Sentinel Node Status and Tumor Characteristics

A Study of 234 Invasive Breast Carcinomas

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Context.—Axillary lymph node status is the most important prognostic factor in patients with breast cancer. Tumor size and lymph node status, the most reliable pathologic bases of the tumor staging system, are practical parameters for estimating survival status. With the advent of lymphatic mapping and sentinel node (SN) identification, there is potential for a more efficient and sensitive evaluation of the axillary lymph node status.

Objective.—To correlate SN status with tumor size, grade, and lymphovascular invasion.

Design.—We examined 234 patients with unifocal breast carcinomas measuring 25 mm or less as detected by preoperative ultrasound during the period May 1998 through December 2002. Sentinel nodes were examined by frozen section and paraffin section as per protocol.

Results.—Of the 234 patients, SN was identified in 221 (94.5%). An average of 1.38 SNs were examined per patient. Seventy-seven of 221 patients were SN positive on paraffin section. Sixty-six (85.7%) of these 77 cases could be correctly diagnosed as positive for metastatic carcinoma on frozen section. Two cases reported as positive on paraffin section were reported as suspicious on frozen section. Logistic regression indicated that tumor size, grade, and lymphovascular invasion were all significantly associated with SN status (P < .001).

Conclusions.—Tumor size, grade, and lymphovascular invasion were significantly associated with SN status in unifocal invasive breast carcinoma.

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MATERIALS AND METHODS

We examined 234 patients with unifocal breast carcinomas measuring 25 mm or less as detected by preoperative ultrasound during the period May 1998 through December 2002. Sentinel nodes were examined by frozen section (FS) and paraffin section (PS), as per protocol. Full axillary clearance was undertaken for SN-positive cases. All patients determined to be SN negative on FS had a minimum of 4 axillary nodes sampled, and these lymph nodes were examined by PS. The SNs received from the operating room were identified, measured, and dissected from the surrounding fat and connective tissue. Small lymph nodes measuring less than 0.5 cm were submitted as 1 piece for FS. Larger nodes were cut into 4-mm slices in longitudinal or transverse planes. Scrape cytologic samples were prepared from all the cut surfaces. The cytology slides were fixed immediately in 95% alcohol and stained with rapid hematoxylin-eosin (H&E) stain. The stained cytology slides were examined for the presence or absence of tumor cells. All lymph nodes were subjected to FS. Frozen section slides were stained with H&E and were reported inoperatively as positive, suspicious, or negative for tumor. The remaining samples, including FS samples, were then fixed in 10% formalin, processed overnight, and embedded in paraffin according to the standard protocol. One 4-μm section was stained with H&E stain and examined for the presence or absence of tumor. If this appeared to be negative, 2 additional levels of sections were then evaluated. In selected cases, the immunohistochemical stains for cytokeratin (AE1/AE3) were performed to exclude micrometastasis.

Statistical Analysis

The association of SN status and tumor characteristics was tested by univariate analysis using the Mann-Whitney test for tumor size and the χ² test for tumor grade and LVI. Binary logistic regression was subsequently performed to test which factors were independent predictors for SN metastasis. The association was considered significant at P < .05.

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RESULTS

Of the 234 patients, the SN was identified in 221 patients; a mean of 1.38 SNs were found per patient, with a range of 1 to 4. Paraffin sectioning identified 77 of these 221 patients as positive for metastatic carcinoma in SN. Sixty-six (85.7%) of these 77 node-positive patients were correctly diagnosed by intra-operative FS. The axillary clearance revealed that in 29 patients, the SN was the only histologically positive node. Two patients reported as suspicious for metastatic carcinoma on FS were later confirmed positive for micrometastasis (Figures 1 and 2) on PS. All node-negative patients had a minimum of 4 nodes examined, except for 5 patients in whom only 3 nodes could be identified.

Two patients with negative SN on both FS and PS had 1 positive intramammary lymph node identified within the wide local excision specimen. One such tumor was in the upper outer quadrant, whereas the other was retroareolar. These patients received chemotherapy but did not undergo axillary node clearance. One of them developed axillary lymph node as well as distant metastases 2 years later and underwent full axillary clearance. To date, this is the only patient who has had recurrent axillary disease. Thirty (76%) of 41 patients with LVI had positive axillary nodes, whereas 42 (24%) of 175 patients had a positive axillary node in the absence of LVI ($P < .001$). Tumor grade was also correlated with node positivity. Tumor grades 2 and 3 were associated with increased risk of lymph node metastasis: 45.3% of grade 2 and 3 tumors and 16.7% of grade 1 tumors had positive SN (Table 1, $P < .001$). The odds ratio of positive lymph nodes in grades 2 and 3 versus grade 1 was 4.15 (95% confidence interval, 2.1–8.2). Increasing tumor size was positively associated with axillary lymph node metastasis. The median size of the node-positive tumors was 20 mm, compared with 15 mm for node-negative tumors ($P < .001$). Using logistic regression, tumor size and LVI were significantly associated with positive SN status (Table 2). Lymphovascular invasion was associated with a relative risk of 9.8 for SN involvement. The relative risk of SN involvement and tumor size was 1.065 for each increment of 1 mm.

COMMENT

Primary breast tumor characteristics can be used to predict positive SN status. However, the published studies have shown controversial results. Bevilacqua et al7 established a prospective validated model for predicting axillary node metastases based on 2000 SN procedures. Their results demonstrated that age, tumor size, LVI, nuclear grade, histologic subtype, and the tumor’s location in the breast were independent predictive factors for axillary node status. Choi et al8 reported an analysis of SN mapping in early breast cancer. They claimed that the absence of estrogen and progesterone receptors by immunohistochemistry and the presence of LVI predicted SN status in patients with early breast cancer. However, histologic type, nuclear grade, $HER-2/neu$ and $p53$ oncogene status, DNA ploidy, and S-phase fraction did not predict SN status. Another study, by Chen et al,9 found that tumor size and LVI were the only variables predictive of positive SN. Sentinel lymph nodes were positive in 73 (28.4%) of 257 patients: stage T1a, 5 (13.5%) of 37 patients; stage T1b, 19 (20.4%) of 93 patients; stage T1c, 37 (35.9%) of 103 patients; and stage T2, 12 (50.0%) of 24 patients. Although LVI was not correlated with tumor size, it was the stron-
gest predictor of positive SN in their study. Our results also showed that LVI was the strongest predictor of positive SN status.

Intraoperative diagnosis of SN is necessary, because patients with positive SN may be treated immediately with axillary lymph node dissection, but both FS and imprint cytology have limitations for detecting micrometastases. In our study, FS was able to correctly diagnose 66 (85.7%) of the 77 cases. Although the detection rate was high, 15% of cases were missed. There is an interesting dilemma for both surgeons and pathologists as to whether to perform an intraoperative FS in terms of analyzing the SN for breast cancer. Chao et al10 conducted a formal decision analysis to quantify the relative value of the patient's quality of life with regard to performing intraoperative FS versus PS analysis of SN for breast cancer. The results suggested no definite preference for either procedure. The decision to choose FS or PS should be based on an individual patient's risk and preference, because the decision analysis indicated that these 2 options are equivalent with respect to patients' quality of life. Assumptions for this analysis were based on data from 203 nodal basins, where the prevalence of nodal metastasis was 26.1%; the FS sensitivity was 68% and the FS false-positive rate was 0.7%. The 2 branches of the tree represent the 2 surgical options of either FS analysis intraoperatively, accompanied by immediate axillary dissection for positive nodes, versus PS analysis followed by reoperative axillary dissection.

Sentinel lymph node biopsy is accurate and safe while providing less surgical morbidity than axillary node dissection. In a recent clinical study, Reitsamer et al11 evaluated the rate of axillary recurrences after SN examination only in SN-negative patients. A total of 200 (61.0%) of 328 patients were SN negative and had no further axillary lymph node dissection. The mean tumor size of SN-negative patients was 16.5 mm. The mean number of SNs removed was 2.1 per patient. There were no local or axillary recurrences at a median follow-up of 36 months. The significance of positive intramammary lymph nodes in breast cancer patients is not known. However, it seems that a positive intramammary node in proximity to the main tumor may be a potential pitfall for SN identification. In such circumstances identification of SN may be inaccurate, and even axillary clearance may fail to allow the surgeon to stage the tumor accurately.

In summary, tumor size, grade, and LVI were significantly associated with SN status in unifocal invasive breast carcinomas 25 mm or less in size. The SN technique represents a considerable improvement in our ability to evaluate the regional lymph nodes for prognosis without significant morbidity to the patients, and it is useful in selecting early breast cancer patients for adjuvant therapy. Our results showed that in the majority of cases, assessment of SN alone could clearly identify those patients with node-positive disease.

References