins is performed with the patient supine. The arm is elevated for examination of the axilla and brought back down for examination of the infraclavicular region, supraclavicular fossa, and low neck. During the examination of the axilla, the landmarks are the axillary and subclavian vessels and the pectoralis minor muscle, whose lateral and medial borders separate axillary levels I, II, and III (infraclavicular).

The sentinel node cannot be reliably identified with standard gray-scale US. A few research studies have focused on the use of US contrast agents to identify the sentinel node, but these techniques are not yet ready for clinical use [23, 24].

Examination of the IM chains is done by scanning along the edge of the sternum [25]. In all nodal basins, PDUS is used to evaluate the nodes' internal vascularity, especially when the nodes have an indeterminate appearance on gray-scale sonograms.

When there is any doubt about the ipsilateral nodal findings, the contralateral nodal basin is examined. This provides a reference for normality, although some systemic diseases (e.g., lupus) may result in abnormal nodes bilaterally.

### US Appearances of Normal Lymph Nodes

On US, normal axillary lymph nodes are elongated, with an elliptical shape. They contain a high proportion of central echogenic tissue, which is generally considered to represent fatty involution but may also represent the reflective network of blood and lymphatic vessels in the hilum. The cortex is usually hypoechoic, with an echogenicity similar to that of the hypoechoic subcutaneous fat (supplemental online Fig. 4). Sometimes, the central portion of the echogenic hilum is also hypoechoic, leading to a target pattern consisting of three even, concentric areas of alternating echogenicity: hypoechoic, echogenic, and hypoechoic (from the periphery to the hilum). The normal nodes in the axilla show a wide range of sizes, from a few millimeters up to several centimeters. Some large, totally fat-replaced nodes, which are homogeneously echogenic, are difficult to detect, and their identification relies on the very thin, smoothly lobulated residual hypoechoic cortical lining.

In normal nodes, PDUS shows scant harmonious vascularity branching from the hilum toward the periphery of the node or no vascularity at all.

Breastfeeding is usually associated with enlargement and decreased echogenicity of the axillary nodes bilaterally. In a breast-feeding patient diagnosed with breast cancer, such an



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appearance should not be mistaken for nodal metastases; the clue to the correct diagnosis is the grossly similar appearance of the bilateral axillary nodes.

Intramammary nodes are very common and are found in the outer breast quadrants. Their mammographic appearance is often characteristic, and so is their US appearance, with the fatty echogenic hilum correlating with the radiolucent notch on mammograms. PDUS may show typically benign hilar vascularization.

Normal IM nodes measuring 2–3 mm are sometimes seen on MRI but are not visible on US. On US, subcentimeter fat-containing nodes are seen occasionally in the infraclavicular region, less rarely in the supraclavicular fossa, and commonly in the jugular territories.

## US Appearances of Lymph Node Metastases

Based on the physiological circulation of lymph inside nodes, metastatic deposits are expected to appear first at the periphery of a node, where the afferent lymphatics enter. Therefore, the periphery of nodes requires the greatest attention of the sonologist. Although we tried to develop US shape and size indices to distinguish between benign and malignant nodes, none of them proved reliable. In our experience, the US diagnosis of a lymph node metastasis is thus based on two findings: (a) a focal deformity (usually a bulge) at the early stage (Fig. 4) or a global change in shape such as a rounded or even taller-than-wide node at a later stage; and (b) a marked decrease in echogenicity of the abnormal area representing an intranodal metastatic deposit (supplemental online Fig. 5), with the eventual disappearance of the echogenic hilum at a very late stage of nodal involvement [26]. Detection of nodal metastasis is easiest in the case of a markedly hypoechoic metastatic deposit contrasting with the echogenic background of a node that is otherwise completely replaced by fat. In that case, metastatic deposits as small as 5–6 mm can be detected (Fig. 4). However, if the metastatic deposit is not markedly hypoechoic (e.g., a metastasis from invasive lobular carcinoma in which the tumor is composed of fibrosis and few cells), the absence of contrast between the deposit and the echogenic background will lead to the false-negative US diagnosis of a normal node.

The presence of microcalcifications inside a lymph node, especially if the primary tumor contains some, is virtually pathognomonic of metastatic disease.

PDUS has not helped in the differentiation between benign and malignant nodes as much as it has helped distinguish between benign and malignant solid tumors in the breast. The reasons for that are unclear. In our experience, the vascularity associated with nodal metastases ranges from absent to rich and disorganized. This limits considerably the role of PDUS in the diagnosis of early nodal metastases. Some large metastatic deposits are avascular, perhaps because the development of neovessels is outpaced by the fast growth of the metastatic deposit. In such cases, the avascular focal mass displaces the otherwise harmonious existing internal vascular tree (supplemental online Fig. 6). Conversely, we have found that in benign reactive nodal hyperplasia, PDUS often shows a dense harmonious vascular network covering the entire thickened hypoechoic cortex of the node up to the capsule; the vessels are fine and parallel, resembling the perfusion of the renal cortex (supplemental online Fig. 7). Although a micrometastasis cannot be excluded in such cases, a macrometastasis even as small as 4–6 mm would likely disrupt the arrangement of those fine parallel vessels.

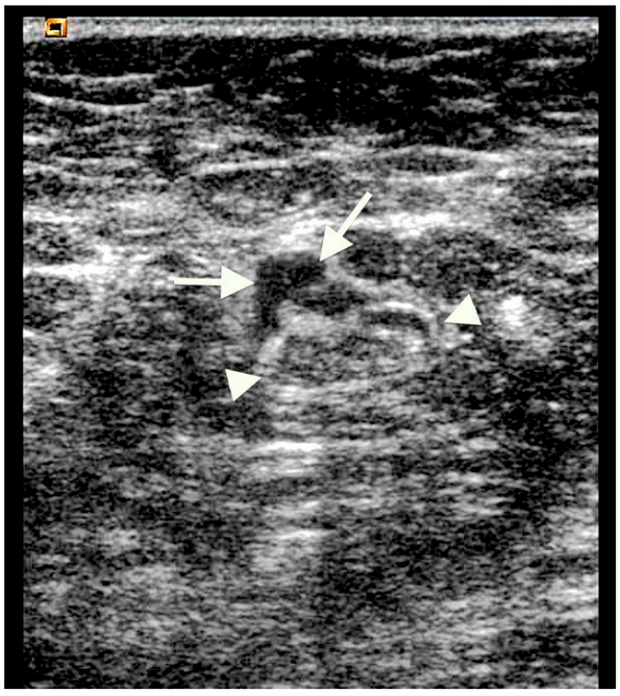

**Figure 4**. Early axillary lymph node metastasis. Sonogram shows a small but prominent bulge (arrows) at the periphery of an otherwise normal, fat-replaced level I axillary node (arrowheads).

In a patient with a known history of breast cancer, a node that is enlarged, deformed, and/or completely hypoechoic on US is almost certainly positive for metastasis, and US-guided needle biopsy is performed to confirm the diagnosis. By contrast, a node that is completely replaced by echogenic fat is benign (with the caveat of invasive lobular carcinoma). Nodes that have an indeterminate US appearance or that are seen in an area in which nodes are not normally seen (IM chains, supraclavicular fossa) are suspicious until proven otherwise and must be diagnosed with a US-guided needle biopsy.

## US-Guided Needle Biopsy of Indeterminate Lymph Nodes

US-guided FNA has been used routinely for more than 2 decades at MD Anderson to aspirate indeterminate lymph nodes to rule out or confirm metastatic involvement in any of the regional nodal basins, including the IM nodes (Figs. 5, 6) [1]. FNA of lymph nodes is easy to perform because normal as well as abnormal nodes contain abundant cellular material; therefore, core-needle biopsy of nodes is not needed unless there is no qualified cytopathologist available to read FNA smears. Furthermore, because most nodes detected by US (except for level I axillary nodes) are located close to blood vessels, it is not advisable to use a long-throw automatic cutting needle. In fact, in some basins, such as the IM chains, core-needle biopsy is not feasible because of the nodes' proximity to the internal thoracic vessels and pleura. Prior to any needle biopsy attempt on a lymph node, verifying the location of adjacent vessels with PDUS is recommended.

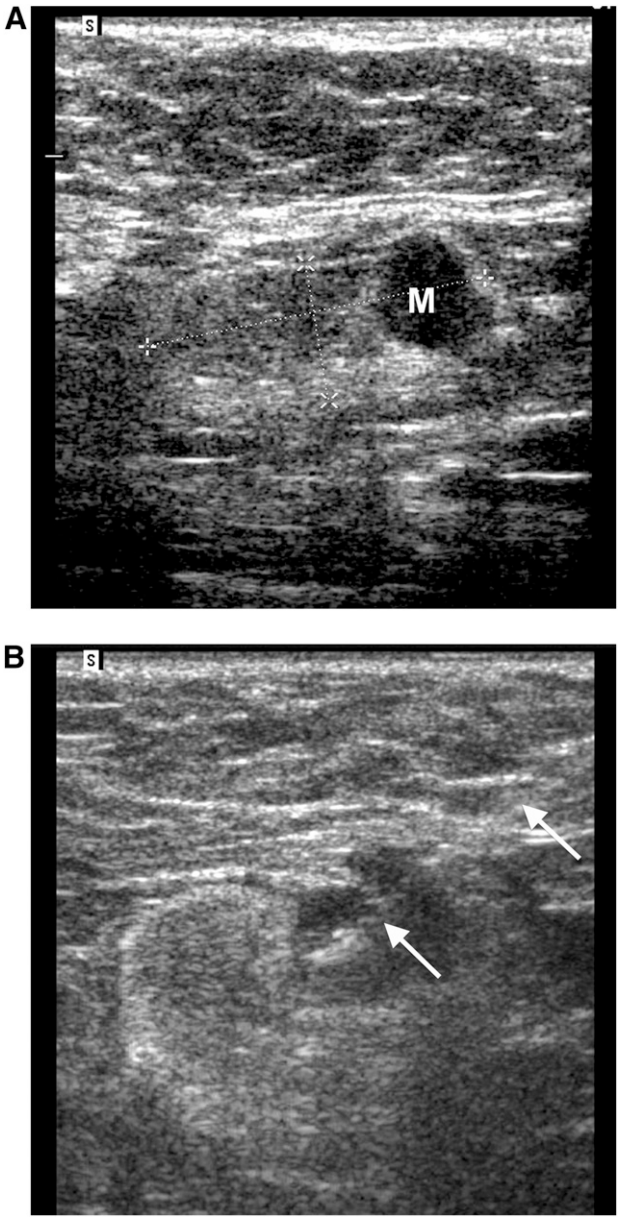


**Figure 5**. Axillary lymph node metastasis. Ultrasound-guided fine-needle aspiration (FNA). **(A):** Sonogram shows the markedly hypoechoic malignant deposit deforming the lower pole of an otherwise normal, fat-replaced node (calipers). **(B):** Sonogram obtained during ultrasound-guided FNA shows the bright tip of the echogenic fine needle (arrows) in the center of the metastatic deposit.

Abbreviation: M, malignant deposit.

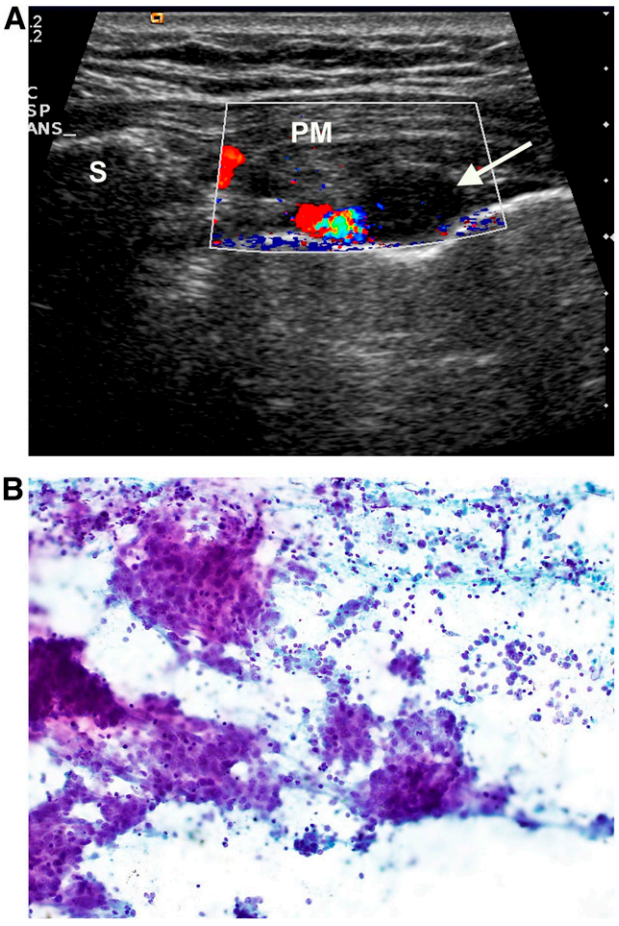


**Figure 6**. Internal mammary lymph node metastasis. **(A):** Transverse color Doppler sonogram of the second left intercostal space shows an 8-mm × 5-mm markedly hypoechoic node (arrow) lateral to the internal thoracic artery (in green) and vein (in red). Note the indentation of the pleura by the node. **(B):** Low-power photomicrograph of the cytological smear from the ultrasound-guided fine-needle aspiration shows abundant adenocarcinomatous material consistent with metastatic breast cancer of low grade (Papanicolaou stain).

Abbreviations: PM, pectoralis major muscle; S, edge of the sternum.

With proper technique and equipment (usually a 20-gauge, 1.5-inch-long or a 21-gauge, 2-inch-long hypodermic needle, depending on the depth of the target lesion), a single FNA pass is sufficient to obtain an adequate specimen from a lymph node, and the rate of nondiagnostic specimens should be close to 0% [14]. Except in the case of metastases from invasive lobular carcinomas, which require meticulous screening and cytokeratin staining, the cytopathological diagnosis of lymph node metastasis is relatively straightforward as long as the submitted specimen is adequate. Causes of false-negative results of US-guided FNA include errors in targeting a small lesion (missed target) or inadequate aspiration technique, which failed to extract a quantitatively and qualitatively satisfactory specimen. A regional nodal metastasis also may have been missed because the lesion was not seen owing to an incomplete examination of the axilla or because the operator failed to interpret an abnormal node as suspicious.

When multiple suspicious nodes are detected in different basins, the node that should be aspirated first is the one that would have the greatest effect on the stage. For example, in the presence of suspicious infraclavicular and axillary nodes, FNA should be done on an infraclavicular node first. Should it yield a benign diagnosis, then an axillary node should be sampled [26].

Because of the difficulty accessing the IM nodes with FNA and the risk of major complications of FNA owing to their proximity to vital structures, US-guided FNA of IM nodes should be performed only by imagers with extensive experience in interventional US and only in patients in whom the result of the procedure is expected to alter both staging and



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management. For FNA of IM nodes, the internal thoracic vessels are carefully identified using CDUS or PDUS. Then, adequate local anesthetization is performed under full US monitoring, following a lateral-to-medial approach through the pectoralis major muscle. Next, the FNA needle is inserted with a very shallow angle to remain as parallel to the pleura as possible for maximum safety. Extreme care must be taken to clearly visualize the needle tip during its entire progression and to keep it at a safe distance—sometimes only a few millimeters—from the internal thoracic vessels and from the pleura (supplemental online Fig. 8). The rare location of an abnormal node behind the sternal edge or behind a costal cartilage may render FNA even more challenging or impossible.

## Impact of US and US-Guided FNA of Regional Nodes on Staging

The impact of US and US-guided FNA of regional nodes on staging can be substantial, and the added information can significantly alter a patient's treatment [27]. After the detection and confirmation of at least one clinically occult (axillary, infraclavicular, or internal mammary) nodal metastasis in a patient with a newly diagnosed breast cancer, the disease becomes de facto at least stage II [13]. At MD Anderson, the confirmation of such lymphatic spread will trigger a recommendation for neoadjuvant therapy.

After the detection and confirmation of at least one clinically occult (axillary, infraclavicular, or internal mammary) nodal metastasis in a patient with a newly diagnosed breast cancer, the disease becomes de facto at least stage II. At MD Anderson, the confirmation of such lymphatic spread will trigger a recommendation for neoadjuvant therapy.

The finding of an axillary nodal metastasis makes a sentinel lymph node biopsy unnecessary; these patients will typically undergo a complete axillary dissection instead [28–32]. However, the complete strategy to evaluate and treat the axilla is currently being revisited in light of the results of the Z-0011 trial of the American College of Surgeons Oncology Group: that study showed no reduction in the locoregional recurrence rate with completion axillary dissection in patients with positive sentinel nodes [33].

Detection of an ipsilateral infraclavicular lymph node metastasis (N3a), an ipsilateral IM nodal metastasis in the presence of positive axillary node(s) (N3b), or an ipsilateral supraclavicular lymph node metastasis (N3c) makes the disease stage IIIC. Metastasis to more distant nodal basins, such as the ipsilateral neck, and to any contralateral nodal basin is coded as distant metastasis (M1) and therefore makes the disease stage IV [13].

After the detection and diagnosis of an IM nodal metastasis (stage IIIA or IIIB in the absence and stage IIIC in the presence of a positive axillary node), chemotherapy will be given to the patient. Following a response to neoadjuvant therapy, the radiation therapist will likely include the involved IM chains in the radiation fields. A change of management—institution or omission of radiotherapy to the IM chain, adjuvant systemic therapy, or omission of an axillary lymph node dissection—has been reported in 29% of patients found to have IM nodal metastases [34].

US often detects very low-volume metastases in basins that are not evaluated during routine clinical staging for early breast cancer, such as the infraclavicular region and IM chains. Additionally, the literature has shown the impact of such involvement on prognosis, hence the importance of screening these basins with US during the staging process [35].

## Staging Considerations for Each Regional Nodal Basin

### *Axillary Nodes*

To stage the axillary nodes accurately, the sonologist must identify the pectoralis minor muscle, which delineates the three levels of axillary nodes (supplemental online Fig. 9), as the presence of positive level III (infraclavicular) nodes would change the stage from II to IIIC.

Pitfalls in axillary staging include a number of benign conditions that can result in indeterminate or suspicious nodes on US. These include any inflammatory or infectious condition that can cause reactive nodal hyperplasia. For example, systemic diseases such as rheumatoid arthritis or lupus are often associated with bilateral axillary lymphadenopathy. In patients with a history of silicone-gel implants, silicone-induced granulomas can be found in the axilla, in any other regional nodal basin, and in surrounding soft tissues. These granulomas have a pathognomonic "snowstorm" appearance on US. However, it is possible for a metastasis to develop in a silicone-induced granuloma. Other benign lesions appearing as small, elongated, nonspecific hypoechoic masses that may mimic a suspicious node include nerve sheath tumors, lipomas, fibromas, and postoperative neuromas.

### *Intramammary Nodes*

Intramammary nodes are coded as axillary nodes in the TNM system. When a prominent intramammary node is seen close to a recently diagnosed invasive cancer, the node should be viewed with suspicion and sampled with FNA. However, there is a possibility that the lymphatic spread bypassed it and progressed to involve the axillary nodes. Therefore, a negative FNA of an intramammary node close to a primary cancer should prompt FNA of other suspicious nodes in the axilla.

### *IM Nodes*

Although the status of the IM nodes is unknown in the majority of breast cancer patients treated today, IM nodal metastases are found more frequently in patients with medial tumors, in patients with larger tumors, and in young patients [36, 37]. In a historical series of cancer patients who underwent mastectomy with IM node dissection, 9% of patients who did not have axillary node metastases had an IM node metastasis [38]. Because normal IM nodes are too small to be seen on US, in a patient with breast cancer, any solid hypoechoic mass along the IM chains should be viewed as suspicious for metastasis until proven otherwise. Benign lesions that may mimic an IM nodal metastasis include inflammatory nodes, neurofibromas, sarcoidosis, and prominent or ectatic vessels. A complete history before the US examination should be taken to understand any



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previous alteration of the anatomy of the IM nodal basin, such as free flap breast reconstruction or cardiovascular surgery.

## Distant Metastases Detected Incidentally During US

As the scope of the US examination is expanded to cover the regional nodal basins, other structures and organs may come into sight, and new, unusual metastases may be found incidentally. These include metastases to the pectoralis muscles (supplemental online Fig. 10); thyroid metastases, which have the same US appearance as a primary thyroid cancer (supplemental online Fig. 11); or regional bone metastases with cortical destruction, for example, of a rib, the clavicle, or the sternum. US-guided FNA of any of these incidentalomas can be performed and the diagnosis of distant metastasis (stage IV) confirmed within minutes.

## Communicating the Results of the Staging Examination

### Between the Technologist and the Radiologist

At the beginning of our experience, I designed the following color codes to be used by our technologists to plot detected lesions on a diagram of both breasts and the regional nodal basins: red for malignant masses, black for cysts, green for benign solid neoplasms (e.g., fibroadenomas, papillomas), orange for benign fluid collections (e.g., seromas, hematomas, oil cysts), yellow for fat-containing masses (e.g., benign intramammary nodes), and no color (an open circle) for indeterminate masses. Each technologist fills out the diagram upon completion of the US examination so that the radiologist checking the case can understand in a few seconds what the technologist's findings are. This document is scanned and integrated into the digital US examination file. Figure 7 shows an example of such a diagram detailing the results of a staging US examination in a patient referred with an undiagnosed palpable breast mass. The diagrams are useful not only for staging but also when comparing a US examination with a previous one, such as when evaluating the response of a breast cancer to neoadjuvant chemotherapy or when following patients with metastatic breast cancer who are receiving maintenance chemo- or hormonotherapy.

At our institution, the cost of breast US is approximately one tenth that of breast MRI, and the cost of a US-guided FNA is one third that of an MRI-guided biopsy. As important as the cost reduction are the time and the number of patient visits needed to obtain complete (i.e., pathologically verified) information about the local and regional stage of a given patient. Having that information at the end of the day of the patient's first visit is invaluable.

### Between the Radiologist and the Patient

At MD Anderson, the radiologist checks every US examination and at the end discusses the findings with the patient. When staging a suspicious or already diagnosed breast cancer, the preliminary results of the staging FNAs that are performed to confirm multicentricity or lymphatic spread are available within 15 minutes and can therefore be shared with the patient. The findings may indicate that an anticipated breast-conserving surgery will need to be replaced by a mastectomy or performed only after 6 months of neoadjuvant therapy. Giving such bad news to a patient—who may not even have known that she had breast cancer when she entered the room—requires both professionalism and compassion.

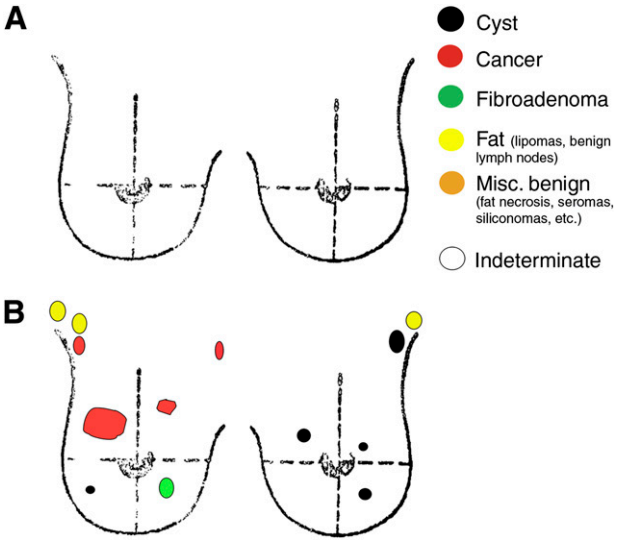


**Figure 7**. Color-coded diagram used at MD Anderson to convey staging information obtained from the sonographic examination. **(A):** Color code. **(B):** How to read the diagram. Theoretical example of a staging sonographic examination performed immediately after the mammographic workup of a patient with a palpable right breast mass and very dense breasts on mammograms. Sonography (US) confirms that the palpable mass in the 10–11 o'clock position that is suspicious on mammograms is indeed a typical malignancy (in red). US-guided core biopsy is done, followed by clip placement. The diagram represents the primary tumor in the 10–11 o'clock position of the right breast; a second nonpalpable and mammographically occult focus of malignancy (in red) in the 1 o'clock position has been detected by US and diagnosed via fine-needle aspiration (FNA), confirming multicentric disease; one nonpalpable axillary lymph node metastasis and one ipsilateral internal mammary lymph node metastasis (both in red) have been detected by US and confirmed via US-guided FNA, confirming stage IIIC disease. A density suggested at 4 o'clock on the right breast mammograms is confirmed by US as a typical fibroadenoma (in green). In the contralateral breast, US detects a few small simple cysts (in black). Benign fat-replaced nodes (in yellow) are seen in the bilateral axillae.

## Restaging After Neoadjuvant Chemotherapy

At MD Anderson, the responses of the primary tumor and nodal metastases to neoadjuvant chemotherapy are evaluated with US. The staging US examination is the baseline study. A second US examination is performed at 3 months—after 12 weeks of paclitaxel or docetaxel and before 3 months of 5-fluorouracil-doxorubicin-cyclophosphamide or 5-fluorouracil-epirubicin-cyclophosphamide (or vice versa) [39]. A third US examination is performed at the end of neoadjuvant treatment, that is, approximately 6 months after the initial examination, and the disease is restaged and the malignant lesions are mapped and measured again [40, 41]. At that point, tumors often have completely regressed and the attention is focused on the identification of the tumor bed(s) and the

metallic marker(s) that may have been deployed for preoperative localization.

## Conclusion

In summary, in daily practice, if a technically satisfactory US examination can (a) measure the primary breast tumor, (b) detect and pathologically confirm one additional lesion that proves multicentric disease, and (c) detect and pathologically confirm a lymph node metastasis, with all diagnoses confirmed within 15 minutes, then US has done the job. However, whenever the US examination is technically limited (e.g., in the case of invasive lobular carcinoma or breasts with extensive diffuse fibrocystic changes, the so-called "hard-to-scan" breasts), MRI should be called upon. This occurs in less than 10% of breast cancer cases.

The cost effectiveness of breast cancer staging with US has rarely been measured, and only the role of preoperative US of the axilla has been addressed, with the confirmation of a cost reduction associated with the use of axillary US [42]. At our institution, the cost of breast US is approximately one tenth that of breast MRI, and the cost of a US-guided FNA is one third that of an MRI-guided biopsy. As important as the cost reduction are the time and the number of patient visits needed to obtain complete (i.e., pathologically verified) information about the local and regional stage of a given patient. Having that information at the end of the day of the patient's first visit is invaluable.

In patients with suspected or recently diagnosed breast cancer, the US examination must include the entire breast and the ipsilateral nodal basins, including the axilla, the infraclavicular region, and the IM chains. US-guided FNA is used to confirm multifocality or multicentricity and lymph node metastasis. US is the only real-time cross-sectional imaging modality and for that reason retains its status of best imaging modality for guiding needle biopsies.

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