

Viewpoints and debate

Axillary management in breast cancer: What's new for 2012?

Hiram S. Cody III^{a,**}, Nehmat Houssami^{b,*}^a *The Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, The Weill Medical College of Cornell University, USA*^b *Screening & Test Evaluation Program, School of Public Health, Sydney Medical School, University of Sydney, Edward Ford Building (A27), Sydney, Australia*

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ABSTRACT

Sentinel lymph node (SLN) biopsy has become standard care for management of the axilla in invasive breast cancer, replacing axillary lymph node dissection (ALND) in most subjects, with a progressively diminishing role of ALND. Advances in preoperative imaging have also changed the algorithm for axillary management, and ultrasound-guided needle biopsy has been shown to triage >50% of subjects with node metastases to ALND. However, the past two years have witnessed remarkable and practice-changing advances in our knowledge and approach to management of the axilla, with availability of high-level evidence that demands reappraisal of practice and challenges the role of routine ALND for SLN-positive patients. In particular, for the group of patients defined by eligibility criteria in the Z0011 trial, it appears that ALND has little or no effect on local recurrence and survival, or on the choice of local or systemic therapies. We review the available evidence on staging and management of the axilla in breast cancer, and outline our interpretation of its implications for clinical practice.

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Introduction

For all cancers, the importance of the regional lymph nodes is threefold: staging, local control, and the possibility of a survival benefit. From the era of Halsted (1894)¹ until quite recently, these goals have been addressed in breast cancer by axillary lymph node dissection (ALND). Since the pioneering reports of Morton (1991),² Krag (1993)³ and Giuliano (1994),⁴ sentinel lymph node (SLN) biopsy has now become standard care at many institutions worldwide, and the role of ALND is diminishing. Advances in preoperative imaging and in image-guided needle biopsy have further changed the algorithm for axillary management, allowing some patients to avoid ALND, or SLN biopsy. The last two years in particular have witnessed remarkable and practice-changing advances in our approach to the axilla. What have we achieved? In this paper, we discuss current evidence relevant to management of the axilla in breast cancer, and outline our interpretation of its implications for clinical practice.

Preoperative assessment

Given that knowledge of the status of axillary nodes prior to surgical intervention can assist surgical planning and may support

informed discussion of management options, preoperative testing that reliably identifies metastases to the axillary nodes has a role in streamlining axillary staging.^{5,6} Preoperative evaluation of the axilla in invasive breast cancer has been applied as a triage to axillary surgical management, and in assessment of axillary nodal status in the neoadjuvant setting, using a strategy of imaging with imaging-directed needle biopsy. In this context, imaging-directed assessment of axillary nodes must have adequate sensitivity but more importantly it requires high specificity – this is because a false-positive result may cause unnecessary surgical intervention to the axilla, whereas a false-negative test means a woman proceeds to standard staging^{5,6} usually with initial SLN biopsy. Therefore, it is important to have information on the accuracy and also on the *utility* of preoperative axillary assessment as a practical measure of whether a test is effective in correctly triaging subjects to axillary management. Furthermore, the current value of preoperative imaging and image-directed biopsy of the axilla is likely to change in light of evolution of the surgical management of the axilla in breast cancer: if future changes in management of the axilla entail increasingly less surgical intervention, then preoperative assessment needs to be highly sensitive to minimize the risk of false-negative axillary staging.

Imaging

Ultrasound (US), magnetic resonance imaging (MRI), positron emission tomography (PET), and PET integrated with computed tomography (PET/CT), have been evaluated for preoperative staging

* Corresponding author. Tel.: +61 2 0419 273510; fax: +61 2 9351 5047.

** Corresponding author.

E-mail addresses: codyh@MSKCC.org (H.S. Cody), nehmath@med.usud.edu.au (N. Houssami).

of the axilla in invasive breast cancer. Of these imaging technologies, there is sufficient evidence (based on a large number of observational studies) allowing meta-analysis of test accuracy for US⁵ and for PET.⁷ While there is much interest in (and debate relating to) the application of preoperative MRI for staging newly diagnosed breast cancer,^{8,9} published evidence on its accuracy for detection of axillary node metastases is relatively limited. Although MRI is capable of detecting pathological nodes, there are no standardized criteria for MRI parameters that define metastatic axillary nodes in breast cancer. The presence of axillary nodes without a fatty hilum on MRI has been shown to correlate with axillary nodal positivity¹⁰ however enhancement kinetics features do not appear useful in identifying metastatic nodes.

Ultrasound (US) and US-guided needle biopsy

A recent overview from Houssami et al.,⁵ that included US data for 4313 subjects from 21 studies, reported a median *ultrasound* sensitivity of 61.4% (interquartile range (IQR) 51.2%–79.4%), and a median specificity of 82.0% (IQR 77.0%–89.0%). Corresponding accuracy for US-guided (fine or core) needle biopsy in the 1733 subjects selected to needle biopsy using ultrasound criteria (in these 21 studies) were a median US-guided needle biopsy sensitivity of 79.4% (IQR 68.3%–8.9%) and a median specificity of 100% (IQR 100%–100%). Importantly, positive predictive value for US-guided needle biopsy of the axilla was shown to be high across all studies (median 100%).⁵ This consistently high specificity and positive predictive value for US with US-guided needle biopsy, and the relative efficiency, lower cost, and availability of US in standard breast assessment, makes it a suitable preoperative axillary staging approach.

Using a larger data-set (31 studies, 6166 subjects) for US-guided needle biopsy in 2874 subjects al,⁵ the same meta-analysis reported on the *utility* of preoperative US-guided needle biopsy of axillary nodes: the median proportion of subjects who could be triaged directly to axillary dissection based on a positive test result was 19.8% (IQR 11.6%–28.1%); and the proportion of subjects with *metastatic axillary nodes* potentially triaged to axillary surgery through systematic use of US-guided biopsy was a median 55.2% (IQR 41.8%–68.2%). The odds ratio for the proportion of subjects with *metastatic axillary nodes* triaged in studies with a median tumor size ≥ 21 mm relative to < 21 mm was 2.57 (95%CI 1.29, 5.09); $P = 0.009$. As shown in Fig. 1, meta-analysis also provided evidence of a positive correlation between US-guided needle biopsy *utility* and the underlying prevalence of axillary node metastases across 31 studies (correlation co-efficient 0.751). Hence, preoperative US-guided needle biopsy will have better clinical *utility* when used in cases with higher underlying risk of having node metastases.

Positron emission tomography (PET)

Although PET, or integrated PET and computed tomography (PET/CT) which allows concurrent visualization of tissue anatomy and metabolic activity, have been shown to be sensitive in staging for *distal* metastases in newly diagnosed breast cancer,¹¹ inconsistent results have been reported for the accuracy of PET (or PET/CT) in axillary staging.^{12–14} A comprehensive systematic review and meta-analysis from Cooper et al.⁷ estimated that PET (with/out CT), across 26 studies (2591 subjects), had a mean sensitivity of 63% (95%CI 52–74%) and a mean specificity of 94% (95%CI 91–96%). Of note, there was wide variability in study-specific sensitivity (20%–100%), and specificity (75%–100%). The evidence review from Cooper et al.⁷ did *not* recommend PET for axillary staging of women with clinically node-negative axillae, and at present there is little evidence on the *utility* of PET or PET/CT for routine staging of the axilla in breast cancer.

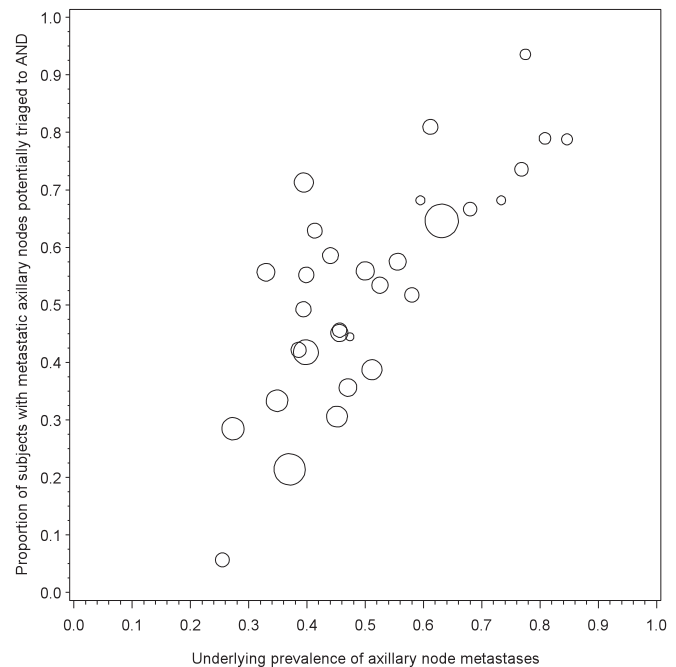


Fig. 1. Utility of ultrasound-guided needle biopsy of axillary nodes in breast cancer: Correlation between the proportion of subjects with *metastatic axillary nodes* potentially triaged to axillary node dissection (AND) and the underlying prevalence of node metastases (adapted from Houssami et al.⁵). Bubbles show study-specific proportion of women with *metastatic axillary nodes* potentially triaged directly to AND [median proportion 55.2% (IQR 41.8%–68.2%)] if ultrasound-guided needle biopsy is used preoperatively, estimated in 31 studies, relative to underlying prevalence of node metastases. Size of bubble reflects the *weight* of study-specific estimates, with larger bubbles reflecting larger studies (more precise estimates), and smaller bubbles representing smaller studies (less precise estimates).

Surgical assessment

The justification for surgical axillary staging in breast cancer is that axillary nodes remain one of the most important prognostic factors, and there is no combination of clinico-pathologic features which allows $>90\%$ accuracy in the prediction of axillary node status. For patients with clinically node-negative breast cancer, SLN biopsy has largely replaced ALND and in the process has taught us valuable lessons.

First, the SLN hypothesis is valid. Two elegant studies have shown that the SLN is the node likeliest to be positive¹⁵ and that a negative SLN reliably predicts a negative axilla.¹⁶ Second, SLN biopsy works. An overview¹⁷ of 69 published studies of SLN biopsy validated by a backup ALND confirms an overall success rate of 96%, with a 7% false-negative rate (the proportion of node-positive patients with negative SLN biopsy), results which have been confirmed in five randomized trials.^{18–22} Few false-negative SLN procedures result in axillary local recurrence, an event which occurs in about 0.4% of SLN-negative patients^{23,24} at a median 8-year follow-up. Third, many of the earliest (and relatively easiest) questions relating to SLN biopsy have been asked and answered. These involve the *definition* of a SLN (blue, “hot” or palpably suspicious),²⁵ *case selection* for SLN biopsy (selected cases of DCIS and virtually all operable cN0 invasive breast cancers), *technique* (dye plus isotope appears best),²⁶ *learning curve* (probably short²⁷), and *morbidity* (less than ALND but not zero).²⁰

Fourth, several areas of surgical controversy remain, including the significance of non-axillary (especially internal mammary) SLN and the timing of SLN biopsy relative to neoadjuvant chemotherapy. In 6 systematic studies,^{28–33} internal mammary SLN were imaged in about 20% of patients but were the sole site of nodal

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