Staging Investigations in Patients With Breast Cancer
The Role of Bone Scans and Liver Imaging

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Hypothesis: Metastatic workup for patients newly diagnosed as having breast cancer is variable, especially for early disease (T1-2 N0-1). Routine bone scans and liver imaging are often performed without any evidence to support their usefulness.

Design: A retrospective review of patients with breast cancer referred to our center during a 2-year period was performed to determine the value of staging investigations in detecting metastases.

Results: Of the total 250 patients referred to our center after initial diagnosis, 25 (10.0%) were diagnosed as having metastases, 23 of whom had either clinical symptoms or signs suggestive of metastatic disease or abnormalities on routine blood work or chest x-ray examinations. Only 2 patients with metastatic disease were diagnosed solely on bone scan results; none were diagnosed solely on liver imaging (either with an ultrasound or radionuclide isotope liver scan). Overall, 3% (5/161) of patients with pathologic T1-2 N0-1 disease had metastases diagnosed compared with 30% (18/61) of patients with pathologic stage T3-4 or N2 disease.

Conclusions: Our results confirm the low yield of routine bone scans and liver imaging among patients with asymptomatic, pathologically confirmed, early stage (T1-2 N0-1) breast cancer. Therefore, we do not recommend these tests for such patients, although intensive investigations are appropriate for more advanced (stage T3-4 or N2) tumors.

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MANY PATIENTS have extensive staging investigations to complete their metastatic workup following a diagnosis of breast cancer.1-3 The goal of these tests is to identify those patients with incurable disease so that a more realistic prognosis can be given and their treatment can be tailored accordingly. Isotopic bone scans along with isotopic liver scans or liver ultrasound are still commonly used to detect subclinical metastatic disease at these sites.4 The usefulness of these tests is debatable,5-8 especially when one considers both their sensitivities and specificities.

Despite improvements in imaging modalities, clinical staging is still considered by many to be the most useful and cost-effective.5-8 However, there is as yet no consensus on the most appropriate initial staging investigations. It remains to be determined whether tests apart from routine preoperative chest x-ray examination and blood work significantly improve the yield of a metastatic workup in asymptomatic patients.8

We have not previously had a standard policy regarding staging investigations for patients with breast cancer at our center, although extensive investigations are no longer routinely performed. Therefore, we decided to review the yield from the initial metastatic workup on our patients in previous years, specifically to see if routine liver and bone imaging done soon after diagnosis added much information once the patient’s clinical status and surgical staging were taken into account.

RESULTS

Almost all patients had a chest x-ray examination and blood work performed (usually preoperatively) before their referral. Their subsequent investigations were at the discretion of the oncologist or referring physician, and at that time, our center did not have any specified guidelines regarding the staging workup. Of the 250 evaluable patients, 249 were women and 1 was a man, with ages ranging from 26 to 85 years. It was not possible to retrospectively determine the menopausal status, but 106 patients were 50 years or younger and 144 patients were older than 50 years. Below is the distribution of

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METHODS

The medical records of patients with breast cancer referred to the Newfoundland Cancer Clinic in St Johns (recently renamed the Dr H. Bliss Murphy Cancer Centre) from January 1990 to December 1991 were retrieved for analysis. Initially, 329 charts were reviewed, but 79 were excluded for the following reasons: insufficient information in the chart (n = 5), no evidence of invasive disease (n = 17), bilateral or previous breast cancer (n = 8), unusual histological findings (n = 2), previous cancer excluding nonmelanoma skin cancer (n = 1), and referred more than 6 months after initial diagnosis (n = 46). A total of 250 patients referred to the Newfoundland Cancer Clinic after initial diagnosis of a pathologically confirmed, unilateral, invasive breast carcinoma and no previous malignant neoplasms (apart from nonmelanoma skin cancer) were evaluable. The investigations and staging performed on each patient as documented in the cancer clinic chart were retrospectively reviewed along with the clinical condition (ie, signs and symptoms of metastases). From these data, the incidence of metastatic disease along with the investigations performed were analyzed.

After the initial staging investigations, 25 patients (10% of our entire evaluable group) were diagnosed as having metastatic disease based on clinical and/or radiographic findings (a biopsy was not always necessary). As shown in the Table, 21 of the 25 patients appeared to have signs and/or symptoms suggestive of metastatic disease noted in the cancer clinic chart. Only 4 patients with metastatic disease were entirely asymptomatic at initial presentation. The Figure shows the distribution of metastases among the patients according to the TNM classification. The T and N stage were based on pathologic criteria after surgery. Overall, only 5 (3%) of our 161 patients with early (T1-2 N0-1) breast cancer had documented metastases at initial presentation, regardless of tumor grade and other pathologic features, compared with 18 (30%) of our patients with advanced (T3-4 or N2) disease. Two (7%) of the 28 patients with incomplete locoregional staging (Tx N1) had metastases diagnosed after completion of staging investigations.

Most patients had at least a chest x-ray examination (anterior-posterior and lateral) and blood work (including a complete blood count; electrolytes, creatinine, calcium, and alkaline phosphatase levels; and liver function tests) performed. The use of more extensive investigations was somewhat variable. Radionuclide isotopic bone scans, liver scans, and liver ultrasounds were most commonly used to detect metastatic disease, although plain x-ray films, skeletal surveys, isotopic brain scans, and computed tomographic scans of the upper abdomen were occasionally used as well (although on a more sporadic basis).

Of the 143 isotopic bone scans initially performed, 15 (10.5%) were considered positive for metastases, but only 2 (1.7%) of the 118 isotopic liver scans revealed metastases. Of the 4 asymptomatic patients found to have metastases, 2 had other abnormalities on either the chest x-ray film or liver function test results (specifically, an elevated alkaline phosphatase level). Only 2 patients (8% of those with metastases and 0.8% of the total evaluable group) were diagnosed as having metastatic disease based solely on routine bone scan results. Both these patients had stage TX N1 tumors. Four other patients had asymptomatic bone metastases noted on bone scans, but had clinical signs or symptoms suggestive of metastatic disease elsewhere. No patients were diagnosed as having metastases based solely on liver imaging (with either isotopic liver scans or ultrasound). The results of liver imaging were abnormal in 2 patients, but they had locally advanced disease (T3 or T4 tumors) and clinical evidence of metastases elsewhere. Other investigations, such as x-ray examinations and computed tomographic scans, did not improve the detection of metastases.

Traditionally, isotopic bone scans and liver imaging (with isotopic liver scans and, more recently, liver ultra-

### Table

<table>
<thead>
<tr>
<th>No. (%)</th>
<th>Entire Group, %</th>
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<tbody>
<tr>
<td>Asymptomatic</td>
<td>21 (84)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>39 (16/41)</td>
</tr>
<tr>
<td>Normal preoperative investigation results</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Abnormal preoperative investigation results</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Total Group With Metastases</td>
<td>25 (100)</td>
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</tbody>
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### Figure

- Title: Distribution of Patients With Metastases
- X-axis: Incidence of Metastases, %
- Y-axis: Distribution of metastatic disease identified according to locoregional classification (based on the Union Internationale Contre le Cancer TNM staging classification).
sounds) have often been used to rule out bone and liver metastases and definitive-stage patients with breast cancer. However, the overall yield of these investigations is reportedly low, especially with early (pathologic stage T1-2 N0-1) disease. Often, fewer than 5% of patients with early breast cancers have bone metastases at presentation, and the incidence of liver metastases is even lower. With locally advanced breast cancer (pathologic stage T3-4 or N2), the incidence of metastases is much higher, and in such cases, more extensive investigations are justified. Approximately 25% of patients with T3-4 tumors present with bone metastases at initial diagnosis. The diagnostic accuracy of these tests is quite variable. Bone scans can be notoriously inaccurate, with more than 15% producing false-negative results and more than 30% producing false-positive results. Isotopic liver scanning is associated with a 5% to 25% rate of false-negative and false-positive results. Although ultrasonography of the liver is more accurate than isotopic liver scanning, it is also not completely reliable. In fact, we have found that some of our patients described as having normal staging investigations at presentation developed obvious metastases soon afterward. In retrospect, the results of their initial investigations (such as bone scans) were not entirely normal. This illustrates that, even with extensive investigations, it is not always possible to correctly identify patients with metastases.

Our results show that 25 (10%) of the 250 patients with breast cancer had metastatic disease at initial presentation, which is probably because we had a large number of patients with locally advanced (T3-4 or N2) tumors. Actually, 61 (24%) of the 250 patients in our series had locally advanced disease, presumably due either to many patients in our province initially presenting with locally advanced breast cancer or to a significant number of patients with early cancers not being referred to our cancer center (resulting in disproportionately more advanced tumors). However, only 3% of the patients with T1-2 N0-1 breast carcinoma had metastases diagnosed at initial presentation compared with 30% of patients with T3-4 or N2 breast carcinoma. These data are similar to other published reports.

Our results confirm that most patients (84%) with metastases at presentation had clinical signs or symptoms suggestive of metastatic disease, and this has also been noted elsewhere. Of the 4 patients diagnosed as having metastatic disease based on the bone scan results, 2 already had abnormalities on blood work results and/or chest x-ray films. Therefore, routine bone scans only picked up 2 additional patients with metastatic disease. Liver imaging by itself did not detect any patients with subclinical metastatic disease, although 2 patients with metastatic disease identified elsewhere were also found to have abnormalities suggestive of liver metastases after liver imaging.

Therefore, when one considers the sensitivities and specificities of bone scans and liver imaging, it remains doubtful whether these investigations should be performed routinely for patients with asymptomatic, pathologically confirmed, early-stage breast cancer if the results of the chest x-ray examination and blood work (including liver function tests and alkaline phosphatase levels) along with the clinical assessment are unremarkable. They are likely to be of low yield, yet time-consuming and expensive.

CONCLUSIONS

Our results confirm the low yield of metastases at initial presentation of operable early (pathologic stage T1-2 N0-1) breast cancer and the relatively low yield of routine bone scans and liver imaging in asymptomatic patients. Therefore, we no longer recommend these investigations routinely unless the results of initial clinical assessment, chest x-ray examination, or blood work (including alkaline phosphatase levels and liver function tests) reveal abnormalities. However, in locally advanced (pathologic stage T3-4 or N2) breast cancer, the incidence of metastases is much higher, and more extensive investigations (with bone scans and liver ultrasound) are warranted. We believe this is the most efficient and cost-effective approach to staging patients with breast cancer.

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REFERENCES

I applaud the effort of the authors of this article to determine the value of bone scans and liver scans in the search for metastatic disease in patients who are newly diagnosed as having stage I or stage II breast cancer. This study demonstrated metastasis in only 0.8% of early stage breast cancer in 250 patients. In the 5 patients found to have unexpected metastatic disease, the therapeutic benefits are probably minimal in terms of overall survival. In addition, there are considerable disadvantages in the false-positive outcomes encountered with routine bone and liver scans. The false-positive rate reported in this article is 25% to 35%. The additional patient encounters resulting from false-positive test results and the exaggerated patient anxiety are not to be capriciously discounted. The elimination of nonproductive testing is essential to quality of care. This applies not only to evaluation at the time of initial breast cancer diagnosis but also to testing associated with long-term follow-up of patients with breast cancer.

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ARCHIVES OF INTERNAL MEDICINE

Prediction of the Risk of Bleeding During Anticoagulant Treatment for Venous Thromboembolism

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Objectives: To construct and validate the bleeding risk prediction score, which is based on variables identified in the literature that can be easily obtained before the institution of anticoagulant therapy, in a large independent cohort of patients who were treated with anticoagulant therapy for established venous thromboembolism to allow for quantitative assessment of the risks and benefits of the therapy and to adapt the patient’s management accordingly.

Methods: We constructed a bleeding risk prediction score, based on variables and their odds ratios identified in the literature, which can be easily obtained before the institution of anticoagulant therapy (score = [1.6 \times \text{age}] + [1.3 \times \text{sex}] + [2.2 \times \text{malignancy}]). Subsequently, we evaluated the score in a test group of 241 patients treated with anticoagulant therapy for venous thromboembolism to determine the optimal cutoff points for the prediction of hemorrhagic complications, using receiver operating characteristic curve analysis. We then validated this score in an independent cohort of 780 patients. A score of 3 or more points, 1 to 3 points, or 0 points represented a high, intermediate, or low bleeding risk, respectively.

Results: The score in about one fifth of the patients in the test group was classified as predicting high risk for bleeding complications. The risk of all bleeding complications was 26% in this group and the risk of major bleeding complications was 14%. The area under the curve was 0.75 (95% confidence interval, 0.64-0.84) and 0.82 (95% confidence interval, 0.66-0.98) for all bleeding complications and major bleeding complications, respectively. When validated, there was a moderate loss of predictive power of the score, but the categorization of the patients by the score remained clinically useful; 20% of the patients were classified as high risk, and the bleeding rate was 17% for all bleeding complications and 7% for major bleeding complications compared with 4% and 1%, respectively, in those categorized as low risk.

Conclusions: With the use of 3 easily obtainable, clinical variables in a prediction model, it is possible to identify a subgroup of patients at the start of anticoagulant therapy who have a high risk of developing hemorrhagic complications. Further studies should address whether additional measures to prevent bleeding decrease the bleeding incidence without compromising efficacy. (1999;159:457-460)

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