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ORIGINAL ARTICLE – BREAST ONCOLOGY

Axillary Ultrasound: For All, for None, to Diagnose Positive Nodes, or to Support Avoiding Sentinel Lymph Node Biopsy Altogether

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ABSTRACT Axillary ultrasound is increasingly utilized for nodal staging preoperatively in patients presenting with invasive breast cancer to provide guidance for preoperative chemotherapy or proceeding directly to surgery. Improvements in ultrasound technology make it possible to assess the nodal burden in order to identify those patients not eligible for ACOSOG Z0011 management. However, its ability to detect metastasis is variable and dependent on operator's skills, size of metastatic deposit, and primary tumor histology subtype. Therefore, sentinel lymph node biopsy is still performed with a normal axillary ultrasound. Current debate questions whether there is a benefit to diagnosing metastasis with ultrasound-guided needle biopsy as this may lead to more axillary node dissections in an era of its decreasing role. In node-positive patients, axillary ultrasound has been preliminarily shown to be helpful in assessing nodal response after preoperative chemotherapy and improve the accuracy of sentinel node dissection which may spare future patients' axillary node dissection. Improvements in axillary ultrasound and other imaging modalities along with predictive models based on tumor biology may make axillary surgery a procedure of the past for many breast cancer patients.

Advancements in imaging now make it possible to stage invasive breast cancers quite accurately, challenging the concept of surgical intervention as the only method for diagnosing axillary node metastasis. Axillary node staging still has prognostic value and impacts the management of invasive breast cancer even with increasing use of prognostic models that assist with treatment recommendations. The importance of preoperatively detecting nodal metastasis has emerged as an active debate, especially in the context of a decreasing role for axillary node dissection.

Axillary node evaluation for early breast cancer has evolved from assessing for abnormal palpable adenopathy on physical examination, which has approximately 50 % accuracy. Mammography has lower accuracy in staging the axilla, especially for detecting micrometastasis; therefore, accurate axillary staging was initially dependent on axillary lymph node dissection (ALND). ALND is accurate but may miss small metastases given that nodes are not entirely sectioned and evaluated; however, ALND has significant complications, including wound infection, lymphedema (15–40 %), paresthesia, and decreased arm range of motion.[1,2] Therefore, sentinel lymph node dissection (SLND) was developed for axillary staging in early invasive breast cancer given its high accuracy[3] with comparable disease-free survival and regional control compared with ALND.[4] SLND has a lower complication rate compared with ALND (incidence of lymphedema of 5–7 %) and has replaced ALND as the standard of care for axillary staging in patients with early invasive breast cancer. As imaging techniques have improved, the goal has progressed to accurately stage the axilla prior to surgery.

Ultrasound is the most commonly used modality for axillary evaluation given its wide availability and safety. Advancements in ultrasound technology with high resolution transducers up to 12–15 MHz provide detailed depictions of nodal morphology, and also provide real-time ability to biopsy abnormal-appearing lymph nodes. Visualizing lymph node morphology changes from metastasis can be subtle and operator-dependent. Cortex thickening >3 mm, an eccentric cortex, reduction or loss of the central fatty hilum, and a round rather than elongated node

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shape are features associated with metastasis.[5] The ability to detect metastasis with axillary ultrasound (AUS) preoperatively enables the physician to counsel the patient to begin with preoperative chemotherapy or proceed directly to ALND and avoid SLND. The sensitivity of AUS ranges from 25 to 87 %, with a higher specificity of 77–100 %, and sensitivity and specificity increase with needle biopsy of abnormal-appearing nodes. Patients were spared SLND in 8–28 % of cases and hence proceeded with ALND.[6–9] In a meta-analysis of 31 studies including 4830 patients, Houssami et al. reported a sensitivity of 75 % and specificity of 98.5 % for ultrasound-guided axillary node biopsy, which resulted in approximately 20 % of patients avoiding SLND and proceeding to ALND.[10] In our series, axillary staging with AUS and fine-needle aspiration (FNA) of suspicious nodes had a sensitivity of 86.4 % and specificity of 100 %, while the negative predictive value was 67 %. Small metastases <0.5 mm had a 44 % probability of detection with FNA, while metastases >0.5 mm had a 93 % probability of detection.[11]

Clinicopathologic features associated with an increased ability to detect nodal metastasis include tumor size ≥2.1 cm, palpable adenopathy, ductal histology, high grade, and higher TNM stage.[12] This impacted patient management, with 62 % of those having FNA-detected metastasis receiving preoperative chemotherapy compared with 21 % of those with a negative FNA. AUS and FNA sensitivity for detecting nodal metastasis in invasive ductal cancers was higher than for invasive lobular cancers (98 vs. 53.6 %). The false negative rate (FNR) for invasive ductal cancer was 2 % compared with 46 % for invasive lobular cancer, for which Topps et al. recommended considering core needle biopsy of suspicious axillary nodes.[13] Limitations of AUS in detecting metastasis include lower sensitivity in invasive lobular cancers (sensitivity 39 %), receipt of preoperative chemotherapy, and operator dependency.[14]

The National Comprehensive Cancer Network (NCCN) guidelines for staging the axilla in invasive breast cancer recommend AUS if a patient presents with palpable lymphadenopathy. If suspicious-appearing nodes are evident on AUS, needle biopsy is recommended. Furthermore, ALND is recommended if the needle biopsy is positive for metastasis. In clinically node-negative patients, the NCCN recommends SLND.[15]

If AUS is negative then there is usually not a high burden of axillary metastasis; however, if AUS is falsely negative with metastasis detected on SLND, 5-year recurrence-free survival (RFS) is similar to patients with node-negative disease. In clinical T1 and T2 node-negative breast cancer, Tucker et al.[16] reported a non-significant slight decrease in 5-year RFS in sentinel lymph node biopsy (SLNB)-positive patients with low numbers and the curve starting to separate at 5 years. Patients with an abnormal AUS and pathologic positive disease had lower 5-year RFS compared with those who had an abnormal AUS but pathology was negative; however, this finding did not reach statistical significance. These initial findings suggest that AUS has the potential to become an alternative to SLND for axillary staging; however, larger patient numbers and longer follow-up are needed.

Two prospective, randomized trials are ongoing comparing AUS with SLND. The Sentinel node versus Observation after axillary UltraSouND (SOUND) trial is comparing the outcomes of AUS alone versus SLND in patients with T1 clinically node negative cancers,[17] and the ongoing trial being conducted by the Washington University School of Medicine includes patients with T1 and T2 disease.[18] In future, breast cancers will likely be treated based on predictive models incorporating genomics, and minimal axillary node metastasis may become less relevant.

AXILLARY ULTRASOUND (AUS)-DETECTED METASTASIS AND THE AMERICAN COLLEGE OF SURGEONS ONCOLOGY GROUP (ACOSOG) Z0011 TRIAL

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial has changed clinical practice in many patients with positive SLNs, sparing them ALND. Briefly, Z0011 randomized patients with clinical T1 or T2 node-negative disease who were undergoing breast-conserving therapy. Patients having a positive sentinel lymph node (SLN) were randomized to ALND or no further surgery. All patients received whole-breast irradiation, and systemic therapy decisions were at the treating oncologist's discretion. Ineligibility criteria included matted nodes, three or more positive SLNs, metastasis identified on immunohistochemistry only, and third-field nodal irradiation.[19] AUS was not part of the study.

Axillary burden in the majority of patients in the ALND cohort of the Z0011 trial had N1 disease (85.3 %) and most had one to two positive nodes (78.8 %).[20] After a median follow-up of over 6 years, no differences were observed in locoregional recurrences and 5-year overall survival in the ALND group compared with the SLND group.[19] Results of the Z0011 trial were quickly incorporated into surgeons' practices. In an academic setting, ALND decreased from 85 to 24 %, but clinicopathologic features still had a role in decision making.[21] A survey of members of the American Society of Breast Surgeons showed that 56 % of surgeons would not perform ALND in Z0011-eligible patients.[22]

DOES AUS CORRELATE WITH NODAL BURDEN TO IDENTIFY PATIENTS NOT ELIGIBLE FOR Z0011 MANAGEMENT?

An abnormal AUS and positive needle biopsy correlates with a higher nodal burden and with patients eligible for ALND. These patients more often have higher nodal burden on final pathology compared with patients with metastasis identified on SLNB. Farshid et al.[23] found that 89 % of patients with abnormal AUS and a positive FNA were ineligible for Z0011 management. With regard to negative AUS, 22 % of patients had nodal metastasis on SLNB, and 87 % had one to two positive nodes.

A suspicious AUS and positive needle biopsy correlates with higher nodal burden compared with a normal AUS or a suspicious AUS with a negative needle biopsy. Hieken et al.[24] found that patients with a normal AUS had pathologic metastatic disease in 22 % of cases compared with 31 and 100 % of cases with a suspicious AUS and negative needle biopsy, and those with a suspicious AUS and positive needle biopsy, respectively. Patients with a suspicious AUS and positive needle biopsy more often had more than two positive axillary nodes, larger nodal metastasis, and a higher presence of extranodal extension compared with those having a normal AUS and those with a suspicious AUS with a negative needle biopsy. Half of the suspicious AUS and positive needle biopsy patients had more than two metastatic nodes, which would make them ineligible for Z0011 management; however, AUS does not always detect high nodal burden. In the same study, 30 % of patients with more than two metastatic nodes had only one abnormal node identified on AUS. Approximately 30 % of patients received streamlined surgery by proceeding to axillary node dissection.

In patients with a negative AUS and FNA who underwent sentinel node biopsy, the nodal burden was lower, with a mean of 2.2 metastatic nodes,[25] which suggests that a negative AUS and FNA predicts a low axillary nodal burden and can help identify those patients who may be suitable for the Z0011 protocol.

Caudle et al.[26] found similar results. Patients having metastasis identified on SLND compared with AUS had a lower number of positive nodes (2.2 vs. 4.1), smaller metastasis (5.3 vs. 13.8 mm), and less extranodal extension (24 vs. 53 %). When AUS visualized two or fewer abnormal nodes, patients had three or more metastatic nodes (45 %) compared with metastasis identified on SLND (19 %). Therefore, many patients with AUS-detected metastasis more often have higher nodal burden compared with SLND-detected metastasis. These patients may not be comparable with those in the Z0011 trial.

DOES AUS OVERESTIMATE NODAL BURDEN, LEADING TO UNNECESSARY AXILLARY LYMPH NODE DISSECTION?

Pilewskie et al.[27] found that approximately 70 % of Z0011-eligible patients with abnormal axillary imaging would have unnecessarily received axillary node dissection. Between 2010 and 2013, a total of 425 clinically node-negative cases met the Z0011 criteria and had metastasis identified on SLND. Imaging mainly showed one or two abnormal nodes, and 71 patients had ALND. Study indications for ALND were more than two positive SLNs, and gross extracapsular extension/matted nodes. With negative and positive AUS and FNA, 14 and 45 % of patients required ALND, respectively. The authors suggested performing preoperative FNA if only more than three lymph nodes visualized on imaging or if there were matted nodes. The differences in this study may be due to interpreting ultrasound images performed at various institutions, other than the treating institution, for the majority of patients.

In general, most studies show that AUS is able to identify those patients with high metastatic nodal burden, which would make them ineligible for Z0011 management; however, limitations still exist in detecting nodal burden in all patients as some are missed or even overestimated. Further research with regard to omitting ALND in AUS-guided node-positive breast cancer is needed. Working towards this, AUS reports should include the number of abnormal-appearing nodes visualized, documentation of lymph node images, and clip placement into needle biopsy-positive axillary nodes. In future, contrast-enhanced ultrasound with intradermal injection of microbubble agents into the breast to identify the SNL for needle biopsy may prove useful for assessing SLNs non-operatively.[28]

AUS CAN IMPROVE ACCURACY OF SENTINEL LYMPH NODE DISSECTION AFTER PREOPERATIVE CHEMOTHERAPY IN NODE-POSITIVE BREAST CANCER

Preoperative chemotherapy converts node-positive disease to a pathologic complete response (pCR) in 40–60 % of cases, making the role of ALND controversial in patients presenting with FNA-proven metastasis. ACOSOG Z1071 determined the FNR of SLND in patients presenting with clinical T0–T4, N1–2, M0 breast cancer who received preoperative chemotherapy. Overall, the FNR of SLND was 12.6 %; however, the use of dual-tracer mapping decreased the FNR to 10.8 % and evaluating three or more SLNs (9 %).[29] AUS correlated with residual nodal disease after receipt of preoperative chemotherapy. In 430 patients having a normal AUS after preoperative chemotherapy,

over half had nodal metastasis on ALND. Seventy-two percent of patients with suspicious AUS had residual nodal metastasis, with an increased number of positive SLNs, larger SLN metastasis, and increased number of additional positive non-SLNs, and were more likely to have residual disease in the breast.[30]

Excising the clipped metastatic node during SLND (termed 'targeted axillary dissection') further improves the FNR of SLND. In 85 patients, Caudle et al.[31] performed radioactive $I^{5,12}$ seed localized excision of the clipped metastatic node in addition to the SLND, resulting in an FNR of 2.0 % with TAD followed by ALND. Interestingly, the clipped node was not the SLN in 24 % of cases, highlighting the importance of evaluating both.

WHICH BREAST CANCER PATIENTS BENEFIT FROM AUS?

Axillary staging with ultrasound can identify those with a high nodal burden who can forgo SLNB and have an ALND. AUS also influences decisions regarding neoadjuvant chemotherapy. According to NCCN guidelines, patients with palpable lymphadenopathy should receive an AUS. In patients undergoing preoperative chemotherapy for locally advanced disease or node-positive disease, AUS is useful in monitoring tumor response.

Patients presenting with clinical T1–2, N0 disease can benefit from AUS in order to identify those not eligible for Z0011 criteria or to recommend preoperative chemotherapy. Furthermore, incorporating additional clinicopathologic features may be helpful in identifying which of these patients benefit the most from AUS.

No data are available to support routine AUS in patients presenting with ductal carcinoma in situ (DCIS).[32] In 82 patients with DCIS diagnosed on core biopsy, Ansari et al.[32] found that 16 % had an abnormal AUS and FNA was negative in all cases. Of 74 % of patients undergoing SLND, two had macrometastasis (3 %) and one had isolated tumor cells. None of the patients with metastasis had an abnormal AUS.

Overall, 170 patients enrolled in Z1071, with clinically N1 disease and at least two excised SLNs, had a clip placed into the metastatic node at the time of ultrasound-guided needle biopsy. Removing the clipped node with the SLN resulted in an FNR of 6.8 % compared with 19 % when the clipped node was in the ALND specimen.[33]

CONCLUSIONS

AUS correlates with nodal burden but can miss some metastasis. AUS with needle biopsy has improved sensitivity and specificity, and identifying patients with nodal metastasis can improve patient counseling for preoperative systemic therapy, or identify those who should be considered for ALND. The role of AUS in node-positive patients receiving preoperative chemotherapy is important in

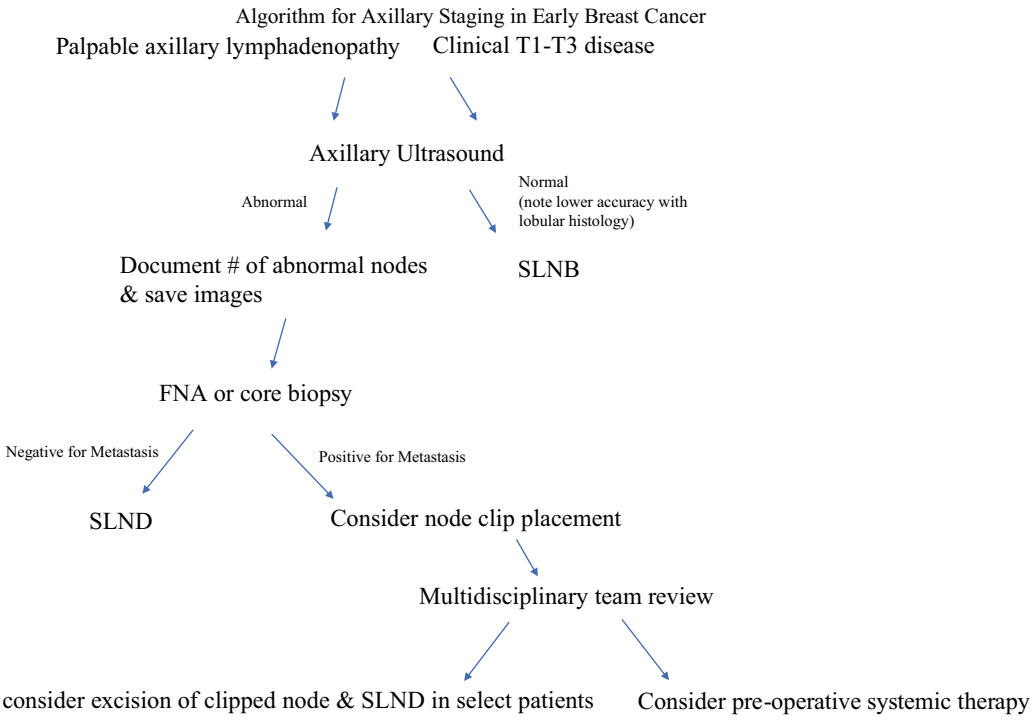

FIG. 1 Algorithm for axillary staging in early breast cancer

identifying future patients who may be able to be spared ALND with a negative SLND (Fig. 1). New technologies to improve the accuracy of preoperative axillary staging in patients with invasive breast cancer, along with prognostic models for treatment recommendations, may make SLND a procedure of the past.

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