The Promise of Axillary Imaging in Individualized Surgical Management of Breast Cancer Patients: Another Step Forward

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Breast surgical oncologists are to be commended for moving forward rapidly to embrace selective and individualized therapy for their patients. Eleven years after publication of the first report and 3 years after reporting results from the largest randomized controlled clinical trial of sentinel lymph node resection (SLNR) versus axillary lymph node dissection (ALND) for clinically node-negative breast cancer patients, SLNR is widely accepted as standard in this setting and endorsed by national and international guidelines.^{1–4} Moving forward, there is considerable interest in further refining and individualizing management of the axilla for newly diagnosed breast cancer patients, especially for those patients with node-positive disease. We have become champions of further minimizing patient morbidity. Enhanced axillary imaging as an approach toward more accurate preoperative nodal staging is an area of active investigation. At one end of the spectrum, there are patients without nodal disease who might be spared axillary surgery altogether, and at the other, there is growing interest in distinguishing node-positive patients who might be managed appropriately with SLNR alone from those who will benefit from ALND, with or without adjuvant radiation.

In this issue of *Annals of Surgical Oncology*, Caudle and coauthors address the use of preoperative axillary ultrasound (AUS) for nodal staging of breast cancer patients in the era of American College of Surgeons Oncology Group (ACOSOG) Z0011 and International Breast Cancer Study Group (IBCSG) 23-01 trials. These well-publicized studies and others suggest the noninferiority of SLNR alone to

ALND for many early stage breast cancer patients with one or two metastatic sentinel nodes undergoing (for the most part) breast-conserving surgery, planned whole-breast radiation, and adjuvant systemic therapy.^{5–7} Publication of these reports has caused many to question the value of preoperative AUS. Some centers have abandoned preoperative AUS for early stage breast cancer in tandem with adoption of Z0011. However, as demonstrated by the data presented by Caudle et al., this may not be the most appropriate reaction. Caudle and coauthors challenge us to move forward yet again from a one-size-fits-all approach and thoughtfully examine how we best might use enhanced imaging technology to further stratify patients and improve oncologic outcome for our breast cancer patients.

The authors report on a group of 708 node-positive T1 and T2 invasive breast cancer patients evaluated between 2002 and 2012 who were operated on directly after diagnosis and did not undergo neoadjuvant chemotherapy.⁸ Patients were stratified by whether their node-positive disease was identified by preoperative AUS and fine needle aspiration (FNA) (190 patients) or at the time of SLNR (518 patients). They found that patients with a suspicious axillary lymph node who were documented node-positive by a preoperative ultrasound-guided FNA were substantially more likely than those with a negative AUS or suspicious AUS but negative FNA to have 3 or more metastatic axillary nodes, larger nodal metastases, and extranodal extension of disease. They also identified significant axillary disease burden in patients who had 1 or 2 sonographically suspicious axillary nodes and a positive preoperative lymph node FNA (45 % with ≥ 3 positive nodes). The authors additionally noted that infiltrating lobular histology, but no other clinicopathologic feature, was associated with ≥ 3 positive nodes at operation. Further, a finding of ≥ 3 sonographically suspicious nodes among the FNA-positive patient group was associated with pathologic stage N2 or higher disease in 60 %. They

concluded that AUS and FNA predicted nodal disease burden and suggest caution in omission of ALND for these patients who may well be outside Z0011 guidelines.

Our experience with AUS and FNA has been similar. Among a similar cohort of invasive breast cancer patients not treated with neoadjuvant chemotherapy, 29 % had a preoperative AUS with suspicious findings. Axillary lymph node FNA and the AUS finding of solitary versus multiple abnormal nodes allowed us to identify a small group (<10 %) of T1 and T2 patients with a high likelihood of ≥ 3 metastatic nodes, extranodal extension, and/or pathologic N2 or N3 disease who fell outside the population enrolled in Z0011.⁹ In our study, 22 % of patients with a negative AUS were SLN positive at operation, but only 4 % had 3 or more positive nodes at operation. These data may prove helpful in further refining indications for ALND in the presence of a positive sentinel node. Namely, AUS-negative patients who are SLN positive at operation are likely to have low-volume metastatic disease and mirror those patients eligible for Z0011 and IBCSG 23-01. On the other hand, FNA-positive patients after a suspicious AUS, especially with >1 sonographically suspicious node, are highly likely to have ≥ 3 positive nodes, fall outside these guidelines, and merit ALND.

These messages are echoed by others. A plenary session at the European Breast Cancer Conference 9 in March 2014 entitled "Management of the Axilla: Ensuring Best Practices Today" focused on the clinical value of AUS. Verheuve and colleagues from the Netherlands presented their data on 307 node-positive breast cancer patients, of whom 143 were diagnosed by preoperative AUS and 164 after SLNR. Their findings mirror those of our group and Caudle et al. in that patients diagnosed by AUS and FNA had more extensive nodal disease as determined by number of involved nodes, metastasis size, and extranodal extension than patients diagnosed as node positive after SLNR. The authors and ensuing discussants suggested redefinition of the role of AUS to select patients with a high axillary disease burden who are likely to benefit from multimodality therapy including ALND.¹⁰ Reports of smaller series also corroborate the value of AUS and FNA for identification of patients likely to have a high axillary disease burden at operation.^{11,12}

Many forward-thinking surgical oncologists are now evaluating how to stratify patients into three groups: (1) those for whom axillary surgery might be avoided altogether, (2) those for whom SLNR alone might be important to for nodal staging and suffice for those with (limited) node-positive disease, and (3) those who will derive the greatest potential benefit from ALND directly or after a positive SLNR within the context of multimodality therapy. AUS with FNA has been shown to be a cost-effective method for preoperative nodal staging predicated on triage

to ALND.^{13,14} It may actually prove to be even more cost-effective than previously reported if we can safely and thoughtfully expand its use in the future.

Much discussion on limiting axillary surgery for node-positive disease has focused on axillary recurrence rates, which are very low among the recent trials of ALND versus SLNR (mainly with whole-breast radiation), i.e., 0.5 versus 0.9 % in ACOSOG Z0011, 0.2 versus 1.1 % in IBCSG 23-01, and 0 versus 9 % in INT09/98.^{5,7,15} However, the real question is the effect of leaving clinical or subclinical disease in the axillary nodes that may become the source of distant (and lethal) failure in the future. In the INT09/98 trial, the one with the longest reported follow-up (median 128 months), one-third of SLN-positive patients treated without ALND developed distant metastatic disease despite receipt of adjuvant chemotherapy among patients with biologically less favorable T1 tumors. Whether the findings regarding low-volume axillary disease in patients with biologically favorable tumors might be extrapolated to other patient scenarios and confirmed with long-term follow-up remain to be elucidated.

From a practical standpoint, where do we need to look next? Unfortunately, the authors of the current study did not provide us with their criteria for defining suspicious axillary nodes nor their threshold for biopsy. There has been wide variability in the criteria used to define sonographically suspicious nodes and to perform percutaneous lymph node biopsy.^{16,17} Such variations affect the sensitivity and specificity of the test. Ideally, the totality of the axilla is scanned and commented on so that distinctions are made between a solitary sonographically abnormal lymph node and multiple or an enumerated number of abnormal nodes, but this is not yet routine. Greater standardization of both the conduct and reporting of AUS is desirable.

Further investigation regarding the interplay between locoregional therapy and breast tumor biology in the modern era of targeted systemic therapies is needed so that we may identify those patients for whom less extensive surgery will not compromise long-term oncologic outcome. In the meantime, on the basis of current evidence regarding low-volume axillary disease and short-term outcome, utilization of ultrasound findings to help us gauge the volume of axillary disease in order to best counsel our patients is another step forward toward individualized patient care.

CONFLICT OF INTEREST The author declares no conflict of interest.

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