Axillary burden of disease following false-negative preoperative axillary evaluation

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Abstract

BACKGROUND: Preoperative axillary ultrasound (AUS) and fine-needle aspiration (FNA) are sensitive and specific for breast cancer nodal metastases. We hypothesize that false-negative result predicts minimal axillary disease (≤2 nodes).

METHODS: A retrospective review of breast cancer patients receiving AUS identified T1/T2 tumors and positive sentinel node with axillary dissection. Chi-square analysis was performed using Fisher’s exact test.

RESULTS: Of 903 AUS cases, 384 had T1/T2 tumors. False-negative rate of AUS and FNA was 48% and 45%, respectively. Of 384 cases, 73 were sentinel node positive and had axillary dissection; 55 (75.3%) were invasive ductal carcinoma (IDC). Negative predictive value for greater than or equal to 2 nodes was 71% in IDC versus 44% for in non-IDC patients. Sixteen (29.0%) IDC patients had greater than or equal to 3 positive nodes versus 10 (55.5%) non-IDC (P = .05) patients.

CONCLUSION: The high negative predictive value for AUS with FNA for IDC suggests that the AUS plus FNA interpretation may be better limited to the ipsilateral nodes of IDC.

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negative predictive value of axillary ultrasound are increased significantly, with specificity and positive predictive value up to 100%. The sensitivity of axillary ultrasound has been shown to increase with not only the size of the primary breast lesion, but also the size of the nodal metastasis and the number of lymph nodes involved. Axillary ultrasound coupled with fine-needle aspiration has a false-negative rate of 25% with reduced sensitivity for micrometastatic disease (axillary metastasis between .2 and 2 mm) resulting in a higher false-negative rate for that subgroup. This supports the idea that axillary ultrasound and a fine-needle aspiration generally identify gross nodal disease. If metastases are identified preoperatively, patients generally forego sentinel lymph node biopsy proceeding directly to axillary lymph node dissection.

Recently, the American College of Surgeons Oncology Group (ACoSOG) Z0011 results suggested that select node-positive patients on sentinel node biopsy could forego axillary node dissection. This trial did not specify the use of axillary ultrasound findings, allowing for a wide variation of its use in participating centers. Based on these data, incorporation of axillary ultrasound and percutaneous biopsy (via either fine-needle aspiration or core biopsy) remains an open issue in preoperative planning. A retrospective patient study by Ibrahim-Zada et al supports the use of preoperative axillary ultrasound in the Z0011 population for identification of macrometastatic lesions and eliminating the need for intraoperative sentinel lymph node testing. We hypothesize that in patients without palpable adenopathy, a negative axillary work up of axillary ultrasound (with or without fine-needle aspiration) is predictive of minimal axillary disease (≤2 positive nodes), even if patients are pathologically node positive at definitive surgery.

Methods

A single-institution, institutional review board approved, prospective database of patients receiving axillary ultrasound from 2004 to 2013 was reviewed for female breast cancer patients with clinical T1 or T2 tumors and node negative by physical examination. Node-negative patients on clinical examination were identified based on their documentation in the medical records. Patients who underwent preoperative chemotherapy, had recurrent breast cancer, had incomplete medical records, or had inconclusive fine-needle aspiration (2 cases) were excluded. Clinical breast tumor size was determined by both imaging and clinical examination with priority given to magnetic resonance imaging followed by ultrasound, mammography, and then physical examination.

All images and procedures were either completed or confirmed at a single tertiary comprehensive cancer center by breast fellowship-trained radiologists. Abnormal lymph nodes on axillary ultrasound were defined as having cortical thickening greater than 3 mm, rounded shape, or loss/replacement of the fatty hilum (Fig. 1). If an abnormal node was identified, ultrasound-targeted lymph node biopsy was performed, primarily by fine-needle aspiration. At our institution, the current practice is to obtain ipsilateral axillary ultrasound on all invasive breast cancers greater than 2 cm on clinical examination or radiographic imaging; for smaller lesions, axillary ultrasound is performed based on clinical suspicion.

Patients with a negative evaluation (± fine needle aspiration) but a subsequent positive sentinel node biopsy and completion axillary lymph node dissection were selected for further evaluation. Both breast conserving surgery and mastectomy patients were included. Clinical, radiologic, and pathologic data were collected, including axillary ultrasound and fine-needle aspiration results, tumor histology and grade, hormone receptor status, and total number of lymph nodes with metastasis. Minimal axillary disease was defined as less than or equal to 2 positive nodes after sentinel lymph node biopsy plus axillary lymph node dissection. Data were then analyzed by chi-square test using Fisher’s exact test. Fig. 2 illustrates the case distribution.

Results

The study population consisted of 384 women who fit the inclusion criteria; 24.5% (94/384) had breast conserving surgery, and 213/384 (55.5%) patients had a negative axillary ultrasound. The sensitivity and specificity for axillary ultrasound and fine-needle aspiration in this population was 55% and 93%, respectively. The negative predictive value was 78%, with a false-negative rate of 48% (Table 1).

From this population, 115 cases had negative preoperative axillary work up and a subsequent positive sentinel lymph node biopsy. Forty-two patients had a positive sentinel lymph node biopsy but declined completion axillary lymph node dissection. The remaining 73 patients went on to completion axillary lymph node dissection; this subset was selected for further analysis. The median age
was 57 years (range 34 to 80). Fifteen of the 73 (20.5%) patients received breast conserving surgery. The mean tumor size on final pathology for the group was 29.0 mm; 27.8 mm for patients with breast conserving surgery and 29.3 mm for mastectomy patients. The mean size of the largest nodal metastasis in the entire population was 8.5 mm. There was no difference in axillary ultrasound sensitivity between invasive ductal carcinoma and invasive nonductal carcinoma (invasive lobular/mammary carcinoma) for axillary disease ($P = .76$).

Stratified by histology, the negative predictive value of a negative axillary work up was 71% for minimal nodal disease in invasive ductal carcinoma compared with 44% for the invasive nonductal carcinoma group. The mean tumor size in the invasive ductal group was 28.7 mm versus 29.8 mm in the nonductal group. Nineteen of 55 (34.5%) patients with invasive ductal carcinoma had nonsentinel lymph node metastasis after axillary lymph node dissection compared with 10/18 (55.5%) nonductal carcinoma patients ($P = .17$). Only 16 patients (29.0%) of the ductal carcinoma group had greater than or equal to 3 positive lymph nodes (range 3 to 10) versus 10 (55.5%) in the nonductal group (range 3 to 17) ($P = .05$). Only 2 patients in the nonductal carcinoma group had breast conserving surgery with the mean tumor size of 18.5 mm; 16 patients had mastectomies with the mean tumor size of 31.3 mm. The mean size of the largest nodal metastasis was 8.3 mm for ductal carcinoma and 8.8 mm for nonductal carcinomas.

**Comments**

The treatment of axillary metastasis for breast cancer has been debated for many years. The National Surgical Adjuvant Breast Project B-04 trial evaluated over 1,700 patients randomized to radical mastectomy, total mastectomy with axillary radiation, or total mastectomy. Forty percent of radical mastectomy cases were node positive. Because of the randomization in the trial, there was an expected 40% axillary relapse rate in the other arms. Yet, only 18% of patients had an axillary failure with no difference in disease-free survival or overall survival, even after 25 years of follow-up. Because no adjuvant therapy was given beyond the radiation in one arm, the results of this landmark trial sparked the current controversy.

Axillary lymph node dissection remains the standard procedure for patients with axillary metastasis, although this is a shifting paradigm, given the ACoSOG Z0011 results. While awaiting the trial results of ACoSOG Z0011, many surgeons turned toward predictive nomograms, like the Memorial Sloan-Kettering nomogram, to estimate additional nodal disease after a positive sentinel lymph node biopsy.
Furthermore, the role of radiation in axillary management is in evolution. The After Mapping of the Axilla: Radiotherapy or Surgery trial compared axillary radiation with axillary lymph node dissection in node-positive patients with early breast cancer. The results suggested good local–regional control with few short- and long-term complications. Although not yet in print, this prospective trial may further strengthen the practice of routine preoperative axillary ultrasound.16 As yet not in print, this prospective trial may further strengthen the practice of routine preoperative axillary ultrasound.16 Although axillary dissection remains the standard for node-positive disease, sentinel lymph node biopsy has dramatically affected the clinically node-negative population. With the After Mapping of the Axilla: Radiotherapy or Surgery and Sentinel Node versus Observation Axillary Ultrasound trials evaluating radiation versus observation for the clinically negative axilla, ultrasound may ultimately supplant sentinel lymph node biopsy. In order for this to be achieved, the inherent predictive properties of axillary ultrasound must be high to accurately predict axillary nodal tumor burden. Our study suggests that histology may affect preoperative evaluation with axillary ultrasound and should be considered both in clinical decision making as well as in ongoing research.

### Table 1

| Histologic characteristics of final pathology after preoperative axillary evaluation |
|----------------------------------|-----------------|
| Number of cases | Percentage (%) |
| **Tumor size** | |
| T1 | 22 | 30.1 |
| T2 | 51 | 69.9 |
| **Histologic type** | |
| IDC | 55 | 75.3 |
| ILC | 16 | 21.9 |
| IMC | 2 | 2.7 |
| **Histologic grade** | |
| 1 | 9 | 12.3 |
| 2 | 36 | 49.3 |
| 3 | 28 | 38.4 |
| **ER status** | |
| Positive | 68 | 93.2 |
| Negative | 5 | 68.4 |
| **PR status** | |
| Positive | 60 | 82.8 |
| Negative | 13 | 17.8 |
| **Her2/neu status** | |
| Positive | 7 | 9.6 |
| Negative | 63 | 86.3 |
| Equivocal | 0 | 0 |
| Unknown | 1 | 1.4 |

**ER** = estrogen receptor; **IDC** = invasive ductal carcinoma; **ILC** = invasive lobular carcinoma; **IMC** = invasive mammary carcinoma; **PR** = progesterone receptor.

This study demonstrates that even after false-negative preoperative axillary ultrasound, the pathologic burden of axillary disease is low in invasive ductal carcinoma, with fewer than 2 total positive nodes in the majority of cases after completion axillary lymph node dissection. There was a notable trend to higher pathologic burden of axillary disease in nonductal carcinomas after a false-negative evaluation ($P = .05$). With a low nodal burden after false-negative preoperative evaluation in invasive ductal carcinoma, histology could be useful when determining whether pathologically node-positive patients can be managed without axillary node dissection.

At our institution, axillary ultrasound has been routinely used for T2 or larger tumors since 2007, whereas T1 tumors are evaluated on surgeon preference or clinical suspicion. This does introduce some selection bias, in addition to the retrospective nature of the data. On a more practical level, ultrasound is operator dependent, and results are highly variable among practitioners and institutions. These factors may have impacted the higher false-negative axillary ultrasound rate in this series. Also of note is the low rate of breast conservation at our institution; the national trend toward mastectomy in recent years is remarkable, and certainly reflected in this patient population.

### Conclusions

The management of the clinically node-negative axilla in breast cancer continues to evolve, as does the role of preoperative axillary ultrasound. Although axillary dissection remains the standard for node-positive disease, sentinel lymph node biopsy has dramatically affected the clinically node-negative population. With the After Mapping of the Axilla: Radiotherapy or Surgery and Sentinel Node versus Observation Axillary Ultrasound trials evaluating radiation versus observation for the clinically negative axilla, ultrasound may ultimately supplant sentinel lymph node biopsy. In order for this to be achieved, the inherent predictive properties of axillary ultrasound must be high to accurately predict axillary nodal tumor burden. Our study suggests that histology may affect preoperative evaluation with axillary ultrasound and should be considered both in clinical decision making as well as in ongoing research.

### References