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The prospective role of duplex ultrasound and magnetic resonance imaging in the evaluation of axillary lymph node involvement in breast cancer

Jill Suzanne Oxley

Yale University

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THE PROSPECTIVE ROLE OF DUPLEX ULTRASOUND AND MAGNETIC RESONANCE IMAGING IN THE EVALUATION OF AXILLARY LYMPH NODE INVOLVEMENT IN BREAST CANCER

JILL SUZANNE OXLEY

Yale University

1996
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[Date]
The prospective role of duplex ultrasound and magnetic resonance imaging in the evaluation of axillary lymph node involvement in breast cancer.

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by
Jill Suzanne Oxley
1996
In this investigation, we hypothesized that evaluation of axillary lymph nodes with ultrasound examination, using both morphologic and flow characteristics, and/or evaluation with gadolinium-enhanced magnetic resonance imaging (MRI) may detect metastatic involvement of the axillary lymph nodes in breast cancer patients.

We first set out to establish a protocol for gadolinium-enhanced MRI of the axilla using cadaveric dissection and MRI, and MRI of a normal subject. Subsequently, patients with biopsy-proven breast cancer were recruited to undergo axillary ultrasound and/or MRI examinations prior to axillary lymph node dissection. Six patients underwent axillary ultrasound examinations; one patient underwent MRI as well. The results of the exams were compared with the surgical pathology; in addition, a retrospective analysis of the identified lymph nodes was performed in order to identify specific characteristics that may prove useful in distinguishing benign from malignant axillary lymph nodes.

Of the six patients studied, ultrasound examination correctly classified two of three histologically positive axillae, and one of three histologically negative axillae. Both ultrasound and MRI failed to detect metastatic involvement in one patient. Retrospective analysis of the lymph nodes identified with ultrasound suggests that the length-to-width ratio (L/W ratio) of the nodes may correlate with tumor involvement; lymph nodes with a L/W ratio of >1.5 were more likely to be normal, while lymph nodes with a L/W ratio of <1.5 were more likely to be metastatic. Other characteristics which were not quantified,
such as abnormal flow patterns and loss of central echogenicity, may also point toward
tumor involvement in axillary nodes.

In conclusion, as a direct result of this preliminary work, an ongoing investigation
is underway using ultrasound in the evaluation of axillary lymph nodes in patients with
breast cancer. While the accuracy is limited to date, further refinement of this technique
may identify which characteristics are most valuable in differentiating benign from
malignant lymph nodes. Patients with normal-appearing nodes would still need to undergo
axillary lymph node dissection in order to rule out micrometastases, but patients with
abnormal-appearing nodes, especially in the context of high clinical suspicion, could
potentially proceed directly to adjuvant therapy. In addition, although not investigated
here, the use of ultrasound-guided fine needle aspiration biopsy when abnormal appearing
nodes are identified may further refine this technique.
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INTRODUCTION

BREAST CANCER AND AXILLARY LYMPH NODE DISSECTION

Statistics

Cancer is the second leading cause of death for women of all ages, and the leading cause of death for women ages 35-74 in the United States. Broken down by site, breast cancer is the second leading cause of cancer death for women of all ages, and the leading cause of cancer death for women ages 15-54, with 43,583 deaths due to breast cancer reported in 1991. It is estimated that one in eight women in the United States will develop invasive cancer of the breast in her lifetime, with 182,000 new cases predicted to develop in women in 1995.¹

Axillary lymph node involvement is the most important indicator of prognosis in breast cancer patients. Approximately 50% of patients with breast cancer detected on physical exam, and 10-20% of patients with mammographically detected breast cancer will have histologically involved axillary lymph nodes.²³ The ten-year survival for patients with negative lymph nodes has been reported to range from 65-80%, while for patients with positive nodes, ten-year survival is 25-48%, decreasing in this group with an increasing number of involved nodes.² In addition, axillary lymph node involvement is a major factor in the decision to pursue adjuvant therapy. At present, the presence or absence of node involvement, pre- or post-menopausal status, and the presence or absence of estrogen receptors on the primary tumor are considered in making adjuvant therapy decisions.

Staging

At present, there are both clinical and pathologic staging systems for breast cancer. The most widely used staging system is the clinical staging system of the International
Union against Cancer and the American Joint Committee, which is based on the T, tumor, N, nodes, and M, metastases at the time of clinical presentation (adapted from 2):

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Paget disease without a tumor</td>
</tr>
<tr>
<td>C</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>0.5cm or smaller</td>
</tr>
<tr>
<td>T1b</td>
<td>Larger than 0.5cm, but not larger than 1cm</td>
</tr>
<tr>
<td>T1c</td>
<td>Larger than 1cm, but not larger than 2cm</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor larger than 2cm but not larger than 5cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor larger than 5cm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with extension to chest wall or skin (Note: chest wall includes ribs, intercostal muscles, and serratus anterior muscle, but not pectoral muscle)</td>
</tr>
<tr>
<td>T4a</td>
<td>Fixation to chest wall</td>
</tr>
<tr>
<td>T4b</td>
<td>Edema (including peau d'orange), ulceration of the skin of the breast, or satellite skin nodules confined to the same breast</td>
</tr>
<tr>
<td>T4c</td>
<td>Both T4a and T4b</td>
</tr>
<tr>
<td>T4d</td>
<td>Inflammatory breast cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Nodes (N)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed clinically</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Metastases to movable ipsilateral axillary node(s)</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases to ipsilateral axillary lymph nodes fixed to one another or to other structures</td>
</tr>
<tr>
<td>N3</td>
<td>Metastases to ipsilateral internal mammary lymph node(s)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastases (M)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mx</td>
<td>Presence of distant metastases cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases (including metastases to ipsilateral supraclavicular node(s))</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>TisN0M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T0N1M0</td>
</tr>
<tr>
<td></td>
<td>T1N1M0</td>
</tr>
<tr>
<td></td>
<td>T2N0M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2N1M0</td>
</tr>
<tr>
<td></td>
<td>T3N0M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T0N2M0</td>
</tr>
<tr>
<td></td>
<td>T1N2M0</td>
</tr>
<tr>
<td></td>
<td>T2N2M0</td>
</tr>
<tr>
<td></td>
<td>T3N1M0</td>
</tr>
<tr>
<td></td>
<td>T3N2M0</td>
</tr>
</tbody>
</table>
Stage IIIB  T4 Any N M0
Any T N3 M0
Stage IV  Any T Any N M1

A pathologic staging system is also used, based on histologic examination of the tumor and
the axilla. The pT classification is the same as the T classification except it measures only
the invasive component of the tumor; if there are positive margins, the tumor is pT0.

Lymph nodes are classified as stage I (negative) or stage II (positive), and pathologically
subdivided by the number of positive nodes (adapted from 2):

Pathologic Nodal Involvement (pN)
pN0  No regional lymph node metastasis
pN1  Metastasis to movable ipsilateral axillary node(s)
pN1a Only micrometastasis (none larger than 0.2cm)
pN1b Metastasis to lymph node(s), any larger than 0.2cm
  pN1bi Metastases in one to three lymph nodes, any more than 0.2cm
  and all smaller than 2.0cm in greatest dimension
  pN1bii Metastases to four or more lymph nodes, any more than 0.2cm
  and all smaller than 2.0cm in greatest dimension
  pN1biii Extension of tumor beyond the capsule of a lymph node
  metastasis smaller than 2.0cm in greatest dimension
  pN1biv Metastasis to a lymph node 2.0cm or more in greatest
  dimension
pN2  Metastasis to ipsilateral axillary lymph nodes that are fixed to one
     another or to other structures
pN3  Metastasis to ipsilateral internal mammary lymph node(s)

TECHNIQUE AND MORBIDITY OF AXILLARY LYMPH NODE DISSECTION

The two major primary treatment options for invasive breast cancer are modified
radical mastectomy and lumpectomy with axillary lymph node dissection and postoperative
irradiation. The extent of axillary lymph node dissection may vary. The axilla is bordered
laterally by the latissimus dorsi muscle, and superiorly by the axillary vein; its contents are
subdivided into three levels: level I includes the nodes between the latissimus dorsi muscle
laterally and the lateral border of the pectoralis muscle medially, level II nodes are deep to
the pectoralis minor muscle, and level III (or apical) nodes are between the medial border of
the pectoralis minor laterally and the subclavius muscle (Halsted's ligament) medially; the
interpectoral (Rotter's) nodes are between the pectoralis major and pectoralis minor
muscles. There are an average of 20-25 lymph nodes in the axilla, with an approximate
distribution of from 13, 5 and 2 nodes at levels I, II and III, respectively,\(^3\) to 10, 10 and 5
nodes at each of these levels.\(^4\) The medial pectoral, long thoracic, thoracodorsal and
intercostobrachial nerves are identified and preserved, if possible, during an axillary lymph
node dissection. One or two closed suction drains are usually placed in the axilla and/or
mastectomy site.

The morbidity of axillary node dissection is significant. The most common early
complications are infection (1-14%) and seroma formation (4-30%); others include
superficial phlebitis, venous thrombosis, shoulder stiffness with limited range of motion,
abscess formation and temporary winged scapula.\(^2,3,5,6\) The most significant long-term
complications, however, are lymphedema and pain syndromes secondary to damage to
axillary nerves. Clinically significant arm lymphedema has been reported in 2.7-37% of
patients following axillary lymph node dissection, with both the extent of surgery and
postoperative axillary irradiation contributing to increased incidence.\(^5\) With division of the
intercostobrachial nerve, neuroma formation with significant pain occurs in 4-6% of
patients.\(^2\)

**Areas of Debate in Axillary Lymph Node Dissection**

One important question in performing an axillary lymph node dissection is how to
obtain maximal prognostic information. Fisher et al\(^7\) presented an National Surgical
Adjuvant Breast and Bowel Project (NSABP) update which confirmed axillary node status
as the primary prognostic indicator, and subdivided patients into node-negative, 1-3
positive nodes, and ≥4 positive nodes. Prognosis worsened with increasing number of
positive nodes, with a 5-year disease-free survival of 85% for node-negative patients, 60%
for patients with 1-3 positive nodes, and 30% for patients with ≥4 positive nodes, with
need for further subdivision of this group. They recommended a level I and II axillary
lymph node dissection to quantify node metastases. Barth and Danforth et al\(^8\) confirmed
axillary lymph node status as an important, independent prognostic variable, and demonstrated that it is the number of involved nodes, stratified as above, not the level at which they are found, that impacts on survival. VanLancker et al\textsuperscript{9} have also confirmed that prognosis depends on the number of metastatic nodes, and subdivided the groups into 0, 1-3, 4-9 and \( \geq 10 \) nodes positive, with 5-year disease-free survival 89\%, 82\%, 58\% and 54\%, respectively. Both of these studies have concluded that a level I and II dissection is adequate to quantify disease in the axilla. Complementary analyses of the number of lymph nodes resected\textsuperscript{10,11,12} have concluded that the prognostic information obtained increases up to about 10 nodes resected and examined.

Others, however, recommend full axillary dissection, or clearance, for several reasons. With the use of more aggressive adjuvant chemotherapy or bone marrow transplantation for patients with \( > 10 \) positive nodes, some authors suggest that a level III dissection is necessary to maximize the number of positive nodes identified and more accurately stratify patient prognosis.\textsuperscript{3,13,14,15,16} It is generally accepted that removal of axillary lymph nodes does not impact on overall survival [important exception in \textsuperscript{17}]; however many advocate axillary dissection as a means of regional disease control. Fisher et al\textsuperscript{18} were the first to demonstrate these principles; this group compared the disease-free, distant disease-free and overall survival rates of clinically node-negative women who were treated with radical mastectomy, total mastectomy with regional irradiation or total mastectomy with axillary lymph node dissection delayed until nodes became clinically positive, and of clinically node-positive women who were treated with radical mastectomy or total mastectomy with regional irradiation. No significant differences in survival were found between treatment groups of either nodal status, however in clinically node-positive women, the radical mastectomy group had a lower rate of ipsilateral axillary recurrence (1.0\% versus 11.9\%), but a higher rate of ipsilateral supraclavicular recurrence (5.8\% versus 0\%). They concluded that axillary lymph node dissection is "useful for disease-staging purposes and is therapeutic only in that it reduces the possibility of subsequent
regional recurrences [but] does not alter the incidence of systemic recurrences or patient survival." The rate of axillary recurrence has been shown to vary with treatment by others as well, with an average of 1% with surgical clearance, 3% with axillary irradiation, and up to 20% if the axilla is untreated [review in 13]. Regional node recurrence has also been shown to correlate inversely with the number of lymph nodes removed.19 Since the incidence of clinically significant lymphedema is increased by the combination of surgery and radiotherapy, many authors advocate surgical clearance as a means of decreasing axillary recurrences while avoiding axillary irradiation.13,14,15,16,20

In addition, the question of "skip" metastases impacts on the extent of axillary lymph node dissection. Skip metastases are found in level II and/or level III without involving level I. There is a wide range in the reported occurrence of these metastases. Danforth et al4 studied 136 patients who underwent axillary lymph node dissection in conjunction with a modified radical mastectomy or conservative treatment, and found a 29.2% incidence of skip metastases among node-positive women, or 14.0% overall, with 3.1% of these metastases to level III only; there was an increased incidence of skip metastases among women who were clinically node-negative (36.6% versus 16.7%). They then compared their results to the four previous analyses in the literature [see references in 4], and found that they were compatible with two (whose reported incidences of skip metastases were 25.0% and 27.0%), but discrepant from the others (who found rates of 8.9% and 2.5%), possibly due to differences in defining the boundary between level I and II. Veronesi et al21 analyzed 1446 patients who had undergone total axillary lymph node dissection, 839 of whom had positive nodes, and found only a 1.3% incidence of skip metastases (10 patients to level II, 1 patient to level III); in addition, the probability of upper level involvement increased with the number of positive level I nodes (from 12.1% if 1 positive node, to 83.9% if >4 positive nodes). Likewise Senofsky et al6 found a 2.6% incidence of metastases to level III and/or Rotter's nodes without involvement of levels I or II, and a 43.8% incidence of upper level involvement for all axillae with positive
nodes in levels I or II. Chevinsky et al\textsuperscript{22}, however, demonstrated a 6.7% incidence of skip metastases above level I, and 1.7% above levels I and II; and Toma et al\textsuperscript{23} found a 16.9% incidence of skip metastases (none to level III only). All of the above authors, however, still recommend axillary clearance, either for all patients or for all clinically node-negative patients, for exact determination of prognosis and local control.

There are many, however, who feel that more limited dissections are appropriate, even in the face of skip metastases. Lloyd et al\textsuperscript{24} for example, found that only 1.6% of the 129 patients studied, or 3.2% of the node-positive patients, had skip metastases above level I, but that 45% of patients with positive level I nodes had higher level involvement, comparable to the above studies; they concluded that a level I dissection is appropriate for staging, with further treatment (axillary clearance or radiation) for positive nodes. Likewise, Van Lancker et al\textsuperscript{9} who found a 2% incidence of skip metastases above levels I and II, still recommend a level I and II dissection with the widespread use of adjuvant chemotherapy in node-positive patients. The recommendations from the NSABP\textsuperscript{7}, the American Joint Committee on Cancer\textsuperscript{25} and the National Institutes of Health\textsuperscript{26} however, are a level I and II axillary lymph node dissection for most patients, in order to stage them, determine adjuvant chemotherapy and/or prevent axillary recurrence.

Even more limited dissection has been advocated as an appropriate measure by others. One of the first attempts to limit the extent of axillary lymph node dissection with axillary node sampling (defined as biopsy of the pectoral nodes, i.e. those next to the axillary tail of Spence) by Forrest et al\textsuperscript{27} demonstrated that a mean of only 4 lymph nodes were removed (versus 19 in their axillary clearance patients), but that there were similar rates of positive axillae (43% versus 40%); their false negative rate was nearly 10%, however. There was no difference in survival but an increased rate of axillary recurrence in the group treated with simple mastectomy, axillary sampling and regional irradiation (if node-positive) compared with the group treated with radical mastectomy and regional irradiation (if node-positive). Similarly, axillary sampling, when defined as excision of the
lower half of the axillary fat with any palpable nodes, if present, has been shown to detect fewer nodes overall, but provide the same assessment of the number of positive nodes or positive axillae when compared to a level I and II dissection. This approach has been advocated by others as an adequate qualitative assessment of the axilla, to be used in conjunction with other prognostic information in determining the need for both local radiotherapy and systemic adjuvant chemotherapy. Even the most ardent supporters of axillary clearance (e.g.) acknowledge that axillary sampling may be adequate to stage node-negative patients, but argue that it is not uniformly followed by definitive treatment of the axilla. The debate remains, however, if such definitive treatment is even necessary.

**INNOVATIVE SURGICAL PROCEDURES**

With the continuing debate over the appropriate extent of axillary lymph node dissection, attempts have been made to use lymphatic mapping and sentinel lymphadenectomy to identify metastatic axillary lymph nodes. Giuliano et al describe a modification of the technique used by Morton in melanoma patients. Approximately 5 minutes prior to beginning axillary lymph node dissection, after the induction of general anesthesia, isosulfan blue vital dye was injected into the breast mass (or prior biopsy site) and surrounding tissue. Blunt dissection was begun until either a blue lymphatic tract or a blue lymph node was identified, which was then followed proximally to ensure that the most proximal lymph node was excised. The dissection was then completed to levels I, II and at least part of III.

In the above study, 174 lymphatic mapping procedures were done in 172 patients, and identified 207 sentinel nodes in 114 patients (65.5%); the nodal status was accurately predicted in 109 of these patients (95.6%) with only one false negative. The sentinel nodes were significantly more likely to be positive than other dissected nodes. A further histopathologic analysis of the dissected nodes compared a thorough examination (hematoxylin and eosin plus cytokeratin immunohistochemical stain) of one or two sentinel
nodes with a standard examination (routine hematoxylin and eosin staining) of the remaining axillary specimen. Significantly more metastases were detected in sentinel nodes (42%) than in other axillary nodes (29.1%); micrometastases were also detected in significantly more of the positive nodes (38.2% versus 10.3%) and overall (16% versus 3% of patients). The results of the two analyses led the authors to conclude that, given the unclear benefits of axillary lymph node dissection, lymphatic mapping and sentinel lymphadenectomy with thorough histopathologic examination of the sentinel node or nodes may eventually be used to identify node-negative patients and eliminate axillary lymph node dissection, reserving a complete dissection for node-positive patients.

**Other Determinants of Axillary Lymph Node Involvement**

Since tumor size and axillary node involvement are important prognostic variables in breast cancer recurrence and survival [see STAGING], attempts have been made to determine which characteristics of the primary tumors or the patients themselves impact most on lymph node metastases, and in turn, survival. Research on growth mechanisms in tumors have shown that tumor volume, anatomic stage, estrogen and progesterone receptors, DNA content, proliferation index, oncogene amplification and other clinical and histopathological characteristics all impact on the probability of metastases.33

Studies have attempted to refine the predictive value of tumor size in determining axillary lymph node involvement. One such analysis34 demonstrated that the incidence of axillary lymph node involvement increases with tumor diameter, but also varies with the age of the patient, being lowest in the youngest and oldest age groups. Another group35 demonstrated that when only the invasive component of tumors <3cm is measured, it becomes a more important predictor of node status than the whole tumor size. Others36 propose a modification of the TMN system to add palpability to tumor classification based on their analyses: within a T category, palpable tumors have a significantly increased incidence of axillary lymph node involvement. But while the importance of tumor
size\textsuperscript{37,38,39} and/or the size of the invasive component\textsuperscript{40,41} have been shown to be statistically significant, size\textsuperscript{42,43} and palpability\textsuperscript{39,40,42,43} have also been shown to have no association with lymph node status. Others have examined the impact of the position of the primary tumor on lymph node involvement, with conflicting results.\textsuperscript{40,42} One analysis\textsuperscript{39} included the presence or absence of microcalcifications on screening mammogram, and found a significant association between the absence of microcalcifications and lymph node positivity.

Still others have examined multiple prognostic variables, none of which have been accurate enough to avoid axillary lymph node dissection. For example, studies have shown that tumor grade is\textsuperscript{37,38,39} or is not\textsuperscript{40,42} significantly related to lymph node involvement. Likewise S-phase fraction and patient age were significant predictors of lymph node status in one retrospective study,\textsuperscript{38} but not independently of other factors. Another analysis\textsuperscript{44} demonstrated that tumor size, patient age and S-phase fraction were the most important variables in axillary lymph node status, but could not predict greater than a 95\% chance of being node positive or node negative. An analysis of tumor size, hormonal receptors, DNA ploidy, S-phase fraction and clinical nodal status\textsuperscript{45} demonstrated that patients with clinically negative nodes and tumor size ≤20mm or ≤10mm still had a 25\% and 15\% chance, respectively, of having positive nodes. Some authors view the analysis of these many prognostic variables as promising: Chadha et al\textsuperscript{38} would consider not treating the axilla if several favorable characteristics were present; Walls et al\textsuperscript{39} state that one third of their patients studied could have avoided surgery if certain favorable characteristics were present (tumor <1cm of any grade or a grade I cancer <3mm, with microcalcifications present); and Lehrer et al\textsuperscript{46} have proposed a nomogram which uses tumor size, age and number of pregnancies as an aid in decision-making between axillary node dissection and radiation without node dissection. Many others (e.g. \textsuperscript{37,43}), however still recommend axillary lymph node dissection for all, even the smallest, impalpable tumors.
The Questionable Future of Axillary Lymph Node Dissection

The future role of axillary lymph node dissection is tenuous at best. With the increasing use of adjuvant chemotherapy and identification of other prognostic variables, several authors have suggested that axillary lymph node dissection may become obsolete. Deckers\(^4\) has observed that while prognosis is related to the number of positive nodes, it is systemic therapy, not local treatment, that impacts on survival; and the ongoing evaluation of adjuvant chemotherapy is showing prolonged survival for both node-positive and node-negative women. Likewise Margolese\(^4\) noted that disease in the axilla is not the issue, but who will benefit from adjuvant therapy; axillary lymph node dissection at present identifies the highest-risk patients, who may not be the ones who will benefit most. Cady\(^4\) has observed that this procedure is not cost-effective, especially when used as a diagnostic, not therapeutic procedure; in 100 patients with T1b cancer, for example, he determines that it would cost one million dollars to improve disease-free survival by one patient. In addition, he states that "if management decisions regarding adjuvant systemic therapy for patients with primary breast cancer can be made regardless of the axillary lymph node status [i.e. based on primary tumor characteristics], there is no need for their removal." Halverson et al\(^4\) take this idea one step further, stating that "[axillary lymph node dissection] should be performed only when . . . the patient is thought to be a candidate for adjuvant chemotherapy," and propose an algorithm for patients with tumors \(\leq 10\)mm. They propose that all patients with tumors \(\leq 5\)mm be managed with local therapy alone, axillary observation, and axillary lymph node dissection if a recurrence is noted; all patients with tumors \(>5\)mm who are not candidates for chemotherapy would be managed in the same way, while those who are candidates for chemotherapy would then undergo dissection, and be treated by local therapy alone if the nodes are negative, and by local therapy and chemotherapy if the nodes are positive.

The last argument presents an algorithm based on the feasibility of adjuvant chemotherapy and tumor size, where axillary lymph node dissection is involved in
decision-making in only a subgroup of patients; Lin et al\textsuperscript{50} retrospectively analyzed 283 breast cancer patients with regard to tumor size, DNA, hormone receptors and node status to determine in which subgroups, if any, axillary lymph node dissection actually played a role in management decisions. Dissection was found to have no impact on management decisions for 54\% of the patients studied (i.e. those with clinically negative nodes and unfavorable tumor characteristics). It was important, however, for the 37\% of patients with clinically negative nodes and good tumor characteristics (13\% of these patients were found to have positive nodes at surgery) and for the 15\% of patients with clinically positive nodes (5\% of these patients had favorable tumor characteristics and were spared adjuvant therapy when their nodes were pathologically negative, and 51\% of these patients were found to have ≥4 positive nodes, and were then offered post-operative combined chemotherapy and radiation therapy or high-dose chemotherapy). While the goal of the analysis had been to discover that axillary lymph node dissection played no management role in clinically node-negative patients with favorable tumor characteristics, this was not achieved.

A similar analysis has been attempted at this institution\textsuperscript{51} in an effort to identify subjects in which axillary lymph node dissection could be avoided, either because of extremely favorable prognosis or because node status would not change the management. An analysis of the past 25 years demonstrated a change in management trends by decade: in the 1970s, lumpectomy with irradiation to the breast and regional nodes was common; the 1980s brought increased use of axillary lymph node dissection with consequent irradiation to the breast if node-negative, and hormonal or cytotoxic adjuvant chemotherapy (depending on the menopausal status and tumor pathology) with breast and regional node irradiation; now in the 1990s, systemic adjuvant therapy (either cytotoxic chemotherapy or hormonal) is used for most node-positive women and node-negative women with poor prognostic characteristics of the primary tumor. In the analysis of 292 patients with early-stage disease, only 17.8\% had positive nodes while 91.8\% received adjuvant therapy (38\%
cytotoxic chemotherapy and 53.8% hormonal therapy, with 75% of premenopausal women receiving chemotherapy and 82% of postmenopausal women receiving hormonal therapy). Lymph node status played a role in management decisions for women <50 years of age, for all node-positive women and 67% of node-negative women in this group received cytotoxic chemotherapy; the number of involved nodes influenced the specific regimen chosen. Treatment of patients ≥50 years of age with palpable disease was also influenced by node status, for 68% of node-positive women in this group received cytotoxic chemotherapy, while 72.5% of node-negative women in this group received hormonal therapy. For patients ≥50 years of age with nonpalpable disease, however, which represented >40% of the patient population, lymph node status had little impact on management; 94.9% of these women were node-negative, and 82% of them received hormonal therapy, while the 6.3% that received cytotoxic chemotherapy had primary tumors that were estrogen receptor negative. The author concluded that while axillary lymph node status serves as a prognostic indicator, most patients receive systemic therapy regardless of the result.

Therefore, while many believe that axillary lymph node dissection may eventually become obsolete, there is at present no other reliable prognostic indicator or limited surgical procedure which provides the same information.

**DIAGNOSTIC IMAGING OF AXILLARY LYMPH NODES**

**AXILLARY MAMMOGRAPHY**

For over two decades, many attempts have been made to use various diagnostic imaging modalities to assess axillary lymph nodes. As mammography was developed, attempts were made to image the axilla in the same manner. Kalisher\(^5\) has presented a review of axillary xeroradiography along with his own experience, and concluded that it is of limited but important value. This technique can identify characteristic patterns in lymph nodes, which can then be categorized as normal (but in which micrometastases cannot be ruled out), fatty infiltration, inflammatory or metastatic, or primary lymph node disease.
(hyperplasia or lymphoma). A negative study, however, does not rule out metastases. According to the author, in practice the axillary view is only used when a suspicious lesion is seen or felt, about 10% of cases.

**Computed Tomography**

A similar lack of success has been found with attempts to use computed tomography (CT) as a primary diagnostic modality. The most useful applications of CT have been in staging or follow-up. CT can allow visualization of enlarged, non-palpable, deep axillary lymph nodes as well as distant metastases; metastatic lymph nodes may have increased vascularity, which enhances with contrast administration. A series of 35 patients was evaluated with CT to determine axillary lymph node involvement; abnormal nodes were defined as measuring ≥1cm. While CT could detect enlargement and extracapsular extension of tumor, the sensitivity was only 50%, specificity was 75%, with a positive predictive value of 89% but a negative predictive value of 20%. Since CT is limited to detecting enlarged lymph nodes, it has been shown to be of value in the assessment of inflammatory breast cancer, which more often presents with distant metastases than other breast cancers. A more promising role for CT, however, is in the assessment of recurrent disease in the axilla. CT has been shown able to detect axillary recurrences when disease in the axilla is not palpable, and is as accurate as magnetic resonance imaging (MRI) in distinguishing fibrosis from metastatic disease [the positive predictive value of both is 100%] and usually cheaper and more readily available.

**Magnetic Resonance Imaging**

**Basic Principles**

Magnetic resonance imaging as a diagnostic modality has several clinical advantages, including high contrast in soft tissues, ability to image any plane and no ionizing radiation. It takes advantage of the electromagnetic properties of hydrogen
atoms in the body (or any other atom with an odd number of protons or neutrons). These atoms spin, and when placed in a magnetic field, align parallel or antiparallel to it. Adding a radiofrequency pulse then tilts the protons out of alignment, and in phase with the pulse; when the pulse is removed, the protons become out of phase (T2 relaxation time) and realign with the external magnetic field (T1 relaxation time). Signals are produced during relaxation, which can be converted into cross-sectional images by superimposing a linear gradient field. Basic techniques of spin echo, inversion recovery and gradient echo involve variations of the pulse repetition times, echo times or pulse angles.\textsuperscript{2,58}

Plain MRI attempts to characterize tissues directly by measuring T1 and T2 relaxation times and proton density and by comparing the signal intensities on different pulse sequences.\textsuperscript{59} Early research on magnetic resonance imaging of the breast demonstrated the efficacy of surface coils in improving the signal to noise ratio.\textsuperscript{60} There is, however, much overlap between benign and malignant lesions. In general, on T1-weighted images, fat produces a high-intensity signal, while the nipples, ducts, lobes and most benign and malignant lesions display a low-intensity signal. On T2-weighted images, fibrous tissue has the lowest signal intensity, while tissues with high cell or water content have intermediate to high signal intensities; i.e. all normal tissues again have a low-intensity signal, while fluid collections and malignancies have higher signal intensities, and fibroadenomas may or may not have increased signal intensity [there is a higher cell and water content in fibroadenomas of young women, while there is more fibrous tissue in those of older women].\textsuperscript{58,59,60}

Contrast enhancement attempts to take advantage of the neovascularity of malignancies.\textsuperscript{60} Gadolinium diethylene triamine pentaacetic acid (Gd-DTPA, Magnevist\textsuperscript{®}, Schering) is the first paramagnetic contrast agent approved for clinical use in MRI.\textsuperscript{59} For breast imaging, a T1-weighted pulse sequence is usually used, and the breast is imaged before and after contrast administration. Enhancing tissues have increased signal intensity on T1-weighted images. Diagnosis depends on several variables, including amount,
pattern and speed of enhancement; in general, all malignancies enhance, as well as some benign lesions, but usually to a lesser extent.\(^5\)\(^9\)

**Clinical applications**

The ability of MRI to differentiate post-radiation therapy axillary fibrosis from tumor recurrence has been confirmed, but its cost-effectiveness and whether there is any advantage over CT is still in question.\(^6\)\(^1\) Much more work has been done to assess the ability of MRI to differentiate benign from malignant breast masses, and occasionally assess axillary lymph nodes. One of the first such studies\(^6\)\(^2\) imaged the breasts of 22 patients preoperatively, 21 mastectomy specimens and 12 axillary node dissection specimens. Cancer-infiltrated lymph nodes had the longest T1 relaxation times, and significantly longer T2 relaxation times, leading the authors to conclude that T2-weighted spin-echo imaging and T2 relaxation times show promise in differentiating benign from malignant lymphadenopathy. Another group,\(^6\)\(^3\) however, found that axillary lymph nodes were best visualized on T1-weighted spin-echo sequences; all lymph nodes detected, however, were enlarged to >1cm.

More promising results have been achieved with the use of contrast-enhanced MRI; however, the majority of these studies have concentrated on differentiating between benign and malignant breast masses, not the status of the axillary lymph nodes. Tumor enhancement is caused by increased vascularity, not by properties of the malignancy itself; gadolinium shortens T1 relaxation times, thereby increasing the contrast with the surrounding tissues.\(^6\)\(^4\) Heywang et al\(^6\)\(^5\) were the first to use gadolinium enhancement. A T1-weighted spin-echo MR evaluation of 20 patients with breast masses prior to biopsy, with and without gadolinium, revealed that all 13 carcinomas and 1 fibroadenoma enhanced, and dysplasia enhanced slightly or not at all. This technique was thus felt to be potentially useful in evaluating dense breasts and to improve differentiation between irregular dysplastic tissue, scar and cancer. A further investigation\(^6\)\(^6\) revealed its limitations: in 150 patients, 70 of 71 carcinomas enhanced [the other showed borderline
enhancement] and all 27 fibroadenomas enhanced; although it revealed more cancers than mammography or ultrasound in this study, gadolinium-enhanced MRI did not improve differentiation between benign and malignant lesions.

Many others have attempted variations in gadolinium-enhanced MR imaging to improve the differentiation between benign and malignant breast lesions. Gradient-echo fast low-angle shot (FLASH) sequences and fast imaging with steady precession (FISP) were compared to spin-echo and found to detect lesions as small as 3mm in diameter with gadolinium enhancement. In addition, all 6 carcinomas in this study enhanced suddenly, within 2 minutes, and reached a plateau, while all 16 benign lesions enhanced more slowly to lower levels and did not plateau. Others confirmed that benign and malignant lesions had different rates of enhancement which were significant in the first two minutes after gadolinium administration. Fat suppression was also attempted to improve the resolution and contrast of gadolinium-enhanced MR images. Different techniques demonstrated no enhancement of fat necrosis or scar while all carcinomas enhanced, or improved visualization of the morphology and architecture of breast lesions but did not detect intraductal carcinoma. Consequently, while gadolinium enhancement has yet to prove clinically useful in differentiating benign from malignant breast lesions, the utility of MRI appears to be in delineating the extent of a tumor preoperatively.

ULTRASOUND

Basic Principles

Ultrasound uses high-frequency sound waves generated by electrical stimulation of piezoelectric crystals to produce vibrations in the range of 1 to 10 MHz; the resolution of ultrasound depends on the frequency, the shape of the beam and the interaction with the tissue. When ultrasound was initially evaluated as a potential screening tool for breast cancer, whole-breast devices were developed, i.e. dedicated, automated water path scanners, but hand-held, real-time scanners are cheaper, faster and can be adapted for
multiple uses (e.g. needle aspiration). Important factors which impact on the quality of the scan include power (i.e. sound intensity), gain, and the transducer and its frequency and resolution. Ultrasound can detect the size (as small as 2-3mm) and border definition of a lesion, its echogenicity and posterior enhancement or shadowing, but cannot detect microcalcifications. Normal lymph nodes are bean-shaped in appearance with echogenic fat within the sinus; there are afferent blood vessels normally seen around the node, with an efferent vessel at the hilum. Tumor involvement may change the size and contour of the node, result in replacement of the echogenic fat, and/or disrupt the normal parenchymal pattern.

Malignancies stimulate the growth of new blood vessels, which are thin-walled and tortuous with arteriovenous shunting; the resulting abnormal, low-resistance, high-velocity flow can be detected by Doppler ultrasound. Doppler can determine both the frequency shift of flow in a vessel and the velocity of flow if the angle between the beam and the vessel is known. There are two types of Doppler signals in malignant vessels: the first type has high peak systolic frequencies with or without enhanced diastolic flow, and probably results from arteriovenous shunting; the second type has little systolic/diastolic variation, and correlate with sinusoidal spaces with no smooth muscle in the vessel walls. There are three types of Doppler ultrasound equipment which can detect tumor vascularity. The first, continuous-wave (CW) Doppler, is inexpensive and sensitive, but can only be used to evaluate superficial lesions. The second, pulsed duplex Doppler, allows evaluation of the B-scan image and Doppler imaging either in sequence or simultaneously at a reduced rate. Finally, color Doppler can evaluate the mean frequency of flow in a tumor vessel. In all techniques, the lesion is first evaluated with B-mode imaging, then the Doppler evaluation is performed.

Ultrasound evaluation

Ultrasound has also been used in many attempts to differentiate between benign and malignant breast masses, as well as determine the involvement of axillary lymph nodes.
Since the mid-1980s, comparisons have been made between axillary ultrasound and clinical exam. One of the first such studies\textsuperscript{77} found a sensitivity for ultrasound of 72.7%, compared to 45.4% for clinical exam, with equal specificities (97.3%). A positive scan was defined as any visualized nodular image ≥5mm in diameter. Other studies with similar criteria\textsuperscript{78} have produced similar improvements in sensitivity (72.2% for ultrasound versus 32.3% for clinical exam), but acknowledge that these morphologic criteria cannot distinguish benign from malignant enlargement. Other groups,\textsuperscript{79,80} however, have defined a positive scan as any visualized node, stating that normal nodes are not usually seen because they have the same echogenicity as the surrounding fat, and produced varying results. The former found improved sensitivity of ultrasound compared to clinical exam (66% versus 42%) but decreased specificity (75% versus 90%); the latter found a non-significant difference in the sensitivities of the two techniques (56% for ultrasound versus 68% for clinical exam), but improved specificity (89% compared to 68%), and demonstrated that 28% of involved lymph nodes were not detected by either technique.

**Doppler and duplex Doppler evaluation**

Simultaneously, others were investigating the role of Doppler and/or duplex ultrasound in the evaluation of breast masses, a technique which would later be applied to axillary lymph nodes. Britton and Coulden\textsuperscript{81} defined a positive scan as the presence of a Doppler signal, and found for 50 breast lesions in 45 patients a sensitivity of 91% and specificity of 89%. Others, however attempted to quantify the degree of vascularity, with varying results. Adler et al\textsuperscript{82} performed color flow Doppler ultrasound exams in 58 patients with 62 breast lesions; vascularity was categorized as absent, minimal, moderate or marked. Eighty-two percent of tumors had moderate or marked vascularity, but there was poor differentiation between normal tissues and carcinoma. Cosgrove et al\textsuperscript{83} demonstrated Doppler flow in 20 of 21 breast cancers, but only 9 of these had moderate or high velocities. Dock et al\textsuperscript{84,85} have attempted to determine a cut-off value for flow measurements to distinguish benign from malignant breast lesions. A value of ≥0.4m/sec
gave a sensitivity of 65% and specificity of 85%, leading the authors to conclude that a flow velocity ≥0.4m/sec was highly suggestive of malignancy, but that no conclusions could be drawn from lower values; a later investigation using a cut-off of 0.2m/sec was able to detect 80% of malignant tumors, but again no conclusions could be drawn from a lower flow velocity.

In recent years, attempts have been made to extend Doppler ultrasound studies to the axillary lymph nodes. Dixon et al examined both the primary lesions of patients with breast masses and the axillary lymph nodes of the subset of patients with breast cancer; a positive result was defined as the presence of Doppler flow around a solid mass or a lymph node. Similar results were obtained in both parts of the study: Doppler assessment correctly classified 25 of 32 breast cancers and all 21 benign lesions (for a sensitivity of 78%, specificity of 100%, positive predictive value of 100% and negative predictive value of 75%), and correctly classified 9 of 12 positive axillae and all 18 negative axillae (for a sensitivity of 75%, specificity of 100%, positive predictive value of 100% and negative predictive value of 84%). The investigators concluded that since Doppler ultrasound yielded no false positive results in the axillae, it may be most useful in selecting patients for axillary clearance (those patients likely to have positive axillae) versus axillary sampling (those patients likely to be node-negative). After a second investigation yielded a similarly high specificity (98%), the same group confirmed the utility of Doppler ultrasound in selecting the appropriate axillary surgery, and suggested a role for Doppler ultrasound in patients who are candidates for radiotherapy alone. Another group attempted to correlate the Doppler flow of breast masses with axillary lymph node involvement. An analysis of 95 patients with breast masses, where a positive scan was defined as a high frequency shift of ≥1kHz, revealed a sensitivity of 60% and specificity of 92% for differentiating between malignant and benign breast lesions; a negative scan, however, was highly correlated with negative axillary lymph nodes -- only 3 of 22 patients with a negative scan had positive nodes. Others have attempted to use different criteria identified by Doppler sonography.
to determine benign from malignant lymph nodes. In a color Doppler evaluation of 43 patients with palpable lymph nodes (one axillary lymph node, 42 lymph nodes in other sites), resistive index, pulsatility index, peak systolic velocity and end diastolic velocity were measured; all but the peak systolic velocities were significantly different between benign and malignant lymph nodes. Several of these investigations are ongoing.

NUCLEAR MEDICINE

Basic Principles

Lymphoscintigraphy involves injection of a radiolabeled substance, either intravenously or subcutaneously, which will then be taken up by the lymph nodes in the region of interest. Intravenous administration has poor tissue distribution; intradermal or subcutaneous injection is therefore favored for regional studies. For axillary lymph node studies, the radiolabeled agent is injected into the interdigital webs of the hand and the periareolar region of the breast; the chest wall is injected in internal mammary lymphoscintigraphy. The patients are then imaged with a gamma-camera; immediate and delayed images can visualize lymphatic vessels and lymph nodes, respectively. The imaging systems and methods of interpretation are also variable, using planar imaging, emission tomography (SPECT) and computer-assisted subtraction or other manipulation; the time from administration to imaging also plays a role.

The radioactive pharmaceutical agents available for lymphoscintigraphy fall into three major categories: radiocolloids, radiolabeled monoclonal antibodies and radiolabeled metabolites. Regardless of the agent, the mechanism of uptake is assumed to be the same; the agents enter the lymphatic channels passively or are phagocytosed by macrophages and transported within the lymphatics. The accumulation of these macromolecules in lymph nodes, however, depends on the functional state of the nodes; recent surgery or replacement of the node by tumor can decrease the ability of the node to accumulate the agent.
Radiocolloid lymphoscintigraphy

Axillary radiocolloid lymphoscintigraphy has been attempted to aid in planning radiation therapy, to predict a benign or malignant breast mass, and to directly assess the status of the axillary lymph nodes. The technique evolved from internal mammary lymphoscintigraphy, which was first used in 1966; the extensive amount of experience with this technique has provided information about the scintigraphic appearance of these lymph nodes according to the extent of tumor involvement. The nodes first demonstrate enhanced uptake, probably caused by an early antigenic stimulus, then diminished uptake with proliferation of the neoplasm; with extensive tumor involvement, uptake is absent in involved nodes resulting in backup of radiocolloid with increased uptake in more proximal nodes. For potential reasons such as the differences in the anatomy of the axillary lymph nodes versus the internal mammary nodes, and using a peripheral site for injection (the hand), the changes in axillary lymphatics have yet to be as well defined, although attempts have been made to correlate internal mammary lymphoscintigraphy directly with the status of the axillary lymph nodes.

One of the first attempts to assess the axillary lymph nodes using periareolar injections of $^{99m}$Tc-antimony sulfide colloid studied 32 patients; satisfactory scans were obtained in 29 patients, 27 of whom had breast cancer, and within these 27 patients demonstrated a sensitivity of 90% for detection of gross metastases (75% for gross or micrometastases), specificity of 100%, positive predictive value of 100% and negative predictive value of 94% (83% if micrometastases are included). Further attempts, however, were less promising. Hill et al injected both the hand and the periareolar regions for axillary lymphoscintigraphy and found a sensitivity of 67%, specificity of 92%, positive predictive value of 86% and negative predictive value of 79% in 43 patients with breast cancer. Another attempt to predict axillary node metastases with bilateral interdigital injections of $^{99m}$Tc-antimony sulfide colloid in 62 patients assessed the degree of asymmetry in the number of foci of radiocolloid uptake between the axillae as a predictor of
axillary node metastases, with similar results. The sensitivity was 76%, specificity 67%, positive predictive value 63% and negative predictive value 80%, leading the authors to conclude that axillary lymphoscintigraphy may complement, but not yet replace, clinical exam and surgical sampling of axillary lymph nodes.

Monoclonal antibodies in radioimmunolymphoscintigraphy

Attempts to improve the sensitivity and specificity of lymphoscintigraphy have led to the development of monoclonal antibodies against breast cancer antigens to detect nodal metastases. Antibodies have been raised against such potential antigen targets as cytoskeletal proteins, breast epithelial cell products, basement membrane antigens, degradative enzymes, cell receptors for extracellular matrix molecules, multidrug resistance gene products and proliferative markers. As more monoclonal antibodies have been developed, some conclusions have been reached:

1. truly cancer-distinct antigens are not required for [radioimmunolymphoscintigraphy],
2. many are pan-carcinoma antigens, and can therefore be used to image many different tumor types,
3. a particular antibody-antigen system can be used in many different patients with the same tumor type, indicating that an individual or "private" specificity is not required, and
4. shed-tumor antigens do not neutralize the injected antibody, even when very high titres of circulating antigen are present . . . [and] targeting has been achieved even when only 15% of the cells express the target antigen.

Although radiolabeled antibodies should demonstrate increased specificity, the question can also be raised of whether a positive scan could result from antigen drainage as opposed to tumor infiltration. Clinical studies have shown varying results.

One of the first attempts to use a radiolabeled antibody was done by DeLand et al using Iodine (I)-131-labeled antibodies to carcinoembryonic antigen (CEA). Lymphoscintigraphy detected 7 of 7 women with axillary node metastases, only 5 of which were palpable. Four of these women had bilateral involvement on scan which was not
verified histologically; the authors speculated retrograde lymphatic flow in advanced carcinoma versus nonspecific attachment to receptor sites in lymph nodes as possible explanations for this observation. Another equally small study\textsuperscript{100} demonstrated similar sensitivity; immunolymphoscintigraphy with the I-131-labeled antibody 3E1.2 (which reacts with the membrane and cytoplasm of breast cancer cells) resulted in a positive scan in 7 axillae with palpable masses which were histologically proven to be positive, a positive scan in 2 axillae with no palpable masses which were also histologically proven to be positive, a negative scan in one axilla with a palpable mass which was histologically proven to be negative, and a negative scan in a man with palpable axillary lymphoma, although there was a small amount of uptake. The authors speculated that the increased vascularity of diseased lymph nodes, as in the last patient, could result in nonspecific uptake of antibody; they also suggested that using a combination of antibodies could increase sensitivity. In two larger series of patients, Tjandra et al\textsuperscript{101,102} attempted to assess lymph node status with other I-131-labeled antibodies. In the former, immunolymphoscintigraphy of 26 patients with RCC-1 (IgG 2a) revealed a sensitivity of 86% and specificity of 92%, while in the latter, I-131-labeled 3E1.2 (IgM) or RCC-1 scintigraphy of 40 patients was only 33% sensitive overall, and 63% specific. While some unsuspected axillary node metastases were detected, there was much nonspecific uptake in normal lymph nodes.

Others have attempted to use Indium (In)-111-labeled antibodies, but with little improvement in the sensitivity or decrease in the nonspecific uptake by normal lymph nodes. Kalofonos et al\textsuperscript{103} assessed axillary and other metastases with $^{111}$In-labeled human milk fat globule (HMFG1 F(ab')$_2$) antibody fragments with an overall accuracy of 50% (no false positives); while the uptake of antibody measured in the resected specimens was greater in the metastatic nodes than in the primary tumor, it was not significantly higher than in normal nodes. An attempt to use $^{111}$In-labeled antibodies to a mucin-like antigen (MA5) had a similarly poor sensitivity, and was limited to detecting lesions $>3$ cm.\textsuperscript{104}
Lamki et al,\textsuperscript{105} using \textsuperscript{111}In-labeled monoclonal antibody B72.3 (against tumor-associated glycoprotein TAG-72) with digital, planar and SPECT imaging, detected all of 14 malignant breast lesions but none of 7 axillary lymph node metastases, with one false-positive in an HIV-positive patient. Lymphoscintigraphy with \textsuperscript{111}In-labeled anti-epithelial membrane antigen (EMA) antibodies, however, identified 16 of 17 primary lesions and 10 of 14 axillary lymph node metastases;\textsuperscript{106} a subcomparison of planar imaging versus SPECT revealed planar imaging to be more sensitive in both areas (88\% versus 56\% for primary lesions and 59\% versus 53\% for axillary lymph nodes).

Some improvement, however, has been seen with the use of \textsuperscript{99m}Tc-labeled antibodies to CEA. Lind et al\textsuperscript{107} reported a case of a patient with breast cancer and follicular thyroid cancer in whom lymphoscintigraphy with \textsuperscript{99m}Tc-labeled BW431/26 (which reacts with CEA) was able to correctly identify a supraclavicular lymph node as a breast cancer metastasis. Kairemo\textsuperscript{108} used this technique to assess supraclavicular and axillary lymph nodes in 20 breast cancer patients, with a sensitivity of 90\% and specificity of 88\%. In both studies, the patients' serum CEA level did not influence the results.

Similarly, in patients whose primary tumors are known to be estrogen-receptor positive, initial studies\textsuperscript{109} indicate that \textsuperscript{123}I-labeled methoxyestradiol scintigraphy may be useful in the detection of axillary lymph node metastases. Regardless of the technique, however, most authors conclude that much remains to be studied in radioimmunolymphoscintigraphy.

\textbf{Metabolites in lymphoscintigraphy}

The proliferation of malignant cells is associated with increased metabolic activity; this premise has been used in attempts to determine the status of primary lesions or axillary node metastases with radiolabeled metabolites. The compound 2-[F-18]-fluoro-2-deoxy-D-glucose (FDG) is taken up by membrane glucose transport mechanisms; positron emission tomography (PET) produces images based on the accumulation, distribution and metabolism of the administered compound, which is a reflection of the biochemical status
of the tissue.\textsuperscript{110} The first attempt to use FDG and PET was reported in 1989,\textsuperscript{111} in which a woman with a palpable breast mass at the site of a previous biopsy scar showed focal increased FDG uptake, which was then proven to be invasive ductal carcinoma. Wahl et al first demonstrated in rodents that FDG uptake was greater in tumors and metastatic nodes than in normal nodes.\textsuperscript{112} They then imaged 12 patients with known primary and/or metastatic breast cancer;\textsuperscript{113} FDG-PET revealed all primary tumors, bone and soft tissue metastases, and all known plus 4 previously unknown nodal metastases. Other groups have found similar results with FDG-PET: Tse et al\textsuperscript{110} correctly determined the status of 12 of 14 primary breast masses and 7 of 10 axillae; while Adler et al\textsuperscript{114} correctly identified 26 of 27 malignant breast masses, 8 of 9 positive axillae and all 10 negative axillae. The latter group, however, acknowledges that while FDT-PET can miss micrometastases to lymph nodes, it may prove useful by indicating which patients have involved axillae.

A variation of FDG-PET using carbon-11-methionine instead of FDG was studied in 8 patients with known breast cancer and soft tissue metastases (including axillary lymph nodes) to evaluate the response to treatment over 2 years.\textsuperscript{115} Methionine is necessary in cancer cells for increased synthesis of proteins and polyamines, as well as transmethylation reactions, and its uptake is irreversible in cancer cells. The authors found uptake in all metastases, with increased uptake in progressive disease and decreased uptake in regressing metastases. They concluded that metabolic changes in the tumor may indicate disease progression or regression.

Techniques originally used in cardiac assessment have also been extended to the evaluation of breast cancer and axillary node metastases. Thallium behaves similarly to potassium, and its uptake is thought to be increased by the ATPase sodium-potassium transport system as well as a co-transport system in tumors.\textsuperscript{116} In the course of a thallium-201 evaluation for lung cancer, a patient was noted to have a breast mass, which was then found to be a scirrhous adenocarcinoma of the breast.\textsuperscript{117} A preoperative stress thallium-201 examination done to evaluate an abnormal ECG in a woman with a breast mass
revealed uptake in the ipsilateral axilla, which was found to be involved with tumor upon axillary node dissection.\textsuperscript{118} A specific attempt to use thallium-201 scintigraphy to evaluate 81 patients with palpable breast masses prior to biopsy\textsuperscript{116} revealed a sensitivity of 96% and specificity of 91% in differentiating benign from malignant lesions, but a sensitivity of only 57% in detecting axillary lymph node metastases.

Another primarily cardiac agent with future potential to image axillary lymph nodes is Tc-99m MIBI; this agent is thought to bind to the cytosol in tumor cells, as in myocardium, and its uptake may be increased by increased tumor blood flow and capillary permeability.\textsuperscript{119} Chest scintigraphy of two patients with palpable breast masses and axillary lymph nodes revealed increased Tc-99m MIBI uptake in both the primary lesions and the metastatic axillary lymph nodes. Further studies are needed to determine the sensitivity and specificity of either thallium or MIBI on a larger scale.
STATEMENT OF PURPOSE

Axillary lymph node status, therefore, remains the primary prognostic variable in breast cancer patients. While the search continues for other indicators of axillary lymph node involvement, at present, axillary lymph node dissection is the only reliable way to assess the spread of cancer to the lymph nodes. The optimal extent of dissection is controversial; does one need to quantify disease in the axilla or simply classify the patient as node-positive or node-negative? There is substantial morbidity associated with axillary lymph node dissections; for many women this is a second surgical procedure necessitating a separate hospital visit and general anesthesia, and leading to loss of one to two weeks of work during recovery and drain care. In addition, with the increased use of adjuvant chemotherapy in both node-positive and node-negative women, clearly a non-invasive method of determining node status would decrease morbidity and facilitate treatment decisions.

Of the many modalities used in attempts to image the axilla, axillary mammography is unable to differentiate metastatic from inflammatory nodes; CT and plain MRI have been proven useful in differentiating axillary fibrosis from recurrent disease, but have likewise been only able to determine nodal enlargement. Gadolinium-enhanced MR imaging, however, which exploits the neovascularity of malignancies, has shown promise in differentiating benign from malignant breast lesions. Likewise improvements in Doppler ultrasound instrumentation have improved the sensitivity for detection of flow, and initial attempts to characterize axillary lymph nodes have had a high positive predictive value. Lymphoscintigraphy may also prove useful in the evaluation of axillary lymph node disease, although less practical than ultrasound; in addition, although radiolabeled monoclonal antibodies and metabolites have shown improved sensitivity over colloid studies, the optimal radiopharmaceutical(s) have yet to be identified.
We hypothesized, therefore, that ultrasound examination using both morphologic and flow characteristics as identified with duplex Doppler ultrasound, and/or gadolinium-enhanced magnetic resonance imaging of the axilla may detect metastatic involvement of the axillary lymph nodes in breast cancer patients. If a high positive predictive value is achieved, this may lead to a reduction in the number of axillary lymph node dissections performed, for once identified, patients with positive axillae can then proceed to adjuvant therapy, or, if histologic documentation is desired, undergo ultrasound-guided biopsy of the identified nodes. In order to test this hypothesis, we first set out to establish a protocol for gadolinium-enhanced MRI of the axilla, based on cadaveric and normal subject studies, then to perform both ultrasound and MR exams on patients with biopsy-proven breast cancer prior to axillary node dissection, in order to correlate the imaging studies with the surgical pathology.
METHODS

PART I. DEVELOPMENT OF AXILLARY MRI PROTOCOL

Stage i. Cadaveric studies

A 76 year old female cadaver was obtained from the Yale University School of Medicine, Department of Anatomy. The cause of death was recorded as idiopathic pulmonary fibrosis; there was no known evidence of breast cancer. The shoulder and axillary regions were separated from the remainder of the cadaver by two of the investigators (JSO and BAW) using transverse slices through the neck, lower thorax and left and right humeri, and a sagittal slice through the sternum.

Magnetic resonance imaging of the left axilla was then performed under the supervision of one of the investigators (RCS). All imaging of the cadaveric axilla and the normal subject and patients (see below) was performed on an FDA-approved General Electric SIGNA MR system with a magnet strength of 1.5 Tesla. The specimen was placed in a head coil for these studies. Imaging sequences used were as follows:

- Fast Spin Echo: coronal and axial planes, TE=90, TR=5000, 20 fields of view (FOV), 3mm slice thickness with 0.6mm skip between slices, 256x256 matrix, 4 excitations (number of excitations = NEX).
- Coronal Volume Scan Spoiled Grass (SPGR): TE=5, TR=40, 60° flip angle, 16 FOV, 1.5mm slice thickness, 256x256 matrix, 2 NEX.

The right axilla was then dissected by two of the investigators (BAW and JSO) in order to expose the anatomic landmarks and regional lymph nodes encountered during an axillary lymph node dissection.

Stage ii. Normal subject

One of the investigators (JSO) then underwent MRI in order to determine the optimal imaging parameters for human subjects. Specific sequences were as follows:
• Body coil
  1. Axial T1-weighted imaging: TE=11, TR=600, 20 FOV, 5mm slice thickness with 2.5mm skip, 256x192 matrix, 4 NEX.
  2. Axial T1-weighted imaging: TE=16, TR=200, 24 FOV, 5mm slice thickness with 2.5mm skip, 256x128 matrix, 1 NEX.
  • 5-inch circular coil
    Same imaging sequences as above (1 and 2).
  • 5x11-inch rectangular coil
    Same imaging sequences as above (1 and 2)
  3. Same parameters as sequence 2 with the addition of fat suppression.
  4. Axial SPGR: TE=5, TR=50, 30° flip angle, 24 FOV, 5mm slice thickness with 2.5mm skip, 256x128 matrix, 1 NEX.
  5. Same parameters as sequence 4 with the addition of fat suppression.
  • Shoulder coil
  6. Axial T1-weighted imaging: TE=16, TR=800, 20 FOV, 5mm slice thickness with 1mm skip, 256x128 matrix, 1 NEX.
  7. Same parameters as sequence 6 with the addition of fat suppression.
  8. Same parameters as sequence 6 with a saturation pulse in the field of view.
  9. Same parameters as sequence 7 with 2 NEX.
  10. Axial T1-weighted imaging: TE=11, TR=600, 20 FOV, 5mm slice thickness with 1mm skip, 256x128 matrix, 2 NEX.

**PART II. PATIENTS**

**Patient Characteristics**

Patients of one of the investigators (BAW) or other Yale University or community physicians were eligible for entrance into one or both parts of this study. Patients must have had histologically proven breast cancer and been scheduled to undergo axillary lymph
node dissection, either in conjunction with a mastectomy or as a separate surgical procedure. Patients were not excluded because of menopausal status or gender, but were excluded from the MRI part of the study if pregnant or if there were contraindications to MRI (e.g. pacemakers, aneurysm clips or other metallic implants, or history of claustrophobia during a previous MR examination) or to Gd-DTPA administration (e.g. asthma).

This study was approved by the Yale University School of Medicine Human Investigation Committee (HIC), HIC Protocol #7325. Oral consent [see APPENDIX I] was obtained from each patient by one of the investigators (JSO) prior to entry into the study, either by telephone or in person.

Ultrasound

All of the ultrasound examinations were performed by one of the investigators (KJWT). An ATL 3000 or ATL UM9 HDI system was used with a linear array 10.5 MHz transducer and coupling gel. The patient was placed in the decubitus position with the arm on the affected side extended to expose the axilla. Examinations were performed using B mode, color flow and pulse Doppler. The axillary artery and vein, pectoralis major and teres major muscles, and any lymph nodes were identified by B mode and color flow imaging. Measurements of the length and width of the lymph nodes were obtained, and the degree of vascularity was assessed by pulse Doppler imaging.

The radiologist (KJWT) was asked to classify the axilla as a whole and the individual lymph nodes as abnormal (positive), normal (negative) or equivocal if a decision could not be reached. The decision was made based on interpretation of lymph node size, shape, central echogenicity and/or flow characteristics.

MRI

One patient underwent a magnetic resonance imaging examination as described above. The shoulder coil was placed over the axilla of interest. Imaging was performed before and after the injection of Gd-DTPA. Specific sequences were as follows:
• Axial T1-weighted images
  1. TE=11, TR=700, 22FOV, 5mm slice thickness with 1mm skip, 256x192 matrix, 4 NEX.
  2. TE=11, TR=800, 22 FOV, 5mm slice thickness with 2mm skip, 256x192 matrix, 2 NEX, fat suppression.
  3. Same parameters as sequence 1 except 2 NEX, after the injection of 14cc Gd-DTPA.
  4. Same parameters as sequence 2, after the injection of Gd-DTPA.

Pathology

All patients underwent a level I or level I and II axillary node dissection. All of the axillary node specimens were reviewed by the same pathologist (DC).

Analysis

A descriptive analysis of normal and abnormal appearing lymph nodes was first undertaken. A two-by-two table was constructed to compare the sonographic evaluation of the axilla as a whole with the surgical pathology. The sonographic characteristics of the axillary lymph nodes were analyzed with respect to length, length-to-width ratios, and correlation with the surgical pathology.
RESULTS

PART I

Cadaveric studies

Representative images from the MRI of the left axilla are presented in Figure 1. With low resolution images, equal to those obtained with human subjects, the axillary vessels are visible within the brighter surrounding axillary fat. High and super high resolution images were possible given the absence of respiratory movement. A few axillary lymph nodes are visible in these images.

During the right axillary node dissection, first the skin and subcutaneous fat were removed. The pectoralis major muscle was identified and reflected to expose the pectoralis minor muscle, the axillary artery and vein and the thoracodorsal neurovascular bundle. A few normal-appearing nodes were visible at level I, i.e. lateral to the pectoralis minor muscle [see TECHNIQUE AND MORBIDITY]. Photographs at different stages of the dissection are presented in Figure 2.

Normal subject

Unenhanced MR images of the normal subject are presented in Figure 3. Imaging sequences using shoulder coil were felt to provide the best resolution of the area of interest. Axillary vessels were identifiable by the flow void within the brighter axillary fat; no lymph nodes were seen (Figure 3a). As respiratory movement was inevitable, a saturation pulse was used in an attempt to improve resolution; no benefit, however, was felt to be gained (Figure 3b). Fat suppression sequences (Figure 3c) demonstrated the appropriate homogeneous appearance of the axillary tissues for use with Gd-DTPA enhancement.
**Figure 1**: Axial T1-weighted MRI of the left axilla of the cadaver.  
1a) Low resolution image (equal to that which was obtained with human subjects) demonstrates axillary vessels and few lymph nodes [arrow].
1b) High resolution image more clearly demonstrates axillary vessels and lymph nodes [arrow].
c) Super high resolution, attainable due to absence of respiratory movement, allows clear delineation of axillary anatomy [axillary vessels indicated by arrows].
Figure 2: Dissection of right axilla of cadaver, viewed laterally.
2a) [above] Skin and subcutaneous fat are removed revealing the pectoralis major muscle [arrow].
2b) [below] Pectoralis major muscle is reflected to reveal the pectoralis minor muscle (probe).
Level I is inferior and lateral to this muscle, level II is deep, and level III is superior and medial [see text].
2c) [above] Dissection of the axillary fat reveals a level I lymph node (probe).

2d) [below] Close-up view of area described above. Axillary vessels are visible in the left part of the image, running medial to lateral, while the thoracodorsal neurovascular bundle is visible in the center of the image, running superior to inferior, with associated lymph nodes [arrow].
Figure 3: Axial T1-weighted MRI (with the shoulder coil) of a normal human subject. 3a) Axillary vessels are visible as flow voids [thin arrow] in the surrounding axillary fat [thick arrow].
3b) Addition of a saturation pulse in the field of view provides no increase in resolution.
3c) Fat suppression provides a homogenous appearance to the axillary tissues [arrow] in this unenhanced study; when gadolinium is used, this provides contrast between normal and enhancing structures.
PART II

Ultrasound

For each of six patients, the results of sonographic and pathologic examination of the axillary lymph nodes are presented in Table 1. Between 4 and 6 lymph nodes were identified during each examination. The radiologist (KJWT) was asked to classify both the axillae as a whole and individual lymph nodes as abnormal (positive), normal (negative) or equivocal. Decisions were made based on the size, shape, presence or absence of central echogenicity, and flow characteristics. In general, nodes that were classified as abnormal were rounded in appearance and often enlarged, with no central echogenicity. Afferent and efferent flow was identified and qualitatively determined to be normal or increased. Ultrasound examination classified 3 axillae as positive, 2 axillae as negative and one as equivocal due to the patient's increased amount of subcutaneous fat, and uncertainty in classifying one suspicious node as truly a node; of the five axillae in which a decision could be made, there were two true positives, one true negative, one false positive and one false negative (Table 2).

Representative images from the ultrasound examinations are presented in Figure 4. In Figure 4a, a lymph node is seen adjacent to the axillary vessels (the vascularity of which were confirmed by color Doppler), which was felt to be normal secondary to its elongated appearance and central echogenicity. A similarly normal-appearing lymph node is visible in Figure 4b. The lymph nodes in Figure 4c and Figure 4d, however, are more rounded and homogeneous in appearance, and were therefore classified as abnormal. Figure 4e and Figure 4f illustrate two color Doppler views of the axillary artery and vein, landmarks for the most superior extent of the examination. Assessment of the vascularity of the lymph nodes is illustrated in Figure 4g and Figure 4h; in the former, small, normal-appearing afferent and efferent vessels are identified by color Doppler, while in the latter, color power angiography demonstrates increased flow around the node.
<table>
<thead>
<tr>
<th>Patient #</th>
<th>U/S of Axilla</th>
<th>Number of Identified Nodes (Pos/Total)</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Negative</td>
<td>0/5</td>
<td>10 of 10 LNs negative</td>
</tr>
<tr>
<td>2</td>
<td>Positive</td>
<td>3/6</td>
<td>19 of 19 LNs negative</td>
</tr>
<tr>
<td>3</td>
<td>Equivocal</td>
<td>*1/6</td>
<td>16 of 16 LNs negative</td>
</tr>
<tr>
<td>4</td>
<td>Positive</td>
<td>3/6</td>
<td>9 of 19 LNs positive</td>
</tr>
<tr>
<td>5</td>
<td>Negative</td>
<td>0/4</td>
<td>3 of 15 LNs positive</td>
</tr>
<tr>
<td>6</td>
<td>Positive</td>
<td>2/4</td>
<td>1 of 27 LNs positive</td>
</tr>
</tbody>
</table>

**Table 1:** Ultrasound and pathologic results by patient (LNs = lymph nodes).

*In patient #3, five normal-appearing nodes were identified and one suspicious shape was not interpreted with absolute certainty to be a node.*

<table>
<thead>
<tr>
<th>Ultrasound</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>2</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 2:** 2x2 analysis of ultrasound examination. The patient with an equivocal examination (#3) is not included.
Figure 4: Ultrasound appearance of normal and abnormal lymph nodes.
4a) Normal-appearing lymph node [arrow] with bright, echogenic center, adjacent to the axillary artery and vein [short arrows]; vascularity confirmed with color Doppler [not illustrated].
4b) Elongated, normal-appearing node with central echogenicity [arrow].
4c) Enlarged, rounded lymph node without central echogenicity appears abnormal.
4d) Two abnormal-appearing lymph nodes are rounded and more homogeneous in appearance, without central echogenicity.
4e) Color Doppler imaging demonstrates the axillary artery (red) and axillary vein (blue), landmarks in the axillary node dissection [see text].
4f) Transverse view of the axillary artery (red) and vein (blue) with color Doppler imaging.
4g) Color Doppler of a normal-appearing lymph node demonstrates normal afferent and efferent vasculature around the periphery.
4h) Color power angiography demonstrates increased flow in abnormal-appearing vessels draining a suspicious axillary lymph node.
The length (defined as the greatest dimension), width and length-to-width ratio (L/W ratio) of individual lymph nodes were recorded along with the presence or absence of suspicion of malignancy. These results are presented in Table 3. Upon retrospective analysis, excluding the equivocal lymph node, only one node which was suspected of being malignant had a L/W ratio >1.5, and only two nodes which appeared normal had L/W ratios <1.5. This is represented graphically in Figure 5. All of the sonographically abnormal nodes in the true positive axillae (Patients #4 & #6) had L/W ratios ≤1.3, while the nodes in the false positive axilla (Patient #2) had L/W ratios from 1.1 to 2.3. All of the nodes in the true negative axilla (Patient #1) had L/W ratios ≥1.7, while the L/W ratios of the nodes in the false negative axilla (Patient #5) ranged from 1.4 to 1.9; it is impossible, however, to know if these four nodes were histologically involved or not, as Patient #5 had three positive nodes and 12 negative nodes (see Table 1), and no attempts were made to correlate the surgical pathology of individual nodes with their preoperative sonographic appearance. Likewise with patient #6, only one positive node was identified histologically while two abnormal nodes were identified sonographically; it is possible that the truly positive node was one of these two identified nodes, or that it corresponded to another identified or unidentified node, and it is possible that both nodes were truly positive and only one was removed at dissection.
<table>
<thead>
<tr>
<th>Patient #</th>
<th>Node Length (cm)</th>
<th>Node Width (cm)</th>
<th>Length/Width</th>
<th>Ultrasound abnormal?</th>
<th>Histology positive?*</th>
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<td>0.71</td>
<td>0.56</td>
<td>1.3</td>
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</tbody>
</table>

**Table 3:** Analysis of individual lymph nodes.

*Histologic involvement corresponds to the surgical pathology of the axillary specimen as a whole, for precise correlation of nodes identified with ultrasound and at surgery was not attempted.

†This axilla is classified as a true positive as both sonographic and histologic examinations yielded positive results; however only one node was identified as positive histologically (see Table 1).
Ultrasound (US) Appearance of Individual Nodes

Figure 5: Ultrasound (US) appearance of individual nodes as listed in Table 3 versus their length/width (L/W) ratios. The equivocal node is not included. The dotted line represents a length/width ratio of 1.5. Note that only one abnormal-appearing lymph node has a L/W ratio >1.5, and only two normal-appearing lymph nodes have L/W ratios <1.5. All five abnormal-appearing lymph nodes in the true positive axillae (Patients #4 & #6) have L/W ratios <1.5.

The maximum diameter (or length) of the individual lymph nodes was also analyzed with respect to the presence or absence of malignancy. The smallest node identified measured 0.37cm in maximum diameter, while the largest node identified measured 1.74cm in diameter, for a mean length of 0.96cm, and a median length of 0.81cm. Nodes suspected of being malignant ranged from 0.71cm to 1.74cm in length, while normal-appearing nodes ranged from 0.37cm to 1.5cm in length. The average length of the identified nodes in Patient #1 (histologically negative) was 0.45cm, in Patient #2 (histologically negative) was 1.30cm, in Patient #3 (histologically negative) was 1.00cm, in Patient #4 (histologically positive) was 1.33, in Patient #5 (histologically positive) was 0.67cm and in Patient #6 (histologically positive) was 0.77. These results are illustrated in Figure 6.
Figure 6: Average length of sonographically identified nodes compared with the histologic results. Patient number is placed above each column. There is no obvious threshold of discrimination between positive axillae and negative axillae.

MRI

Magnetic resonance imaging was performed on patient number 5. No nodes were seen in the axilla with or without Gd-DTPA enhancement; however, upon review of the films, a lesions was noted outside the area that was imaged which may have corresponded to a lymph node. This is illustrated in Figure 7. As MRI did not show definitive disease in the axillae and this patient had 3 positive lymph nodes out of 15 removed (see Table 1), this exam, while suboptimal since the suspicious lesion was not imaged after Gd-DTPA enhancement, can also be classified as a false negative, the same result obtained with ultrasound examination (see Table 3).
Figure 7: Suspicious lesion [arrow] identified during review of the coronal localizing sequence performed during the MRI of Patient #5, outside of the area that was imaged during axial T1-weighted sequences, with and without gadolinium [these did not demonstrate any lymph nodes and are not illustrated here].
DISCUSSION

One area in which preoperative ultrasound evaluation now holds an accepted role is in the staging of rectal cancer. Endorectal ultrasound can detect cancers in the rectal wall, assess the extent of penetration through the wall, and identify perirectal lymph nodes [review in 120]. While five to seven distinct layers of the rectal wall can be distinguished, the characteristics of the lymph nodes are less well defined. Most normal perirectal nodes are <5mm and often not visualized, but when visualized are oval in shape and of medium echogenicity; metastatic nodes are enlarged, rounder and take on the echogenicity of the primary tumor. The reported accuracy of ultrasound in determining lymph node status ranges from 67-82%, with the primary difficulties encountered in differentiating malignant from inflammatory lymph nodes and in excluding tumor in nodes of normal size.

Attempts are being made at this institution to correlate perirectal lymph node status as determined preoperatively with transrectal ultrasound and MRI with the surgical pathology.121 Along with size criteria, Doppler flow and gadolinium-enhancement patterns are being evaluated. In addition, efforts are being made to ensure that positive nodes identified preoperatively are the same positive nodes that are excised. When a suspicious node is identified preoperatively, its location is noted; then when the specimen is excised, a suture is placed in the suspicious area as defined preoperatively. Results of these attempts are pending. Elsewhere, a prospective comparison has been made between endoluminal ultrasound and MRI in the preoperative staging of both the tumor and perirectal nodes.122 Lymph node involvement was defined as the presence of perirectal nodes ≥5mm in diameter. The accuracy of ultrasound in determining node status was 80% and of MRI was 60%; the difference was of borderline significance. The authors recommend ultrasound as providing more accurate and useful information overall.

In this preliminary investigation, certain sonographic characteristics of axillary lymph nodes hold promise for differentiating between benign and malignant nodes. While
not quantified, flow was often increased around suspicious-appearing nodes. Nodes suspicious for malignant involvement also lost their central echogenicity. The length-to-width ratio, however, may prove to be a quantifiable decision-making tool. Malignant nodes were usually rounded in appearance; a L/W ratio of 1.5 appears to be a potentially useful threshold, above which nodes were most often normal. Further investigation may prove this to be correct; alternatively, another characteristic such as flow or central echogenicity in conjunction with the L/W ratio may better define the presence or absence of metastatic disease. The absolute size, measured in terms of the greatest dimension of axillary lymph nodes, does not appear to be a discriminating factor at this point, however, as individual nodal size as well as the average nodal size within an axilla varied tremendously in both the positive and the negative axillae.

The results of this study suggest a potential role for ultrasound in the preoperative evaluation of axillary lymph nodes. Ultrasound correctly classified two of three positive axillae, and one of three negative axillae. Women with sonographically normal axillary lymph nodes would therefore still need to undergo axillary node dissection; however this result is anticipated, for ultrasound is not expected to be able to detect micrometastases [defined as less than 2mm; see STAGING]. Whether or not false negative results are attributable to micrometastases within examined nodes or to the presence of metastases in nodes that were not visible by ultrasound is not clear from the present study. For women with sonographically abnormal nodes, however, axillary node dissection may still be avoided, especially in the context of poor prognostic characteristics of the primary tumor, by proceeding directly to adjuvant therapy. Because there are false positive results, however, one may instead use ultrasound-guided fine needle aspiration biopsy (FNAB) to clarify the etiology of an abnormal-appearing lymph node. With a positive FNAB one could be fairly certain of disease in the axilla; however a negative FNAB would not provide the same degree of certainty, and the patient would most likely proceed to some form of surgical assessment of the axilla.
Alternatively, within the current practices of administering adjuvant systemic chemotherapy or hormonal therapy to many patients regardless of nodal status, one may speculate that ultrasound examination may also prove useful in particular situations. In the lowest risk groups, e.g. postmenopausal women with estrogen receptor positive tumors, where most receive hormonal therapy, if metastatic nodes were identified the adjuvant therapeutic regimen could be changed accordingly; in the highest risk groups, e.g. young women, where most receive adjuvant chemotherapy regardless of lymph node status, ultrasound identification of metastatic nodes could provide equivalent information to an axillary node dissection, influencing the choice of chemotherapeutic agents. In any scenario, however, the sonographic result must be interpreted within the context of the expected primary surgical treatment. For women who are to have a lumpectomy as the definitive procedure within the breast, axillary irradiation could substitute for an axillary node dissection, as these patients are already obligated to have breast irradiation, thus sparing them general anesthesia and hospitalization. For women who are to undergo a modified radical mastectomy, however, little additional effort or morbidity is added by including an axillary lymph node dissection. For this technique to reach routine clinical utility, however, further refinement is necessary.

Although limited, the present study also suggests an advantage of ultrasound over MRI in evaluating axillary lymph nodes in breast cancer. While no conclusions can be drawn from this limited investigation, the potential role of MRI in evaluating axillary lymph nodes appears questionable. The one patient who underwent both an ultrasound examination and a magnetic resonance examination had metastatic nodes that were not detected by either modality. The one suspicious lesion outside of the area that was imaged with MRI noted after completion of the examination might have enhanced with Gd-DTPA administration, but since this patient had three positive nodes within the resection specimen, and possibly more at higher levels, in the absence of identifiable nodes or enhancement patterns this may well represent a lack of sensitivity of this technique. In
addition, in order to have included this area as well as lymph nodes as superior as level III, either resolution would have been sacrificed or the time of the examination would have been lengthened considerably.

In addition, practical considerations point to the use of ultrasound for routine evaluation of patients prior to axillary node dissection. Ultrasound is cheaper than MRI, takes less time to perform, and does not require an intravenous injection; in addition, patients do not have to lie in an enclosed space and can move more freely during an ultrasound exam. Perhaps most importantly, however, extreme difficulty was encountered during the course of this study in scheduling patients for MRI within the time frame from diagnosis to axillary node surgery (usually one to two weeks), while ultrasound examinations could be performed even with one day's notice.

There are limitations to this study, however. While no patients in this study had only micrometastases to the lymph nodes, the ability of ultrasound to detect such lesions is questionable at best. The sonographic characteristics used to distinguish benign from malignant lymph nodes rely on enough tumor invasion to change the shape of the node or replace the medullary sinus with tumor, decreasing the echogenicity, or to induce neovascularization. Ultrasound therefore is unlikely to provide definitive staging for all women, but can aid in the accurate determination of lymph nodes involved with macroscopic tumor. Women with clinically and sonographically negative nodes who ordinarily would undergo axillary lymph node dissection would still do so.

In addition, our intent was to demonstrate positivity or negativity of an axilla as a whole; precise correlation of individual nodes identified pre- and intraoperatively was not attempted. In order to achieve such a correlation, one would need either needle localization or a second, intraoperative ultrasound examination. In either scenario, the ease and flexibility of this technique are sacrificed. This assessment of the axilla as a whole introduces a potential source of error only when both the ultrasound results and the surgical pathology are positive; one cannot be certain if the nodes identified as positive with
ultrasound are the same nodes that are proven to be positive histologically.\cite{121} This is of particular concern in patient #6, in whom 2 abnormal nodes were identified sonographically while only one node proved positive histologically; it is possible that one, both, or neither of these two nodes were truly positive. This should not pose a practical problem, however, for patients with sonographically positive axillae will most likely receive adjuvant therapy, while those with sonographically negative axillae will most often undergo axillary lymph node dissection to rule out micrometastases or proceed directly to adjuvant therapy.

In conclusion, ultrasound of the axilla holds promise in differentiating benign from malignant lymph nodes, using characteristics such as the length-to-width ratio, perhaps in conjunction with the presence or absence of central echogenicity and normal or increased flow. While this modality does not appear to have the potential to replace axillary node dissection in all women, it could reduce the need for surgery in certain groups. For high risk women, the presence of an abnormal exam could lead to a decision to proceed directly to adjuvant therapy, while for low risk women who often receive adjuvant therapy regardless of axillary node status, an ultrasound examination may provide equivalent information without surgery. In the intermediate risk groups, patients with normal examinations would still need to undergo axillary node dissection, while patients with abnormal examinations could undergo ultrasound-guided FNAB of the suspicious nodes to further guide treatment. As a direct result of this preliminary investigation, further efforts will be taken to elucidate and clarify which nodal characteristics provide accurate determination of benign or malignant status. In addition, a study which included FNAB of suspicious nodes would provide insight into this currently theoretical extension of the present study. Magnetic resonance imaging of axillary lymph nodes holds less promise, largely for practical considerations as outlined above.
REFERENCES


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APPENDIX I

HIC PROTOCOL #7325

IV. CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
YALE UNIVERSITY SCHOOL OF MEDICINE -- YALE-NEW HAVEN HOSPITAL

Invitation to Participate and Description of Project:
You are invited to participate in a clinical research study to see if magnetic resonance imaging (MRI) and/or ultrasound (US) examinations can aid in determining if breast cancer has spread to nearby lymph nodes. One part of this study uses MRI and a contrast agent to take pictures of your axilla (underarm area). The other part uses sound waves (ultrasound) to take a different kind of picture. You have been chosen for this study because you are scheduled to have an axillary node dissection.

This information sheet gives you details about the research study which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures and possible benefits. Once you understand the study you will be asked if you wish to participate in one or both parts of the study.

Description of Procedures:
In the MR part of this study, you will have MR pictures taken. The MR Center is in the basement of the Fitkin wing of the New Haven Unit [entrance at 789 Howard Ave]. In order to give you the contrast agent that improves the quality of the pictures, you will need to have an i.v. in your arm. You will then lie on a sturdy plastic table inside a cylindrical magnet. You will not feel anything while the pictures are being taken, but the magnet makes a drumming noise, and you must lie as still as you can. You can talk to the technician and the doctor, both of whom can see you, while the exam is going on. The whole procedure should take about an hour.

The US part of the study involves using sound waves to visualize the lymph nodes in your underarm area. This part of the study will occur in the basement of the Yale Physicians Building, Room B 66. For the US examination, you will be asked to lie on the examining table with your arm above your head. A gel will be applied to your skin, and the examining tool, a metal transducer, will be moved across your skin. You should experience no discomfort from either the gel or the transducer. You should lie quietly during the exam, which will take about half an hour, but you can pause to relax and move your arm whenever you desire.

Risks and Inconveniences:
The contrast agent used in the MR exam, called gadolinium, should pose no risk to you -- it is neither radioactive nor iodine-containing. If you have asthma, however, you may be at an increased risk for complications and will not be able to participate in this study; please tell us if you have or think you have asthma. Gadolinium is injected into a vein in your arm; the i.v. should not be uncomfortable, but it may leave a small, temporary bruise. Since MRI uses magnetic fields and radio waves to take the pictures, if you have a pacemaker or any other metallic implant, such as aneurysm clips or heart valves, you may not be able to participate in the study. Again, please let us know if you have or think you have a metallic implant.

We know of no other risks or side effects from gadolinium-enhanced MRI. You may get uncomfortable lying on the table. Some people feel anxious and claustrophobic
(uncomfortably closed-in) inside the magnet. If this happens to you, you can tell the doctor and technician and they will stop the examination.

The ultrasound examination is painless and without risk. We know of no allergic reactions to the gel, and neither it nor the metal transducer should cause you any discomfort. If you become uncomfortable lying with your arm upstretched, you can tell the technician, who will pause the exam so you can relax and stretch.

**Benefits:**

This study may be of no direct benefit to you, but will improve our ability to detect the spread of breast cancer to local lymph nodes in future breast cancer patients.

**Economic Considerations:**

You will not be paid for participation in this study. Neither you nor your insurance company will have to pay for the MRI pictures, the US images, or the visits to the MR Center or the US center.

**Confidentiality:**

In all records of this study, you will be known by a number, and your name will be known only to the researchers. Your name will not appear in any written reports of this study.

**Voluntary Participation:**

You are completely free to choose not to participate in this study, and if you do become a subject, you are free to withdraw at any time. You do not have to have both examinations in order to participate, if you do not wish to do so. If you decide not to participate or withdraw at any time, it will not affect your relationship with the hospital or any of the doctors involved.

**Questions:**

Please feel free to ask any questions about anything about this form or this study which is unclear to you. Take as long as you need to consider this study carefully before you make a decision whether or not to participate.
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NAME AND ADDRESS DATE