Imaging of the lymphatic spread of breast cancer

In patients with breast cancer, the presence of nodal metastases limits the therapeutic options and also indicates a worse prognosis. When a potentially "early" curable cancer has been detected, the next most critical step is therefore to determine whether the nodal basins are involved as part of the staging process. The TNM classification system was recently revised to better reflect the prognostic implications of the discovery of lymph node metastasis in the various nodal basins draining the cancer-containing breast [1].

General considerations

The limitations of physical examination of the relevant nodal basins are well known. For many years, mammography has been the sole imaging modality with which to image the axilla, with very limited results. Recent imaging modalities available to assess the nodal basins include morphologic cross-sectional imaging modalities, which rely on size and morphologic criteria, like sonography (US) and CT, and newly developed functional or molecular modalities, such as dynamic MRI, lymphoscintigraphy, and PET-CT, which rely on tumoral angiogenesis and/or the metabolism of malignant cells.

A few points must be kept in mind when using imaging modalities to detect lymph node metastases from breast cancer:

✔ With all recent imaging modalities, the criteria for the diagnosis of lymph node metastasis remain to be defined (and evaluated).
✔ There are multiple nodes in each basin and a one-to-one correlation between the nodes imaged in vivo and the nodes examined pathologically from the surgical specimen is rarely - if ever - possible, which may lead to errors in the reporting of a modality's diagnostic accuracy. An alternative method of correlation would be image-guided needle biopsy of any abnormal node with placement of a metallic marker for subsequent identification during the pathologic examination of the surgical specimen from axillary node dissection.
✔ Imaging techniques that rely on blood perfusion cannot be used for ex vivo examination of surgical specimens from axillary node dissection.
✔ Currently, no imaging modality can detect micrometastases (<2 mm in diameter), the significance of which remains controversial. Although micrometastases possibly affect long-term survival, there is debate about whether their presence should alter patient management.
✔ In patients with breast cancer, the presence of nodal metastases limits the therapeutic options and also indicates a worse prognosis. When a potentially "early" curable cancer has been detected, the next most critical step is therefore to determine whether the nodal basins are involved as part of the staging process. The TNM classification system was recently revised to better reflect the prognostic implications of the discovery of lymph node metastasis in the various nodal basins draining the cancer-containing breast [1].

Mammography

Mammography can demonstrate some of the axillary nodes but cannot assess the entire axilla. At both ends of the spectrum of metastatic involvement, mammography is relatively reliable in showing completely fat-replaced benign nodes and totally tumor-replaced metastatic nodes (Fig 1), but it cannot detect metastases in unenlarged lymph nodes and cannot differentiate benign reactive hyperplasia (BRH) from metastasis. On the other hand, mammography easily demonstrates small intramammary nodes in fatty breasts and is unsurpassed in showing microcalcifications in metastatic nodes (Fig 2).

CT

Chest CT, like mammography, cannot differentiate between a metastatic node and a node with BRH. Its main
superiority over other imaging modalities is the successful visualization of lymphadenopathy along the internal mammary chains (Fig 3) and in the deepest portions of the axilla and of the infraclavicular region. This is helpful when US is limited by technical factors such as obesity or because of limited access with the transducer.

**MRI**

On MRI, metastatic nodes show irregular contours, high signal intensity on T2, round hila and abnormal cortices, and marked gadolinium enhancement [2]. The accuracy of MRI in the diagnosis of metastatic nodes is somewhat limited but is expected to improve with new techniques such as the use of ultrasmall superparamagnetic iron oxide enhancement [3, 4]. Notable obstacles to MRI’s widespread usage are its high cost and limited availability. Also, because needle biopsy under MRI is not yet a routine procedure, indeterminate findings cannot be unequivocally confirmed via pathologic analysis of a biopsy sample.

When morphologic features like eccentric cortical hypertrophy were used as criteria for malignancy, MRI had a sensitivity of 79%, a specificity of 93%, and an accuracy of 88%. In 16 of 17 false-negative axillae, MRI showed normally sized lymph nodes (<10 mm). MRI is a useful diagnostic method for the evaluation of axillary nodal status but is limited in the detection of small metastatic lymph nodes [2, 5].
**Lymphoscintigraphy**

Lymphoscintigraphy is performed routinely in most high-resource institutions to identify the sentinel node(s) preoperatively and intraoperatively in patients with breast cancer and clinically negative axillary nodes.

A preoperative lymphoscintogram is obtained in most patients who undergo sentinel node biopsy regardless of the location of the primary tumor. At the University of Texas M.D. Anderson Cancer Center, we inject a high dose (2.5 mCi) of technetium Tc 99m sulfur colloid the day before the operation, thus eliminating the need for a repeat injection the day of the operation [6] (Fig 4). The radiolabeled colloid is injected around the tumor into the breast parenchyma. In patients with nonpalpable tumors, the radiolabeled colloid is delivered under US or mammographic guidance. Most studies have demonstrated an average of 2 axillary sentinel nodes per patient.

Approximately 20% of patients will have drainage to infraclavicular, supraclavicular, or internal mammary nodal basins either alone or in combination with drainage to the axillary nodes.

The role of lymphoscintigraphy is restricted to pointing out where the sentinel node is without the capability of telling whether the node is benign or malignant, hence the need for its excision and pathologic analysis.

**PET**

PET - now combined with CT for a more accurate 3D localization of lesions - has become the modality of choice for global staging of many cancer patients and for evaluation of response to treatment. The identification of tumor spread to the axillary nodes or to more remote nodal groups (i.e., internal mammary or supraclavicular nodes) is probably the most practical information that PET can offer. Currently, however, its accuracy in the detection of early nodal involvement appears limited, with sensitivity, specificity, and positive and negative predictive values of PET in the diagnosis of axillary metastasis of 20%, 100%, 100%, and 58.6%, respectively [7]. Because its cost is even higher and its availability more limited than that of MRI, PET is not recommended for routine local/regional staging of breast cancer [8]. Smaller, dedicated PET scanners are being developed which may well modify this recommendation.

**US**

US is more sensitive than physical examination in the detection of axillary nodal metastases and can visualize high axillary, infraclavicular and internal mammary lymphadenopathy that cannot be assessed with palpation and mammography.

**Instrumentation and examination technique**

Recent advances in US equipment used for small body parts include very high-frequency and multi-array transducers that operate at peak frequencies of up to 17 MHz and provide exquisite spatial resolution. Such transducers now allow visualization of lymph node metastases as small as a few millimeters.

Among recent image-processing techniques, real-time compound scanning, which was initially predicted to provide higher-quality images than those attainable with conventional US, has not proved as beneficial as hoped. In fact, in our experience, the significant blurring associated with this technique has had a negative effect on image quality.

Tissue harmonic imaging slightly increases spatial resolution and boosts contrast. In our experience, though, it does not provide any substantial benefit in the sonographic evaluation of nodal metastases.

Three-dimensional US is still investigational but should be helpful in the not-too-distant future and is expected to facilitate the guidance of percutaneous needle biopsy. Recently, elasticity imaging with ultrasound (elastography) has been reported as a promising adjunct imaging modality to conventional US [9].

Finally, over the last decade, the sensitivity of power Doppler US (PDUS) systems has dramatically increased, allowing not only detection of the mere presence of Doppler signals within a node but also detailed mapping of the normal
versus disturbed nodal vascularity. This is expected to help differentiate between benign and malignant nodes.

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. Examination of the internal mammary nodes is done by scanning along the edge of the sternum. For the last 15 years at M. D. Anderson Cancer Center, we have included systematic examination of the ipsilateral axilla and internal mammary chains in the sonographic breast examination of patients who have or have had breast cancer. If suspicious nodes are demonstrated, examination of the nodal basins is extended to include the supraclavicular fossa and the low neck [10].

At the least doubt, examination of the contralateral nodal basin is performed. This usually (although not always) provides a reference for normality.

PDUS (not color Doppler imaging) should be used in most cases to evaluate the internal vascularity of the nodes, especially when they are indeterminate on gray-scale sonograms.

**Normal sonographic anatomy**

In normal adults, the axillary lymph nodes appear as ovoid or elongated (sometimes sausage-shaped) structures containing a large amount of fat, which is usually (but not always) echogenic (Fig 5). PDUS shows harmonious vascular branching from the hilum toward the periphery of the node. During breast-feeding and for a few months afterwards, axillary nodes become moderately swollen and hypoechoic. Such an appearance may be confusing and misinterpreted as suspicious in a woman diagnosed with breast cancer postpartum.

A special mention must be given to intramammary nodes. They frequently appear on mammograms in the outer breast with a characteristic appearance. However, when they grow, a sonographic examination may be required to confirm their benign nature. The demonstration of a small rounded structure with a central echogenic component and hilar vascularization on PDUS is pathognomonic of a benign intramammary node.

Normal internal mammary nodes are not usually visible on US, but tiny fat-containing oval nodes are occasionally seen in the supraclavicular fossa and, more commonly, in the low neck.

**Sonographic diagnosis of lymph node metastases**

The sonographic diagnosis of a lymph node metastasis is based on the enlargement and/or focal deformity (bulge) at the periphery of the node and – at least as importantly – on the marked decrease in echogenicity exhibited by an intranodal metastatic deposit. Because the lymph circulates from the periphery to the hilum of the node, early metastatic deposits develop preferentially at the periphery of the nodes.

**Axillary nodes**

Minute (measuring at least 4 or 5 millimeters) metastatic foci can be detected at the periphery of a totally echogenic node or if they produce a focal hypoechoic bulge on the surface of the node (Fig 6). Even when the central fat is hypoechoic, metastatic deposits appear darker than the hypoechoic fat. Lymph nodes that are massively involved with metastatic tumor are easily recognized on US as rounded (when small) or irregularly shaped (when large) masses with little or no residual central echogenic fat (Fig 7).
If the primary tumor contains microcalcifications, identification of microcalcifications within a node is synonymous with metastatic involvement.

On PDUS, the Doppler signals associated with metastatic nodes range from absent to numerous and disorganized. This wide range of PDUS appearances of malignant nodes considerably limits the role of PDUS in the diagnosis of nodal metastases – at least of small ones. On the other hand, we have found that the demonstration on PDUS of a dense harmonious vascular network covering the thickened cortex of a moderately enlarged node in a fashion similar to the cortical perfusion of a kidney (i.e., with fine, parallel, vessels nearly reaching the capsule) correlates well with the diagnosis of BRH (Fig 8).

Although US with state-of-the-art equipment can reliably detect lymph node metastases larger than 7 or 8 mm, it cannot, like other “nonfunctional” imaging modalities, demonstrate metastases that are only a few millimeters in size.

Because of the paucity of the cellular component of the metastatic deposit, nodal metastases from invasive lobular carcinomas, like the primary tumors from which they derive, can also have a deceptive sonographic appearance and be very difficult to recognize. It is not unusual for such metastatic nodes to appear with an evenly thickened cortex and residual central fat, suggesting a benign node. On cytology, only a few scattered cell groups are seen, and cytokeratin stain is often required for confirmation of the metastatic involvement.

**INTERNAL MAMMARY NODES**

The internal mammary chains constitute the second pathway for lymphatic drainage of the breast. Sonographic examination of the parasternal region is a simple, fast, and effective method of detecting internal mammary lymphadenopathy [11]. Because normal internal mammary nodes are too small to be visible on US, any hypoechoic mass seen along the internal mammary chains in a patient with breast cancer should be viewed as a potential metastasis (Fig 9).

Metastatic internal mammary nodes are classified as N2 (in the absence of clinically evident axillary lymph node metastasis) or N3b (in the presence of clinically evident axillary lymph node metastasis) (Table 1). Detection of an internal mammary nodal metastasis (in addition to axillary metastases) therefore qualifies the disease as stage IIIIC (Table 2).
OTHER NODES

Affected infraclavicular nodes are important to detect and confirm by FNA because their adverse prognostic significance is worse than that of axillary nodes [12].

The presence of metastatic supraclavicular nodes (N3c) qualifies the disease as stage IIIC.

Metastasis to any other lymph node, including the cervical or contralateral internal mammary lymph nodes, is coded as a distant metastasis (M1).

INTRAMAMMARY NODES

When they are involved with metastatic disease, intramammary nodes are coded as axillary nodes. Any suspicious intramammary node in a cancer-containing breast should be sampled with FNA. However, the remote possibility of metastatic axillary nodes coexisting with a benign intramammary node in the vicinity of a cancer should be kept in mind. Therefore, a benign result of the FNA biopsy of an intramammary node should prompt the verification of any additional indeterminate axillary node.

In general and in simple terms, a node that is completely replaced by echogenic fat (a “white node”) is benign. A node that is enlarged, deformed, and completely hypoechoic (a “black node”) is metastatic until proven otherwise.

Table 1 • Classification of the regional lymph nodes in the TNM classification system [1]

| NX | Regional lymph nodes cannot be assessed (e.g., previously removed) |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in movable ipsilateral axillary lymph node(s) |
| N2 | Metastasis in fixed ipsilateral axillary lymph node(s) or in clinically apparent* ipsilateral internal mammary lymph node(s) in the absence of clinically evident axillary lymph node metastasis |
| N2a | Metastasis in axillary lymph node(s) fixed to one another or to the other structures |
| N2b | Metastasis only in clinically apparent* internal mammary lymph node(s) and in the absence of clinically evident axillary lymph node metastasis |
| N3 | Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement; or in clinically apparent* ipsilateral internal mammary lymph node(s) in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement |
| N3a | Metastasis in infraclavicular lymph node(s) |
| N3b | Metastasis in internal mammary and axillary lymph nodes |
| N3c | Metastasis in supraclavicular lymph node(s) |

Note: * Clinically apparent = detected by clinical examination or by imaging studies (excluding lymphoscintigraphy).

Table 2 • Stage grouping of breast cancer in the TNM classification [1]

| Stage 0 | Tis | N0 | M0 |
| Stage I | T1* | N0 | M0 |
| Stage IIA | T0 | N1 | M0 |
| | T1* | N1 | M0 |
| | T2 | N0 | M0 |
| Stage IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T0 | N2 | M0 |
| | T1* | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1, N2 | M0 |
| Stage IIIB | T4 | N0, N1, N2 | M0 |
| Stage IIIC | Any T | N3 | M0 |
| Stage IV | Any T | Any N | M1 |

Note: T1* includes T1mic (microinvasion 0.1 cm or less in greatest dimension).
A hypoechoic node seen in an area where nodes are not normally seen (e.g., internal mammary chains, supraclavicular fossa) is suspicious until proven otherwise.

**Clinical effect of the detection of unsuspected metastatic nodes**

The effect of the sonographic detection of clinically occult metastases in the regional nodal basins on breast cancer staging is substantial. For example, the detection of a nonpalpable metastatic lymph node in the axilla makes the disease at least stage II. The detection of a metastasis in ipsilateral infraclavicular lymph node(s) (N3a), in ipsilateral internal mammary and axillary node(s) (N3b), or in ipsilateral supraclavicular lymph node(s) (N3c) makes the disease stage IIIC (Table 2).

Also, at a time when efforts are being made to reduce unnecessary axillary node dissections, the sonographic detection of a nonpalpable metastasis in an axillary node (confirmed with US-guided FNA) has a substantial effect on patient management because it eliminates the need for a sentinel lymph node biopsy in 14–17% of patients [13, 14].

**US-guided FNA biopsy of indeterminate and/or suspicious nodes**

US-guided FNA biopsy readily permits ruling out or confirmation of metastatic involvement of enlarged lymph nodes in any of the nodal basins, including the internal mammary chains [15] (Fig 10). FNA of lymph nodes is easy to perform because of their rich cellularity; as a rule, a single pass is sufficient to obtain an adequate specimen from a lymph node – benign or malignant – and there is never a need for core biopsy, unless the services of a cytopathologist are not available.

In a review of 103 cases of US-guided FNA biopsy of nonpalpable indeterminate or suspicious/metastatic-appearing lymph nodes in any of the nodal basins, including the internal mammary chains [15] (Fig 10), FNA of lymph nodes is easy to perform because of their rich cellularity; as a rule, a single pass is sufficient to obtain an adequate specimen from a lymph node – benign or malignant – and there is never a need for core biopsy, unless the services of a cytopathologist are not available.

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Possible causes of discrepancies (essentially false-negative results) in US-guided FNA biopsies of axillary nodes include small size of the metastasis (metastases ≤5 mm cannot be visualized), the small number of metastases, and human error, such as incomplete examination of the axilla, the operator’s failure to see the abnormality or to interpret it, and improper technique in performing US-guided FNA (e.g., error in targeting the lesion or inadequate aspiration, resulting in insufficient specimen). Because nodes are easy to aspirate, the rate of obtaining nondiagnostic specimens from lymph nodes should be close to 0%.

**Evaluation of response to neoadjuvant chemotherapy**

At M. D. Anderson, we have used US to quantify the response of breast cancer to preoperative chemotherapy by measuring the volumes of both the primary breast tumor and the metastatic nodes before, during, and after the treatment. The formula for calculating the volume of a prolate ellipsoid (0.52 times the product of the three longest diameters) is used to obtain the volumes of the primary tumor and those of the metastatic nodes, which can then be compared with the volumes of the same lesions calculated on the previous study. This allows the breast imager to provide the clinician with a percentage decrease in volume that accurately reflects the response of the tumor to chemotherapy. Usually, the nodal metastases regress faster and resume a normal appearance sooner than the primary tumor does.

As shown in studies correlating sonographic with pathologic findings after adjuvant chemotherapy, and because of
the known size limit in sonographic detection of nodal metastases, the complete sonographic disappearance of metastatic nodes does not mean complete healing of the nodes. However, the residual pathologic disease in those patients without residual abnormal nodes on US after neoadjuvant chemotherapy has been shown to be of low volume, including micrometastases [17, 18].

Future of sonographic imaging of lymph nodes

It has been shown that contrast-enhanced US with microbubble agents can be used to differentiate benign from malignant superficial nodes [19]. Recently, a 25% albumin solution was used as a negative contrast agent for sentinel lymph node imaging; 5 mL of the solution was injected superficial to the breast primary tumor. Gray-scale US was able to identify the sentinel node on the basis of the hypoechoegenicity generated by the arrival of the albumin solution in the sentinel node [20].

Oddly, US has received very little attention to date as a molecular imaging tool. Recently, however, the use of a lymph node-specific microbubble agent, which incorporates an antibody that targets the L-selectin ligand expressed in lymph node venules, was reported [21].

References

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Conclusion

In 2007, US with US-guided FNA remains the most practical and cost-effective technique for evaluating the lymphatic involvement of a newly diagnosed breast cancer.