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Editorial

Axillary Lymphoscintigraphy for Breast Cancer: Should We Do It? Can We Do It?

When cancer is diagnosed, identification of micrometastases is important in patients for whom effective adjuvant systemic therapy is available, since patients with micrometastases are more likely to relapse distantly in spite of local therapy. Although several malignancies may be successfully treated in the adjuvant setting, breast cancer has become the paradigm candidate disease for this approach. Evaluation for micrometastases to the axillary lymph nodes has been performed in patients with breast cancer since the advent of surgical approaches for local treatment (*1*). For decades, full axillary lymph node dissections were performed in an effort to surgically "sterilize" what was felt to be the primary regional drainage area. The objective of this aggressive surgical approach was to prevent the secondary escape of malignant cells to distant organs. Subsequent randomized trials comparing more to less aggressive local therapy have demonstrated that breast cancer is in most cases a systemic disease in which distant metastases occur simultaneously with those to local/regional lymph nodes (*2–5*). These studies led to the adoption of less aggressive surgery and to the investigation of adjuvant systemic therapies. Nonetheless, sampling of the axillary lymph nodes to determine whether metastases were present remains a very sensitive indicator of the metastatic potential of each patient's cancer, and axillary lymph node status has been recognized as one of the most important prognostic factors in patients with newly diagnosed primary breast carcinoma (*6*). Retrospective studies have suggested that patients with pathologically negative axillary lymph nodes have a recurrence rate of only 20%–40% over a 10-yr period (*6–10*), while those with one to three involved axillary lymph nodes have a recurrence rate of almost twice that (*6*). Moreover, of patients with 10 or more positive nodes, less than 20%–30% remain relapse-free after only five years of follow-up (*6*).

Most early trials of adjuvant systemic therapy focused on newly diagnosed breast cancer in patients with relatively poor prognoses, particularly those with positive axillary nodes. The successes of these early trials have now been well documented (*11*), although not all patients with positive lymph nodes benefit from adjuvant systemic therapy. In this regard, combination chemotherapy is indicated for premenopausal node-positive women, while antiestrogen therapy (tamoxifen) is appropriate adjuvant therapy for postmenopausal node-positive women with estrogen receptor positive tumors (*11*). The benefit of adjuvant systemic therapy in node-negative patients remains controversial (*12–14*). Four recently published studies in which node-negative patients were randomly assigned to some form of chemo- or hormonal therapy or to observation only have demonstrated two rather surprising findings (*15–18*):

1. Node-negative patients in these trials (treated or not) had a worse prognosis than expected from historical reviews.

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2. The use of adjuvant systemic therapy improved the disease-free survival compared to observation only.

Do these data imply that evaluation of axillary lymph nodes is no longer clinically indicated? On the one extreme, few if any clinicians will argue that removal of the entire axillary contents provides any substantial long-term clinical benefit, particularly since full axillary nodal dissections frequently result in substantial morbidity, including lymphostasis, arm edema, and subsequent infections of the ipsilateral extremity (*19*). On the other hand, it is premature to suggest that adjuvant systemic therapy is indicated for all patients, regardless of their prognostic category, and that therefore we should abandon all axillary lymph node samplings. While the results of the four recently published node-negative adjuvant trials are encouraging, many authors consider such therapy to remain investigational, since (a) over 50% of node-negative patients will never suffer a relapse of their cancer and (b) no overall survival benefit has yet been demonstrated (*20*). Importantly, those breast cancer patients treated with local therapy who are not destined to relapse cannot benefit from systemic therapy but will suffer the short and potential long-term toxicities related to treatment. Unfortunately, other prognostic factors are not as reliable as axillary lymph node status. Therefore, without knowledge of whether the axillary lymph nodes contain micrometastases, we do not currently have the ability to satisfactorily identify those patients who are more likely to relapse and would, therefore, be better candidates for adjuvant systemic therapy. While the recently closed node-negative trials continue to mature and while we continue to investigate the optimal form of therapy in ongoing trials, the information gained from knowledge of the axillary nodal status still has direct clinical application.

Axillary lymph node sampling is associated with less morbidity than full axillary dissection, but still requires an incision separate from the primary surgical procedure, adding to the morbidity and cost of treatment of primary breast cancer. Therefore, a noninvasive technique to evaluate axillary lymph nodes might be safer and more economical. In this regard, several authors have investigated the use of radiolabeled microcolloids injected intradermally into the hand or chest wall in order to nonspecifically evaluate the draining axillary lymph nodes (*21–23*). Although quite safe, the sensitivity and specificity of radiocolloid axillary lymphoscintigraphy, compared to surgical axillary evaluation, are ~60%–75% and 65%–90%, respectively (*21–23*). In general, the performance characteristics of this technique have not been sufficiently satisfactory to permit its use in general clinical practice.

In order to more specifically identify nodal micrometastasis, radiolabeled monoclonal antibodies that react with cancer-associated cell surface antigens have been used as scintigraphic agents. Imaging after intravenous injection of radiolabeled monoclonal antibodies has been unsatisfactory, due to the poor pharmacologic distribution of these macromolecules (*24*). In order to more efficiently deliver radiolabeled antibody to its target, investigators have studied regional injections for scintigraphic purposes, and studies in animal models have demonstrated that this approach can successfully identify lymph node metastases (*25–30*). Preliminary clinical trials have suggested that immunolymphoscintigraphy with antibodies against antigens expressed by lymphomas, melanomas, and certain carcinomas can be performed safely (*31–34*). Three studies have been published regarding the use of monoclonal antibodies for immunolymphoscintigraphy in breast cancer patients (*35–37*). Unfortunately, while these studies suggest that immunolymphoscintigraphy may be more accurate than clinical evaluation, which is notoriously poor (*38*), the sensitivity and specificity still remains less than that obtained with surgical axillary nodal sampling.

In this issue of the *Journal*, Wahl and colleagues (*39*) report the use of PET imaging after administration of a fluorine-18 derivative of 2-deoxy-2-fluoro-D-glucose (FDG) to identify human ovarian cancer xenografts in nude mice. Theoretically, the abnormal metabolic pathways of glucose in tumor cells result in accumulation of 2-deoxyglucose. Higher levels of 2-deoxyglucose in tumors can be exploited with the use of exogenously administered radiolabeled derivatives of this compound. In this study, intravenously administered radiolabeled FDG accumulated at increased levels in xenografts than in normal lymph nodes. Likewise, mice containing murine B-cell lymphomas also manifested substantially higher lymph node to blood ratios following injection. However, subcutaneous injection of radiolabeled FDG resulted in increased uptake in normal lymph nodes, suggesting that lymphoscintigraphy with this agent may result in nonspecific, false-positive images. While the use of this agent, and PET scanning in general, is intriguing, these data suggest that a great deal more preclinical work is required before this method will be clinically useful.

In summary, determination of axillary lymph node status should still be considered a routine part of the evaluation of patients with newly diagnosed primary breast malignancies. At the current time, this is most efficiently and effectively performed by surgical axillary sampling. While noninvasive lymphoscintigraphy, either with nonspecific radiocolloids, radiolabeled antibodies, or metabolites such as FDG, offers promise, these methods should be considered investiga-

tional, and their clinical utility has yet to be established.

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SELF-STUDY TEST
Skeletal Nuclear Medicine
ANSWERS

ITEM 1: Approach to the Patient with Vertebral Compression Fracture

ANSWERS: A: *T*; B: *F*; C: *F*; D: *F*

Osteoporosis is a disease associated with low bone mass that results in fractures with minimal trauma. Fractures lead to substantial morbidity and, in the case of hip fractures, to mortality (chiefly secondary to pulmonary embolism). Although any part of the skeleton may fracture, the spine, hip, and radius are the most frequent sites.

Vertebral or crush fractures are the most frequently recognized initial presenting features of involutional osteoporosis. The patient characteristically is a woman of 50–65 years of age who develops acute back pain with minimal trauma while performing a routine activity. The radiographic examination may reveal signs of bone loss and compression fractures, which usually are found in the lower thoracic spine or upper lumbar spine. Asymptomatic compression fractures are frequent. These are recognized on spine radiographs obtained for other reasons. This observation suggests that a compression fracture seen radiographically in a patient with backache cannot be assumed to be the cause of the pain.

Osteoporosis is the most likely diagnosis in this patient. However, other metabolic bone diseases for which specific treatment is available, as well as skeletal metastasis and multiple myeloma, may show a similar picture on the radiographs. Hence, the diagnosis of involutional osteoporosis should not be considered confirmed at this point.

The age of a vertebral crush fracture cannot be estimated reliably from its appearance on the radiograph, and the back pain may be due to unrelated causes even in the presence of a compression fracture. Without typical history (e.g., sudden onset of back pain associated with lifting) or typical results on examination (local tenderness), and especially if a history of remote trauma also exists, it may become necessary to establish the age of the compression fracture and to obtain additional support for the diagnosis of low bone mass as the cause of the crush fracture. Often this can be answered by comparison of radiographs taken at different times. Additionally, bone scintigraphy may be helpful as it generally will show focally increased uptake in cases of recent compression fracture, whereas, older compression fractures (over 18–24 months of age) show only slightly increased or normal uptake of tracer. The use of bone scintigraphy in dating spinal compression fractures has been evaluated by Matin.

A bone mineral measurement is indicated occasionally in this clinical setting to document the presence of low bone mass. When used for this purpose, however, the results of bone mineral measurements have to be interpreted with care, because there is a significant (40%–60%) overlap between bone mineral results in age- and sex-matched normal controls without fracture and patients with osteoporotic fractures. A value within the 5th through 50th percentile range of the normal population, therefore, does not exclude osteoporosis. Osteoporosis becomes less likely when the value is above the 75th percentile. Because low bone mass (below the 5th percentile) is only found in about half of the patients with osteoporotic crush fractures, the test is not routinely necessary in the diagnostic workup at this point but may be helpful later, when treatment is started, to serve as a baseline for monitoring treatment effect.

Whenever the diagnosis of involutional osteoporosis is considered, other causes of low bone mass should be considered and excluded. Though the evaluation need not be extensive, Cushing's syndrome, hyperthyroidism, and hyperparathyroidism as well as osteomalacia, multiple myeloma, and skeletal metastasis should be excluded by conventional laboratory testing.

Bone biopsy and bone mineral measurements are not routinely necessary for diagnosis of involutional osteoporosis, but may play an important role when other metabolic bone diseases are suspected. A measurement of serum calcium and phosphate (hyperparathyroidism), serum protein electrophoresis, and complete blood count (multiple myeloma) should be included in the initial laboratory evaluation of this patient. Additional radiographs, scintigraphy, CT, or MRI may be necessary to evaluate for focal osseous lesions when multiple myeloma or metastatic disease are suspected. Accordingly, estrogen treatment for presumed involutional osteoporosis should not be instituted based on the radiographic findings alone, but should await further diagnostic evaluation.

Obtaining a history of risk factors for low bone mass should be the next step in the evaluation of this patient. Published risk factors for bone loss are numerous, although their importance is often not well established. The risk of fracture associated with low bone mass increases with the number of risk factors present. The major risk factors that should be determined from the patient's history are discussed in the Syllabus.

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ITEM 2: Bone Mineral Measurements

ANSWERS: A: *T*; B: *F*; C: *T*; D: *T*; E: *F*

The rates of bone loss in the axial and appendicular skeleton differ. This is in part explained by the different proportions of trabecular and cortical bone at these sites. Trabecular bone loss is generally earlier and more rapid. An understanding of these differences is also important when the effect of treatment is being measured. It is preferable, therefore, that measurements at the site of interest (e.g., the spine, for osteoporosis) are made for bone mineral assessment in the management of the individual patient.

Bone mineral measurements assess bone mass but

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