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Original article

Accurate classification of sentinel lymph node metastases in patients with lobular breast carcinoma

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ABSTRACT

Among pathologists there is low reproducibility in classifying small volume metastases in sentinel lymph node particularly in cases of invasive lobular carcinoma. We postulate that strict adherence to American Joint Commission on Cancer (AJCC) 2003 criteria may result in inaccurate staging of lobular carcinoma patients. We reviewed cases of metastatic lobular carcinoma in sentinel lymph node biopsies between 1998 and 2008. All sentinel lymph nodes were reassessed using strict adherence to AJCC 2003 criteria. Subsequent axillary lymph node dissection and clinical follow-up were reviewed. Fifty-one patients met our inclusion criteria and were originally classified by the primary pathologist as follows: 10 isolated tumor cells, 8 micrometastases, 27 macrometastases, and 6 'positive' cases without further classification. Cases were re-classified using strict adherence to AJCC 2003 criteria as follows: 21 isolated tumor cells, 2 micrometastases, and 28 macrometastases. Twelve isolated tumor cells cases underwent full axillary dissection, and 3 (25%) had additional macrometastases. All micrometastatic cases underwent axillary dissection; all were negative. Twenty-two macrometastatic cases underwent full axillary dissection and 16 (73%) had additional macrometastases. Diffuse single cells or small clusters should not be interpreted as isolated tumor cells in invasive lobular carcinoma sentinel lymph nodes. The criteria for assessing small volume metastases in the sentinel lymph node of patients with invasive lobular carcinoma need to be more clearly defined.

Introduction

The use of sentinel lymph node (SLN) biopsy to assess lymph node status has become the standard of practice among breast oncologic surgeons. Based on the pathologic findings of the SLN, further management will be determined. Despite the lack of evidence, many institutions (including ours) will perform full axillary lymph node dissection (ALND) when the SLN shows macrometastasis (MAC) or micrometastasis (MIC), whereas no further ALND is performed when there are isolated tumor cells (ITC). The decision to use adjuvant chemotherapy may also be influenced by SLN status. Many institutions will skip adjuvant chemotherapy when only ITCs are detected.

Pathologic SLN assessment is based on guidelines published by the American Joint Committee on Cancer (AJCC) Staging Manual, 6th edition[1] and the International Union Against Cancer (UICC) Tumor Lymph Node Metastasis (TNM) Classification of Malignant Tumors.[2] Studies have shown poor reproducibility in the application of AJCC and UICC/TNM guidelines for SLN classification in both invasive ductal carcinoma and invasive lobular carcinomas (ILC).[3,4,5] Diagnostic variation is particularly problematic in cases of ILC where a dispersed pattern of single tumor cells or small clusters of tumor cells may be seen throughout the lymph node parenchyma, subcapsular sinus or perinodal tissue. A recent paper by Turner et al. studied the use of a digital image study set and expanded criteria to improve interpretive consistency of SLN biopsies.[4] The study criteria were based on the concept that ITC and MIC are distinguished by the size of the largest tumor cell cluster. A pattern of "single cells, as in the dispersed lobular pattern" of ILC was classified as ITC. We postulate that this strict adherence to AJCC 2003 criteria may result

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in erroneous staging of ILC patients. We sought to determine the non-sentinel ALND metastatic rate and possible prognostic factors via clinical follow-up of lobular breast cancer patients using this strict interpretation of the AJCC guidelines.

Materials and methods

Institutional review board approval was obtained. We retrieved all ILC cases with SLN biopsy from the pathology computer database. Consecutive cases of ILC with tumor cells detected in SLN by hematoxylin and eosin (H&E) and cytokeratin immunohistochemistry (IHC) were pulled from 1998 to 2008 at a single institution. The SLN protocol was standardized for all cases. All candidate lymph nodes were dissected, sectioned longitudinally at 0.2 cm levels, and entirely submitted for tissue processing. 150 μm thick serial sections yielded 3 H&E slides and 2 cytokeratin IHC slides, cytokeratin 7 (OVTL12-30, DAKO, Carpenteria, CA) and pan-keratin (Ker AE1 + AE3, Millipore, Temecula, CA), from alternate sections. The ALND protocol was standardized for all cases. For grossly negative lymph nodes, all candidate lymph nodes were dissected, sectioned at 0.2 cm levels, and submitted in their entirety for tissue processing. For large (>2 cm) grossly positive lymph nodes, representative sections were submitted for evaluation and cytokeratin stains were not performed. Only one H&E section was cut, and no IHC stain was performed.

Information extracted from finalized pathology reports included the following: primary tumor modified Bloom-Richardson score, further ILC subclassification (e.g., pleomorphic, signet ring, alveolar, classic), primary tumor size, positive and total number of SLNs. The size of the largest SLN tumor deposit and the original SLN classification (MAC, MIC, or ITC) were recorded based on the primary pathologist's report. For the original SLN classification, a SLN reported as "positive" with no further classification or measurement (usually cases prior to AJCC 2003 published guidelines) was recorded as "not otherwise specified" or NOS. Further information extracted included presence or absence of extracapsular invasion and whether tumor deposits were detected by IHC stain alone. If subsequent ALND was performed, positive and total number of lymph nodes were recorded.

All available H&E and IHC stained slides of both SLN biopsies and axillary lymph nodes were reviewed by an experienced breast pathologist (SKA). Using criteria as outlined by AJCC 2003[1] and further specified by Turner et al.,[4] SLN tumor deposits were measured using a micrometer and assigned to one of three categories: MAC, MIC, or ITC. Briefly, per AJCC 2003 guidelines, MAC was classified as "one or more tumor deposits greater than 2 mm". MIC was classified as a tumor deposit "greater than 0.2 mm but not greater than 2.0 mm in largest dimension". ITC was defined as "single cells or small cluster of cells not greater than 0.2 mm in largest dimension".[1] A cluster was defined as "a confluent focus of tumor cells touching other tumor cells".[4] The single largest cluster was measured by micrometer. Single dispersed cells throughout the lymph node were regarded as ITC if the largest cluster measured less than or equal to 0.2 mm. The reviewer was blinded to the classification originally issued by the primary pathologist.

ITC was further subclassified as "ITC" when a single cluster was present, "ITC multi" when 2 or more clusters were present, and "diffuse" when scattered single cells or small clusters were present throughout lymph node tissue. The location of tumor cells was further classified as being either in the subcapsular sinus or intranodal parenchyma.

H&E slides of ALND were reviewed to confirm metastatic disease. Outcome data was extracted from electronic medical records. Patients were assigned to one of the following categories: "no evidence of disease", "lost to clinical follow-up", "locoregional recurrence", "distant metastases", and development of other significant disease (e.g., second cancer). The time to follow-up was calculated based on the SLN biopsy procedure date. All p-values utilized categorical variables and were calculated using Chi-squared test (MS Excel).

Results

We identified 51 cases of invasive lobular carcinoma with SLN metastases. The median size of the primary tumor was 3.4 cm (range 0.15–13 cm). The median modified Bloom-Richardson score was 6 (range 5–8, data not shown). A modified Bloom-Richardson score was not mentioned in 18 cases. Eighteen patients had a subtype of ILC other than classic, either mixed with other subtypes (including classic type) or as a single subtype: 9 with focal (<5%) ductal differentiation, 5 pleomorphic, 8 signet ring cell, and 2 alveolar types. The remaining patients had pure classic type ILC. A mean of 2.5 SLNs was removed (range 1–7). The mean number of positive lymph nodes was 1.5 (range 1–4). The original classifications of the SLN by original pathologists were as follows: 10 ITCs, 8 MICs, 27 MACs, and 6 NOS. Thirty-six of 51 patients (71%) underwent ALND: 3 ITCs, 6 MICs, 22 MACs, and 5 NOS. A mean of 12.2 axillary lymph nodes was removed (range 1–29) with 2.2 (average) lymph nodes positive (range 0–25). The mean clinical follow-up was 47 months (range 5–120 months).

SLN biopsies were re-classified using expanded AJCC 2003 criteria as described above into the following groups: 21 ITC, 2 MICs, and 28 MACs. Of the 21 cases re-classified as ITC (Table 1), 3 were originally diagnosed as MACs, 8 were originally MICs, and 10 were originally ITC. Twelve of 21 (57%) patients underwent ALND. Three of 12 (25%) patients had multiple additional positive MACs on ALND (Table 1, case #18, 19, 21) (Figs. 1–3). These cases were originally classified by the original pathologist as MAC (2 cases) and MIC (1). Clinical follow-up from the ITC group was as follows: 17 patients with no evidence of disease, 2 patients with contralateral breast cancer, and 2 patients lost to follow-up.

For the cases re-classified as ITC (Table 1), 10 of 21 (48%) cases were detected by cytokeratin IHC stain alone. None of the cases with ALND follow-up had additional positive axillary recurrences. The association between IHC detected metastases and subsequent negative ALND was not statistically significant ($p = 0.2$). Parenchymal involvement (versus subcapsular sinus only) of SLN was noted in 11 of 21 cases re-classified as ITC (including 2 detected by IHC stain alone). There was no association between parenchymal involvement and subsequent positive ALND (($p = 0.5$).

Both of the patients re-classified as MIC on SLN were detected by H&E and IHC stain (data not shown). Both were originally classified as MAC and underwent ALND. There was no additional metastatic disease, and both were alive with no evidence of disease.

All of the 28 cases re-classified as MAC were detected by H&E and IHC stains (data not shown). Parenchymal involvement of metastatic disease appeared to be more common in cases re-classified as MAC (96% compared to 0% and 52% of MIC and isolated tumor cell cases, respectively, $p < 0.0001$). Mixed subtypes of ILC (e.g., alveolar, pleomorphic, etc.) appeared to be more common in re-classified MAC cases, although this was not statistically significant ($p = 0.2$, data not shown).

Twenty-two MAC cases and 6 NOS cases were re-classified as MAC, and 22 of 28 (79%) patients underwent ALND (data not shown). Six patients who did not have further ALND had multiple SLN samplings. These patients opted not to have further surgeries. Sixteen of 22 (73%) patients had additional MACs on ALND. Clinical follow-up from the MAC group was as follows: 19 patients with no evidence of disease, 2 patients with bone and brain metastases, 1 patient with contralateral breast cancer, 2 patients with another primary lung cancer, and 4 patients lost to follow-up.