Reevaluation of baseline staging tests in breast cancer; what should be the standard?

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ABSTRACT

There has been an ongoing debate on staging in breast cancer. In this study, we evaluated the metastasis detection rate with baseline staging of breast cancer after operation. One hundred consecutive breast cancer patients were evaluated with liver ultrasonography, chest X-ray and bone scans. All patients were followed at least for 6 months. More than one third of our patients belong to the high risk group (axillary involvement >3). In 3 patients (3%) metastasis were detected. Two of them (5.8%) were in the group with pT4, N2 or N1 (N >3), one of them (2.7%) was in the group with pT2-3N0-1 (N ≤3). There was no metastasis in patients with pT1N0-1 (N ≤3). To detect one case of occult metastasis 2000 € were spent. As a result, routine staging does not have a major impact on individual adjuvant treatment planning. We recommend routine staging only for patients with pT4 or N1, (N >3) or N2 disease, and we do not recommend staging for patients with pT1N0-1, (N ≤3) positive nodes. Decision about staging of the patients with pT2-3N0-1, (N ≤3) diseases should be individualized according to patients’ and doctors’ preferences and economic resources. [Turk J Cancer 2003;33(3):150-153]

INTRODUCTION

In daily clinical practice, bone scan (BS), chest X-ray (CXR) and liver ultrasonography (L-USG) are frequently used for staging newly diagnosed breast cancer, either preoperatively or postoperatively. However, detection of metastatic disease at presentation is not frequent and these tests alter management of these patients rarely if ever. Moreover, these staging tests are expensive, time consuming and false positive results may cause anxiety.

In an otherwise asymptomatic breast cancer patient, if clinically there is no T4 disease or palpable axillary lymph nodes, presurgical staging is generally omitted. After surgery, a subset of asymptomatic patients may be selected for further staging according to the pathological diagnosis. In this group, prevalence of detectable metastatic disease must be high enough to justify routine testing. Several staging approaches according to pathological diagnosis are defined in the literature by different authors, with no universally accepted standards (1-4).

Studies addressing staging procedures should be verified before clinical implementation for at least two purposes: First, to verify the results of the former studies, and secondly, to show if the results are applicable in different patient populations, countries and hospitals. If the same results are reproducible in different populations, than they can be accepted universally as a staging standard for breast cancer.

KEY WORDS:
Stage, breast cancer
In the present study, we reevaluated staging of breast cancer after surgery, tried to define a subgroup in whom prevalence of metastatic disease is relatively high and thus routine staging is rational. We compared our results with those from other similar studies. We also calculated the cost of catching one patient with distant metastasis.

**PATIENTS AND METHODS**

We prospectively evaluated and followed 100 consecutive breast cancer patients for at least six months. They were referred to Medical Oncology section of Akdeniz University Faculty of Medicine for adjuvant treatment after surgery, between September 2001 and July 2002. All patients were evaluated with L-USG, CXR and BS. Pathological TNM, menopausal status, estrogen and progesterone receptor status, and erb-B2 expression were recorded. Any positive result was further evaluated with more sophisticated methods when needed (MRI, computed tomography, biopsy etc.). Final staging was decided after six months of follow up of all suspicious cases by repeated tests when needed.

Only direct cost of baseline procedures and further tests were taken into account. The costs of X-rays, tomography, BS and MRI were obtained from hospital data. Indirect cost (For example; cost of extra visits due to tests, travel expenses and other personal payments) was not included in the cost. Total cost of all procedures of all patients was divided by patient number to find mean cost of staging per patient, and total cost was divided to number of metastatic patients to find cost of catching one occult metastasis.

**RESULTS**

Details of pathological staging and results of tests are given at table 1. In 2 patients with small nodules (<1cm) in liver, final decision between hemangioma and metastasis could not be made and these two were treated as if they were early breast cancer. In 6 months of follow up these two lesions remained stable. Overall metastasis detection rate was 3%. All of them were bone metastases. Two of the 3 metastatic patients had more than 4 positive axillary lymph nodes, one with 12, and the other with 22 positive

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>pTN stage</th>
<th>Patient number</th>
<th>Overall metastasis (True positive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>T1N0-1 (N ≤3 positive nodes)</td>
<td>29 (29%)</td>
<td>0</td>
</tr>
<tr>
<td>Group II</td>
<td>T2-3N0-1 (N ≤3 positive nodes)</td>
<td>37 (37%)</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Group III</td>
<td>T4 or N1 (N &gt;3 positive nodes) or N2</td>
<td>34 (34%)</td>
<td>2 (5.8%)</td>
</tr>
<tr>
<td>All</td>
<td>All</td>
<td>100</td>
<td>3 (3.0%)</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Pathologic stage</th>
<th>BS (%)</th>
<th>L-USG (%)</th>
<th>CXR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1N0-1 (N ≤3 positive nodes), (n=29)</td>
<td>1 (3,4)</td>
<td>2 (6,8)</td>
<td>3 (10,3)</td>
</tr>
<tr>
<td>T2-3N0-1 (N ≤3 positive nodes), (n=37)</td>
<td>4 (10,8)</td>
<td>3 (8,1)</td>
<td>2 (5,4)</td>
</tr>
<tr>
<td>T4 or N1 (N &gt;3 positive nodes) or N2, (n=34)</td>
<td>3 (8)</td>
<td>1 (2,9)</td>
<td>3 (8,8)</td>
</tr>
<tr>
<td>Total (n=100)</td>
<td>8 (8)</td>
<td>6 (6)</td>
<td>8 (8)</td>
</tr>
</tbody>
</table>
nodes. The third patient had a T3 tumor without positive axillary node. In these 3 patients planned adjuvant radiotherapy was omitted and they were treated according to hormone receptor status either with hormonal therapy or chemotherapy.

Details of false positive results are given at table 2. False positivity rates were between 6 to 8 percent among the three tests. To verify the positive tests, 17 computed tomography, 4 magnetic resonance imaging and 38 direct X-ray of bones were performed. Overall cost of all staging procedures was 6000 €. Mean cost of staging per patient was 60 €. As a result, to detect one case of occult metastasis 2000 € were spent.

**DISCUSSION**

There has been an ongoing debate about staging in breast cancer. To establish a treatment program (chemotherapy, radiotherapy and hormonal treatment), initial staging may have an importance. However, the detection rate and positive predictive value of staging procedures are low and rarely change the treatment plan for the individual patient.

Detection rate of bone metastasis with bone scan was between 3.1 to 10.6 percent in different studies. Mostly in clinical stage I-II disease, detection rate of bone metastasis was between 0.5-3% whereas this increased up to 15-18% in clinical stage III patients (5-9).

L-USG detects liver metastasis very rarely in pathological stage I-II disease and approximately 2-3% in stage III disease (10,11). Chest X-ray has the lowest detection rate. Occult metastasis in lungs was detected 0.1-2% with chest X-ray (12,13).

Is there a group for which staging is meaningful and detection rate is high enough to perform routine staging? This is an open question and some studies mainly focused on this subgroup. Cancer Care Ontario Practice Guidelines Initiative (1) recommends bone scan in all pathological stage II disease and offers to consider L-USG and chest radiography for patients with 4 or more positive lymph nodes. In pathological stage III disease all tests were recommended. However some opposition appeared against L-USG because of very low detection rates (2).

Ravaioli et al. (3) also defined such a subset, offering full procedural staging for pT4 patients and patients with more than 3 positive nodes and N2 patients. Fifteen percent of these high-risk patients were found to be metastatic (3). Patients with pT1N0-1 (N ≤3 positive) and pT2-3N0-1 (N ≤3 positive) disease may be spared from full staging, although the second group had a metastasis detection rate of 2.94% and according to authors this group might be evaluated with caution and results should be verified with further studies. More recently the same group published their updated results with increased patient number (14). They combined the first two group (pT1-3, N0-1, N ≤3) and found metastasis detection rate as 1.46%. In the patients with pT4, N2 or N1, (N >3) metastasis detection rate was 10.68%. Our results are very similar with those of Ravaioli’s study. We detected no metastasis in the patients with pT1N0-1, (N ≤3) positive nodes. Metastasis detection rate was 2.7% in the in the patients with pT2-3N0-1, (N ≤3). Combining the two groups as T1-3N0-1, N ≤3 results in a metastasis detection rate 1.5% in our group that is very similar to Ravaoli’s study (14). However, in our study metastasis detection rate was much lower (5.8%) in the patients with pT4 or N2 or N1, (N >3) than Ravaoli’s group. This difference might be due to different patient profile. In our third group there was no patient with T4 and only 1 patient with N2 disease, all others were T1-3N1 (N >3), but in Ravaoli’s first study there were 42 out of 103 patients who were either T4 or N2 or both (3). This was obviously a group that had relatively higher risk of metastasis than the corresponding third group of our patients. In other studies about staging breast cancer similar metastasis detection rates were found in stage III disease (10-12).

In a former study, we showed that erb-B2 over expression is related with metastatic disease at presentation (15). All three metastatic cases in our group of patients were erb-B2 positive (two of them %90++, one of them %70++). In the whole group, erb-B2 status of 12 patients were unknown, 39 patients had (+++) and 11 patients had (+) staining.

From this study and others it is clear that staging is not beneficial for pT1N0-1 N ≤3 patients. Although a positive psychological effect, which negative staging investigations cause a relief which is familiar for all clinicians who take care of breast cancer patients, might be speculated to justify staging of all patients, concerning high false positive rates, that is not the case. In our opinion, in patients with pT4 or N1, N>3 or N2 disease metastasis detection rate is relatively high and in this group staging must be standard. The second group (pT2-3N0-1, N ≤3 may be tested or not according
to available economic resources because lower limit of “number need to test” may be different in different countries and populations. For example; members of the Breast Cancer Disease Site Group of the Cancer Care Ontario practice Guidelines Initiative felt that tests that detected metastases in less than 1% of patients were not clinically useful and >1% detection rate justifies staging tests. However, they also agreed that choice of that cut-off for detection rate was subjective. In our third group $1020  \in$ was spent to find one patient with metastasis, whereas in the second group this figure was $2240  \in$. Real costs might be higher since indirect costs were not calculated. For areas with limited economic resources such as our country, a higher cut off might be more rational taking into account such high false positive rate.

As a result, we recommend routine staging for patients with T4 or N1, (N >3) or N2 disease, and we recommend against staging for patients with T1N0-1, (N ≤3) positive nodes. Decision about staging of the patients with T2-3N0-1, N ≤3 diseases should be individualized according to patient-doctor preferences and economic resources.

References