Abstract. Sentinel node biopsy (SNB) has largely replaced axillary lymph node dissection (ALND) as the standard-of-care for nodal staging in invasive breast cancer. Preoperative imaging-based staging of the axilla using ultrasound with selective ultrasound-guided needle biopsy (UNB) is moderately-sensitive and identifies approximately 50% of patients (pooled estimate from meta-analysis 50%; 95% confidence interval=43%-57%) with axillary nodal metastases prior to surgical intervention. It is also a highly specific staging strategy that allows patients to be triaged to ALND based on a positive result (positive predictive value approximates 100%), thus avoiding two-stage axillary surgery and unnecessary SNB. Axillary UNB has a good clinical utility: based on an updated meta-analysis, we found that a median proportion of 18.4% (inter-quartile range=13.3%-27.4%) from 7,097 patients can be effectively triaged to axillary treatment and can avoid SNB. However, the changing algorithm of axillary surgical treatment means that UNB will have relatively less utility where surgeons omit ALND for minimal nodal metastatic disease. Research that allows enhanced application of ultrasound and UNB to specifically identify and biopsy sentinel nodes and to discriminate between patients with minimal versus advanced nodal metastatic involvement is likely to have the most impact on future management of the axilla in breast cancer. In the context of continuing evolution of surgical treatment of the axilla, the status of the axillary nodes remains an important prognostic factor in patients with newly-diagnosed breast cancer, and of relevance to decision making on adjuvant systemic therapy. In the past, axillary lymph node dissection (ALND) was the standard-of-care for staging and treating the axilla in invasive breast cancer, however sentinel node biopsy (SNB) has replaced ALND as the primary approach. Emerging evidence on the omission of ALND in selected groups of patients with minimal sentinel node disease has added new debate and opportunities for staging the axilla, including preoperative methods. Given that surgical management of the axilla has changed considerably, so has the role of preoperative staging, in particular the inclusion of axillary ultrasound with ultrasound-guided needle biopsy (UNB). In the present work, we review the clinical utility of axillary ultrasound with UNB as an integrated staging strategy, factoring evidence on its accuracy and utility, as well as evidence on management of the axilla in invasive breast cancer, with emphasis on the role of preoperative testing and consequences in clinical decision-making.

Evolution of Surgical Staging of the Axilla

SNB has largely replaced ALND as standard care for nodal staging in breast cancer and is supported by the results of multiple observational studies (1), seven randomized trials(2), meta-analyses (2-4), and extensive literature covering all aspects of the procedure. These collectively establish that patients with negative SNB do not require ALND, that axillary local recurrence after a negative SNB biopsy is rare (0.3%) (5), that disease-free and overall
survival are unaffected by the addition of ALND to SNB, and that the morbidity of SNB biopsy is less than that of ALND.

It is now also clear that selected SNB-positive patients can avoid ALND. In a retrospective study of practice patterns in the USA, drawing on the National Cancer Data Base, Bilimoria et al. (6) reported on 97,314 SNB-positive patients: 23% with SNB macrometastases (>2 mm, pN1) and 36% with SNB micrometastases (0.2-2 mm, pN1mi) did not have ALND, yet for both pN1 and pN1mi sentinel node disease, axillary local recurrence and 5-year relative survival were the same with and without ALND. A similar study from Yi et al. (7) investigated 26,986 SNB-positive patients and found that 11% of those with sentinel node macrometastases and 33% of those with micrometastases did not have ALND, and that this did not affect overall survival at a median follow-up of 50 months (7). Nine smaller retrospective studies (8) comprising of 1,035 patients with positive SNB and no ALND reported low rates of axillary recurrence, most in the range of 0-2%, at 28-82 months’ follow-up (8).

The highest level of evidence comes from the Z0011 trial (9, 10), a prospective randomized trial in which 813 SNB-positive patients with clinical stage T1-2N0 breast cancer were randomized to ALND versus no further surgery. All were SNB-positive and all had breast conservation including whole-breast radiation. Patients with three or more positive sentinel nodes (or with matted nodes) were excluded and axillary-specific radiotherapy was not allowed. Additional positive nodes were found in 27% of the patients who had ALND, but at six years’ follow-up there were no differences between the ALND and no-ALND arms in local (3.6% vs. 1.9%), regional (0.5% vs. 0.9%), or overall locoregional recurrence (4.1% vs. 2.8%) (9), nor were there any differences in disease-free or overall survival (10). Over the past two years many Institutions and surgeons in the USA (and seemingly to a lesser extent in Europe and worldwide) have found Z0011 findings to be persuasive and practice-changing, however, there is still ongoing discussion regarding this issue and hence differences exist in surgical practice on this setting.

Debate still surrounds the management of SNB-positive patients outside the Z0011 selection criteria (for example, those treated by mastectomy without radiation therapy), and following neoadjuvant chemotherapy. New information from two prospective studies of SNB and neoadjuvant chemotherapy in patients with biopsy-proven nodal metastases, suggests that the success of SNB after neoadjuvant therapy is somewhat lower, and the false-negative rate somewhat higher, than when SNB biopsy is performed up-front (11;12).

Preoperative Staging: Test Accuracy and Clinical Utility Concepts

The accuracy of a test defines its ability to rule-in or-out a condition or disease, whereas the clinical utility of a test relates to the capacity to use the information provided by the test to enable a decision to adopt, or to reject, a therapeutic action or intervention. The clinical utility of a test expresses or quantifies to what extent testing improves health outcomes or clinical decision making (13). Bossuyt et al. (13) report that key features of clinical utility are: use of the test which improves health outcomes (including outcomes that matter to the patient, for example reducing morbidity), and that the test forms part of a strategy whereby health outcomes are generated 'not only by using the test but also by a management strategy that starts with testing but includes all downstream consequences of subsequent clinical management (13). Because knowledge of the status of axillary nodes prior to surgical intervention can assist treatment planning, preoperative testing using imaging with imaging-directed needle biopsy to detect and confirm nodal metastases can triage surgical management of the axilla, allowing for a single operation (Figure 1). In the clinical scenario of preoperative axillary staging, measures of accuracy and, more importantly, measures of clinical utility should be considered. Although the ideal testing strategy should have good sensitivity (true-positive detection of nodal metastases), a very high specificity (true-negative result in those not harboring nodal metastases) is essential. This is because a false-positive test will likely lead to over-treatment of the axilla with unnecessary ALND (and associated morbidity), whereas a false-negative result, due to imperfect test sensitivity, means that the patient would be managed with initial SNB (Figure 1). Measures of a test’s clinical utility, within an overall management strategy, should be quantifiable, and if favourable, would provide a basis to recommend the testing strategy.

Preoperative Imaging of the Axilla

Various imaging modalities can provide information on axillary nodes preoperatively to assist planning of further staging and treatment. Although mammography is the primary test for imaging the breast and can also demonstrate enlarged nodes, it does not completely visualize the axilla, and is neither an accurate nor efficient test for imaging the axilla. Ultrasound, magnetic resonance imaging (MRI), and positron-emission tomography (PET) or PET integrated with computed tomography (PET/CT), have the capability of detecting abnormal axillary nodes. These imaging tests have been evaluated for preoperative staging of the axilla in women with invasive breast cancer however accuracy and clinical utility data for MRI in this setting are relatively sparse (14, 15). PET, also referred to as fluorodeoxyglucose (FDG)-PET, and hybrid PET and PET/CT, have been shown to be sensitive for staging distant metastases (including distant
nodal metastases) in newly-diagnosed breast cancer (16). However, widely variable accuracy data have been reported for PET in axillary staging (17-20), and evidence reviews have not recommended PET-based staging of the axilla in breast cancer (20, 21). Cooper et al. (20) estimated in a meta-analysis (2,591 subjects) that PET or PET/CT had a mean sensitivity of 63% (range=20-100%) and a mean specificity of 94% (range=75-100%), highlighting substantial variability in the reported accuracy of PET or PET/CT.

There are no quantified clinical utility data supporting the use of PET or MRI as alternate or comparable preoperative axillary staging tests to ultrasound with UNB, which may be (at least in part) due to these imaging modalities being more expensive and less widely-available than ultrasound-guided staging of the axilla. In addition, it is noteworthy based on the above-reported data from Cooper et al. (20) that while sensitivity of PET (or PET/CT) for detecting node metastases on average approximates that of ultrasound alone (22), PET
and PET/CT involve exposure to low-level ionizing radiation and are substantially more costly than ultrasound.

**Ultrasound and UNB for Preoperative Axillary Staging**

Integration of ultrasound with UNB for assessment of the axilla in women with newly-diagnosed breast cancer has been evaluated for many years (22-24) and has also been included in guidelines in recent years (25). The application of preoperative ultrasound and UNB to assess axillary node status has been partly due to the accumulation of evidence on this approach (22), and partly due to the efficiency, feasibility, and relative simplicity and modest cost of this staging strategy. Extension of ultrasound scanning of the breast to include the axilla in cases with suspected breast cancer is relatively quick, and UNB skills are easily developed building on experience (and established technical logistics) of ultrasound-guided biopsy in breast diagnosis in general. To elucidate the utility of this preoperative staging approach, we address key questions on axillary ultrasound and UNB based on scientific evidence, and we review information on both test accuracy as well as clinical utility (using a literature search performed in September 2013).

**Is axillary ultrasound accurate?** A meta-analysis (22) of data (4,313 subjects) from 21 studies (24, 26-45) reported that the median ultrasound sensitivity was 61.4% [with an interquartile range (IQR) of 51.2% to 79.4%]; the associated median ultrasound specificity was 82.0% (IQR 76.9%-89.0%). In these studies, for the subset of 1,733 subjects who were then selected for UNB based on ultrasound features, the median UNB sensitivity was 79.4% (IQR 68.3%-89.0%) and the median UNB specificity was 100% (IQR=100%-100%). Hence the addition of UNB (as directed by axillary ultrasound findings) improves the sensitivity of this preoperative staging strategy and substantially improves its specificity (the latter approximating 100%). Various morphological features and node size were applied in the primary studies included in meta-analysis as criteria to identify nodes warranting UNB (22) including, but not limited to, enlarged nodes, rounded nodes (ratio of the longitudinal and transverse dimensions), cortical thickening and/or asymmetry or lobulation, and absence of a fatty hilum. Ultrasound features consistently reported to be predictive of node metastases were cortical thickening (2-3 mm applied to define thickening) (29, 30, 34, 46) and absence of a fatty hilum (30, 33, 41). One of the studies considered in the meta-analysis, by Britton et al. (33), provided relevant information on ultrasound features of axillary nodes through multivariate analysis: the absence versus presence of a hilum, a multi-lobulated versus smooth cortex, and increasing node size were found to be independent predictors of axillary node metastasis. Garcia-Ortega et al. (47) similarly found that the morphological features most predictive of axillary node metastases were absence of a central fatty hilum, and multi-lobulated cortical thickening (47).

The above data clearly show that ultrasound alone has modest accuracy, and on its own, does not provide sufficient accuracy to decide on surgical treatment of the axilla – in particular it is not sufficiently specific to triage patients directly to axillary surgery (ALND). However, using ultrasound to identify patients with abnormal or suspicious axillary nodes, then proceeding to UNB in those cases, leads to both good sensitivity and near-perfect specificity from UNB. Furthermore, the sensitivity of ultrasound-alone (or even for the subset of patients selected to UNB based on ultrasound) appears to be modest and cannot be reliably used to re-assure patients regarding the absence of axillary nodal metastases.

**How often is axillary ultrasound with UNB falsely negative?**

Given that in the absence of preoperative axillary ultrasound and UNB, most patients with invasive breast cancer would undergo SNB to stage the axilla, then a false-negative outcome from a preoperative strategy using ultrasound (with/without UNB based on ultrasound findings) can be measured relative to SNB. This issue has been addressed through a systematic review by Diepstraten and colleagues (48) which included a meta-analysis to estimate the proportion of women with a negative ultrasound with/without UNB that is still proven to have axillary nodal metastases at SNB: the authors referred to this proportion as the false-negative rate. Pooled data from 31 studies (48) that reported on preoperative assessment of the axilla by ultrasound with/without UNB estimated that the false-negative rate was 25% (95% CI=24%-27%), as shown in Figure 2.

There was substantial heterogeneity across studies included in the meta-analysis by Diepstraten et al. (48), therefore meta-regression was performed to assess whether this variance between studies could be explained by the effect of study characteristics that might be expected to vary among the included studies. The following characteristics were investigated: biopsy method (fine-needle aspiration or core needle biopsy), the mean or median tumor size of included patients (whether smaller or larger than 20 mm), whether UNB was indicated only in cases with abnormal lymph node morphology on ultrasound or in all cases where an axillary lymph node could be visualized, the underlying prevalence of axillary metastases in the study population, and study design (whether prospective or retrospective). However meta-regression showed that none of these factors accounted for the between-study heterogeneity, which means that there were unexplained differences between the false-negative rates from various studies. The overall conclusion of the meta-analysis was that one in four women with a negative axillary ultrasound with/without UNB will be proven to have
axillary node metastases at subsequent SNB (48) (Figure 2), and therefore a negative result using this preoperative strategy means that further axillary intervention (usually SNB) is warranted (Figure 1).

Can I rely on the result of UNB to manage the axilla in patients with invasive breast cancer? Two meta-analyses (22, 48), each based on large datasets, have indicated that preoperative axillary ultrasound with selective UNB will correctly identify approximately 50% of breast cancer patients who have axillary node metastases: Diepstraten et al. (48) estimated this staging strategy to have a sensitivity of 50% (95% CI=43%-57%) (48) and Houssami et al. reported this as a median 55.2% (IQR=41.8%-68.2%) across primary studies (22). For sensitivity, Diepstraten et al. (48) performed meta-regression of the same variables as described above and found that underlying prevalence of axillary metastases influenced the sensitivity of the preoperative axillary ultrasound with/without UNB staging strategy: pooled sensitivity for studies with prevalence of axillary involvement <40% was 38.0% (95% CI=30.0%-46.0%), whereas that for prevalence of axillary involvement ≥40% was 62.0% (95% CI=55.0%-68.0%) (48).

In the sub-group of women selected for UNB (meta-analysis of 2,805 UNBs selected on the basis of ultrasound features of axillary nodes from 5,981 patients), Houssami et al. (22) reported modelled estimates for UNB accuracy: excluding insufficient results, UNB was found to have a sensitivity of 79.6% (95% CI=74.1%-84.2%), and a specificity of 98.3% (95% CI=97.2%-99.0%) as also shown in Figure 3. A consistently high positive predictive value (PPV; probability that a patient with a positive test result has axillary node metastases) was also reported across studies (median 100%; IQR=100%-100%) included in the meta-analysis of UNB (22). Although the meta-analysis estimated the sensitivity of axillary UNB at 79.6% based on a large number of studies (22), recent work confirming a similar sensitivity of 79% for all patients with breast cancer additionally shows that UNB sensitivity for axillary nodes is much lower (33%) in the sub-group of patients with invasive lobular histology (49).
Hence data from these two meta-analyses (22, 48) highlight that a positive ultrasound followed by a positive UNB (the latter providing cytological or histological diagnosis of metastatic nodes) provides a very reliable result, allowing for definitive surgical management of the axilla (Figure 1). This is predominantly because in those selected for UNB (based on positive ultrasound), a positive UNB result is so rarely falsely-positive, evidenced by the high specificity and 100% PPV. However, if ultrasound or UNB are negative, then the patient should proceed to SNB because of the moderate and variable sensitivity achieved through the combined testing strategy (Figure 2), and because there is variability in reported sensitivity even in patients selected for UNB (Figure 3). This limitation of axillary ultrasound with UNB is evident in the negative predictive value (NPV, probability that a patient with a negative test result does not have axillary nodal metastases) which is reported to be in the range of 58 to 84% (26-49-52), as well as the false-negative rate of 25% in Figure 2, which represents the compliment of NPV. In patients selected to UNB, a negative result has a moderate NPV: a median of 67.4% (IQR=60.0%-76.2%) based on meta-analysis (22).

What is the clinical utility of ultrasound with UNB of axillary nodes? There is consistent evidence from non-randomized studies that preoperative ultrasound and UNB can be used to effectively triage women with breast cancer directly to axillary surgery (22, 47, 50-54). Because preoperative diagnosis of axillary node metastases using UNB has high specificity and PPV (and assuming at least moderate sensitivity), women who are shown to have nodal metastases on this basis can be managed with ALND thus avoiding unnecessary SNB, meaning that they can have a single axillary operation (26-29, 31, 39, 40, 42, 44, 45, 47, 50-54) (Figure 1). Preoperative ultrasound and UNB can also be used for preoperative axillary staging in patients who are to receive neoadjuvant therapy (26, 30, 36, 39, 41, 43, 47, 50, 54-57). Joh et al. (57) reported that ultrasound with UNB for axillary staging can support planning and initiation of neoadjuvant therapy in a substantial number of breast cancer patients, and other studies have used this axillary staging strategy to determine neoadjuvant therapy followed by axillary surgery (47, 50).

The clinical utility of axillary ultrasound with UNB has been quantified in a meta-analysis (based on 4,941 patients) as a median proportion of 19.8% (IQR=11.6%-28.1%) representing the proportion of all subjects who are triaged, or could be triaged, directly to ALND (22) thus avoiding SNB and two-stage axillary surgery. This proportion is 17.7% (IQR=11.6%-27.1%) if the data on UNB utility are restricted to studies of patients with clinically node-negative disease (22). In this review, we examined utility of axillary ultrasound with UNB using the dataset from the same meta-analysis (22) but including data from additional studies (15, 47, 50, 51, 53, 58) identified in an updated literature search: using data for 7097 patients with breast cancer (from 27 studies), we found a similar utility of a median proportion of 18.4% (IQR=13.3%-27.4%) of patients who are triaged to axillary surgery (ALND) based on UNB result, avoiding unnecessary SNB. These proportions represent good clinical utility from axillary ultrasound with UNB in the context of an overall management strategy (Figure 1).

Test utility can also be quantified in terms of the proportion of women with metastatic axillary nodes who can be triaged to axillary surgery, a measure derived from UNB sensitivity: systematic use of preoperative UNB has been reported to have the potential to triage to ALND a median proportion of 55.2% (IQR=41.8%-68.2%) of patients who have axillary node metastases (22). In this meta-analysis, the proportion of women with metastatic axillary nodes potentially triaged to ALND is reported to be slightly lower (42.2%; IQR=30.6%-49.2%) for studies with a median tumor size <21 mm, and higher (65.6%; IQR=48.9%-69.7%) for studies with a median tumor size ≥21 mm. Therefore, preoperative UNB will have a relatively better utility when used in patients with higher underlying risk of nodal metastases due to having a larger tumour.

It is noteworthy that preoperative axillary ultrasound and UNB as a staging strategy to triage women with node metastases to axillary surgery is also cost-effective by removing unnecessary SNB: a recent study from the USA has estimated a cost-reduction of approximately $4,000 per patient (53).

While the above data illustrate the clinical utility for axillary ultrasound with UNB, given the evidence from the Z0011 trial (9, 10) and its adoption into practice in some settings (59), raises the question of whether axillary ultrasound and UNB remain useful. As indicated in the conceptual algorithm (Figure 1), in the sub-group of patients defined by the Z0011 criteria there may be relatively less utility for UNB because patients with nodal metastases in only 1-2 sentinel nodes would not necessarily undergo ALND: hence the utility of axillary ultrasound with UNB will depend on whether or not the surgeon has adopted omission of ALND in patients with minimal sentinel node disease (Figure 1). Surgeons who have modified their practice accordingly may find preoperative axillary ultrasound with UNB of modest (or even uncertain) utility because there is little evidence that axillary ultrasound with UNB can differentiate between minimal and more advanced nodal disease. Meaning that while it seems reasonable to assume that a negative axillary ultrasound/UNB is less likely in patients with a high burden of nodal metastases, a positive axillary ultrasound and UNB cannot differentiate between minimal nodal disease (1-2 metastatic nodes) and a greater burden of nodal disease (60); hence surgeons who wish to omit ALND in patients with minimal
sentinel node disease cannot use a positive result from ultrasound and UNB of the axilla to guide decision making. In this regard, recent work by Amonkar et al. (58) suggests that structured scoring of ultrasound features of nodes may help identify those with low metastatic burden who can then be triaged to SNB, while those with ultrasound scores suggesting higher nodal burden can proceed to UNB and subsequently to ALND if UNB-positive (58). Further investigation of this approach would be worthwhile.

Although the utility of ultrasound and UNB may be questionable or limited if there is increasing adoption of SNB-only for minimal axillary nodal metastases, it is plausible that the reverse may in fact occur. In the context of changing algorithms for axillary surgical management, axillary ultrasound might be used to assess for the presence of multiple abnormal nodes, and to triage those with multiple metastatic nodes to ALND. Another possibility is that refined use of ultrasound, either through systematic scanning of the axilla [as described by Britton et al. (61)], or through technologic developments [as shown by Sever et al. (62, 63)], may allow for precise identification and sampling with UNB of the sentinel node(s) without any operative intervention to the axilla for the majority of patients. Britton and colleagues have described systematic scanning of the axilla, with emphasis on level I nodes and with particular attention to identifying the lowest 1-2 nodes, and have reported that the use of that approach can lead to UNB of sentinel nodes in 64% of patients with breast cancer (61).

**Future Directions for the Role of Axillary Ultrasound and UNB**

In an attempt to investigate the causes of the shortfall of preoperative axillary ultrasound and UNB, Britton et al. (33, 64) reported research where an axillary core biopsy was undertaken of any node greater than 5 mm in longitudinal section: disease in 73 out of the 139 patients (52.5%) was node-positive, and in 25 out of these 73 cases (36%), the involved node showed no morphological abnormality on
axillary ultrasound. In this group of patients, Britton and colleagues reported a 30% false-negative rate (64). This was due either to failure to sample the sentinel node (45%), or failure to sample the metastatic disease that was in the already biopsied sentinel node (55%), emphasizing the need for improvement in the identification as well as the biopsy of the sentinel lymph node (33, 64).

Contrast-enhanced ultrasound using microbubbles may have the potential to partly address the above-noted limitations of ultrasound with UNB by accurately identifying the sentinel lymph node prior to surgery (Figure 4 A-B). Sever et al. have investigated the use of microbubbles in the identification of sentinel nodes when injected intra-dermally in the periareolar region (62). In their validation study of 54 consecutive patients, the enhancing sentinel nodes were successfully identified in 48 (89%) of cases, which were also confirmed at the subsequent surgery as being hot (n=7) or hot and blue (n=41) (62). In a further study, Sever et al. evaluated the use of targeted needle biopsy of the microbubble enhancing axillary lymph node (63) (Figure 4 A-B): in 136 patients where the initial gray-scale axillary ultrasound was normal, the sentinel nodes were identified in 126 (93%) of cases. Seventeen patients had positive biopsy results (13%) and were treated with immediate ALND. In seven of these patients, the biopsied node was the only metastatic node. SNB of the remaining 109 patients revealed nine (8%) positive cases, four of which had micrometastases only (63). While this study demonstrated an important improvement of the preoperative axillary staging approach using contrast-enhanced ultrasound, due to the remaining false-negative cases, it is also suggested that a negative axillary ultrasound and UNB should not obviate the need for SNB. It can be speculated that once the sentinel node is identified using contrast-enhanced ultrasound, large core vacuum-assisted needle biopsy devices may be employed to biopsy the node(s) more thoroughly in order to reduce the false-negative rate attributable to sampling error. While the use of such devices is routine for in-breast lesions, to the best of our knowledge, there are no studies to have published data on the use of these devices to preoperatively stage the axilla. Advances in ultrasound technology and newer-generation microbubble agents may potentially allow improved accuracy of axillary imaging in the preoperative axillary staging setting, and may identify patients who are likely to have no or limited (minimal) axillary disease. Given the results of the Z0011 trial (9, 10), these patients may not require any axillary surgery at all, so further research to investigate these concepts would be very worthy and could substantially modify practice.

A randomized trial of ultrasound-based axillary staging. A prospective randomized controlled trial which is being conducted in Europe will use axillary ultrasound to decide on surgical management of the axilla: the Sentinel node vs. Observation after axillary Ultra-Sound (SOUND) trial is recruiting patients with early breast cancer (tumours ≤2 cm and clinically node-negative axillae) and who are candidates for breast-conserving surgery (65). Patients will have axillary ultrasound to assess whether or not they have suspicious nodal involvement. Those shown to have a negative ultrasound or (for a single abnormal node) negative UNB will be randomized to receive SNB or no further axillary surgery. This trial represents yet another possibility for a potential shift in axillary management towards less intervention and may see a greater role for axillary ultrasound in future – the SOUND trial is currently in progress (65).

Conclusion

Preoperative imaging-based staging of the axilla using ultrasound with selective UNB is a moderately sensitive but highly specific staging strategy that allows patients to be correctly triaged to ALND based on a positive result, thus avoiding unnecessary two-stage axillary surgery and SNB. There is consistent evidence from non-randomised studies that ultrasound and UNB provide good clinical utility (quantified in this review as a median 18.4% of patients with breast cancer who can be triaged to axillary surgery without SNB). However, the implications of the changing surgical landscape in axillary treatment are that preoperative axillary ultrasound and UNB may have limited clinical utility depending on local surgical practice (for example, it may be used to identify and biopsy only patients with multiple abnormal axillary nodes on ultrasound), and specifically on whether omission of ALND in patients with minimal nodal metastatic burden has been adopted as standard of care. Based on this overview, we conclude that future research that allows enhanced application of ultrasound with UNB to identify and precisely biopsy sentinel nodes and/or to discriminate between minimal versus advanced axillary nodal metastatic involvement is likely to have the most impact on management of the axilla in invasive breast cancer.

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