Perioperative diagnosis of the positive axilla in breast cancer: A safe, time efficient algorithm

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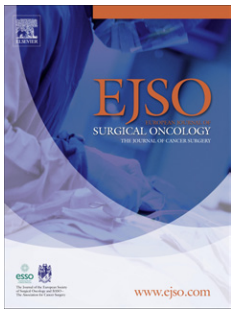

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Title:

Perioperative diagnosis of the positive axilla in breast cancer: A safe, time efficient algorithm.

Background: This study evaluates the combined role of axillary ultrasound (Ax US), fine needle aspiration (FNAC) and intraoperative frozen section analysis of the sentinel node (FS SN) in a practical, time efficient algorithm to reduce the requirement for reoperation for axillary clearance in breast cancer in a busy tertiary unit.

Methods: Between October 2007 and June 2009 188 women underwent Ax US as a first investigation for nodal status. Suspicious nodes were biopsied, negative axillae proceeded to FS SN at time of primary breast surgery. All confirmed positive cases proceeded to immediate axillary clearance.

Results: 93 women had positive axillary nodes at final histology. Ax US + FNAC identified 59 positive axillae and had a sensitivity of 63.4% and specificity of 100%. FS SN identified a further 26 cases with a sensitivity of 76.5% and specificity of 100%. Overall, only 8 women required reoperation for axillary clearance. Sensitivity for the combined procedures was 91.4%. Commencement of adjuvant therapy was significantly less in those women identified earlier compared to those requiring a second operation (23.3 days vs 49.0 days, $p<0.005$)

Conclusion: 95.7% of cases were diagnosed accurately in the perioperative period, preventing delay to triage to definitive oncological care and reducing requirement for costly reoperation.

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Category for submission

We wish to submit this present paper as an original article.

Presentations

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Keywords

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Introduction:

Axillary staging is a vital aspect in the management of breast cancer [1-2]. It predicts prognosis and tailors treatment. The ability to accurately identify the positive axilla at the earliest time point from diagnosis allows for early triage of patients to neoadjuvant or adjuvant therapy. It may also reduce the number of surgical procedures required and reduce the axillary reoperation rate.

Two windows of opportunity exist for diagnosing the patient with a positive axilla perioperatively. Firstly, the employment of axillary ultrasound (Ax Us) and fine needle aspiration cytology (FNAC) can identify positive axillary nodes in the preoperative period, thereby allowing the surgeon to perform immediate axillary lymph node dissection (ALND) at the time of the primary breast procedure [3-5]. Secondly, intraoperative analysis of the sentinel node, via frozen sectioning, imprint cytology, immunohistochemistry (IHC) or more recently 'Genesearch' BLN (Biopsy Lymph node assay) real time RT-PCR assay, can provide an immediate diagnosis of the axilla and thus reduce the requirement for delayed axillary surgery [6-9].

To aid early identification of the positive axilla, the symptomatic breast cancer unit in our institution routinely utilises a combination of both axillary US with FNAC (Ax US ± FNAC) and intraoperative frozen section analysis of the sentinel node (FS SN). The aim of this study was to examine our unit's protocol for axillary staging applying both techniques and to identify potential advantages or disadvantages of such an approach.

Methods:

Patients

Axillary ultrasound and intraoperative frozen section analysis of the sentinel node were routinely adopted in our institution from October 2007. All cases of breast cancer presenting to the symptomatic unit in the period up to June 2009 were prospectively audited for technique efficacy with data entered into a prospectively maintained cancer specific registry database. Patient demographics, clinico-pathological features and axillary node FNAC findings were recorded. Time to post operative medical oncology review in all patients, excluding those who underwent neoadjuvant therapy was calculated (this time was used to estimate time to triage to definitive adjuvant therapy).

Protocol

During the diagnostic process, after clinical examination of the breast and axilla, targeted breast ultrasound was carried out with concomitant ipsilateral axillary ultrasound in cases where cancer was suspected as is the standard for triple assessment clinics. If a positive nodal status was confirmed by FNAC of an abnormal axillary node identified by axillary ultrasound (Ax US / FNAC +ve), an immediate axillary lymph node dissection (ALND) was scheduled concurrently with primary breast surgery. For a negative Ax US or a negative FNAC, a sentinel lymph node biopsy procedure with intraoperative frozen section analysis of the node was performed at time of surgery (FS SN). Similarly, axillary lymph node dissection was executed if a positive node was identified by intraoperative frozen section analysis. All nodal tissue was finally examined in fixed formalin paraffin embedded (FFPE) blocks to confirm axillary nodal status. If at any stage in our protocol axillary status

was ambiguous, the next level of diagnostic testing was employed to ascertain nodal status. Micrometastases detected in a sentinel node were considered to be node positive and thus required ALND.

Exclusion criteria

Patients were excluded from this study if they were treated without surgery, if their care deviated from the protocol, or if the patient underwent neoadjuvant chemotherapy without pathological confirmation of positive nodal status (i.e. Ax US ±FNAC –ve) prior to commencement of therapy.

Axillary Ultrasound

The patient was placed in the anterior oblique position supine with the arm on the affected side extended and placed overhead. The axilla was scanned in two orthogonal planes using a high frequency linear 7.5 to 13MHz transducer with an elevation plane of about 1.5cm. Criteria for a suspicious axillary lymph node included cortical thickness >3mm in short axis diameter, architectural distortion and a replaced or eccentric hilum. Using a 21 gauge needle, under real time ultrasound guidance, 2 fine needle aspirate samples were obtained from the cortex of the lymph node by applying slight negative pressure for 2 seconds. The aspirate was rinsed into CytoLyt® (Cytyc Corp., Boxborough, MA) solution for subsequent analysis by a cytopathologist. If there were multiple abnormal lymph nodes present in the axilla then the lowest (Sentinel node), most accessible and abnormal was selected for fine needle aspiration.

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Intraoperative frozen section analysis of the sentinel node

SN sampling was performed using a combination of a radiolabeled colloid and a vital blue dye. Sentinel nodes were intraoperatively identified by the use of a handheld gamma probe. Sentinel nodes identified as hot by the gamma probe and any blue nodes visualised were excised and sent fresh to the frozen section desk in our pathology lab for analysis. Briefly, the fresh lymph nodes were sectioned at 2mm intervals and checked for any macroscopic abnormality. If any abnormality was seen, this area was submitted for frozen section. Otherwise, one 5x5mm frozen section was submitted per each 10 mm of lymph node up to a maximum of 3 sections per node. Two levels were cut for each frozen section. Time to issuing result was recorded in final pathology report. In the case of multiple nodes, all were analysed before communication with the surgeon.

Statistical Analysis

Fischer exact and chi square tests were utilised to examine categorical data while t-tests and ANOVA were used to examine continuous variables (represented as mean ±SEM). A p value of 0.05 or less was considered significant. Contingency tables were drawn up to determine sensitivity and diagnostic accuracy of the techniques. Statistical analyses were performed with GraphPad Prism software (version 5.02 GraphPad, San Diego, California, USA).

Results:

Patients

We diagnosed 227 invasive breast cancers in 226 women who concurrently underwent Ax US prior to definitive management during the study period. From this initial cohort, 39 were excluded from further analysis, 17 cases were treated medically after positive axillary diagnosis. 9 cases had an axillary US performed with but had an axillary lymph node dissection performed for patient preference. 9 cases deviated from the prescribed intraoperative frozen section sentinel node procedure due to technical reasons and 4 neoadjuvant cases did not have a positive axillary diagnosis prior to treatment and so were excluded. In total, 188 cases (figure 1) were eligible for inclusion for further analysis. Table 1 demonstrates this final cohort's demographic and tumour characteristics.

Axillary FNAC

In our series, 77 women in which a suspicious axillary node was identified at ultrasonography had FNAC performed (table 2). Of these, 59 nodes were confirmed as having malignant cytology. These women underwent immediate axillary lymph node dissection. Of the remaining 18 cases, 16 had a positive Ax US but with negative/inconclusive FNAC. These were ultimately confirmed as negative node at FS SN. One false negative axilla was identified at FS SN and progressed to immediate axillary lymph node dissection, and the second was not detected at sentinel node biopsy and required a delayed axillary lymph node dissection after identification at final pathology (FFPE). The specificity of Ax US ± FNAC was 100% (95% c.i.: 96.2-100%) indicating no unnecessary ALND were performed based on FNAC data.

Positive predictive value (PPV) was 100% (95% c.i.: 93.9-100%). Negative predictive value was 73.6% (95% c.i.: 65.2-81.0%)

Intraoperative analysis of frozen section sentinel node

A total of 129 frozen section sentinel node procedures were performed, comprising 111 Ax US –ve and 18 Ax US +ve (FNAC –ve) cases, as presented above (table 2). Specificity was 100% (95% c.i 96.2-100%), PPV 100% (95% c.i.: 86.8-100%) and NPV 92.3% (95% c.i.: 85.3-96.6%). Median time to intraoperative FS SN report was 24.3 mins (range 11.1 – 56.3 mins). Sensitivity to detect macrometastasis was 88.9% (95% c.i.: 70.8-97.7%), while that of micrometastasis was 28.6% (95% c.i.: 3.7%-71.0%).

Combined analysis of techniques

With the application of the diagnostic modalities in combination in our unit, overall accuracy/ sensitivity to identify the positive axillary node perioperatively was greater than 90%. Delayed axillary lymph node dissection was required in 8 women, due to failure of the procedures to identify these nodes correctly (false negative result). No false positive results arose in this study and hence no unnecessary axillary lymph node dissections were performed. Of these 8 cases classed as being false negative post FS SN, 3 had undergone FNAC with a negative/inconclusive cytology report and subsequently proceeded to FS SN, one of which was reported as a micrometastasis. In the other 5 instances that were Ax US/ FS negative, 4 were ultimately identified as having micrometastasis.

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Cases with a higher nodal burden were more likely to be identified by Ax US±FNAC than FS SN. Ax US±FNAC had a positive mean node burden of 6.8 (±0.85), compared with FS SN 3.4 (±0.74) and false negative SN 2.4 (±1.45), p=0.015. Tumour size (mm) was a factor in determining what modality would detect the positive axilla, so that larger tumours were found in patients who had positive nodes identified on Ax Us compared with FS SN and FN SN (33.07 ±2.4 mm, 25.06 ±2.2 mm and 21.9 ±3.7 mm, p<0.001). Lobular cancers were less likely to be detected by FNAC compared to FS SN but this was did not attain significance (FNAC: Lobular 13.0% vs FS SN: Lobular 28.6%, p=0.109)

It was also noted that the time from diagnosis (days) to commencement of adjuvant therapy was significantly less in those patients who were diagnosed early (Ax US +ve, FS SN +ve) compared to those who required a second operation for axillary lymph node dissection for a false negative FS (23.3 ±1.2, 31.7 ±3.9 and 49.0 ±9.0 days respectively, p<0.005).

Discussion:

Advantages

This study demonstrates the benefits of performing axillary ultrasound ± FNAC in conjunction with intraoperative frozen section analysis of the sentinel node in a practical time efficient algorithm to identify the positive axilla at the earliest point in time. We identified 59 of the 93 positive axillae in the preoperative period with Ax US ± FNAC. A further 26 positive cases were detected with intraoperative frozen section analysis of the sentinel node. Sentinel node procedures were avoided in 31.4% of patients. The individual sensitivities from this study compare favourably with

sensitivities as published for Ax US ± FNAC (31-67 %) [4,10-13] and FS SN (36-93%) [7-8,14-17]. Using our protocol, 91.4% of all positive cases were diagnosed perioperatively and underwent immediate axillary lymph node dissection. Triaging of patients to adjuvant therapy was found to be more expedient in those groups who had ALND performed at the time of the primary breast surgery. Genta et al, demonstrated, in a protocol similar to our institution's, that a saving of €2500/case was attainable for a one stage axillary lymph node dissection after diagnosis with Ax US or FS SN[18]. Although beyond the scope of this study, we agree that this protocol is extremely cost effective, as compared with the requirement of performing a second axillary procedure at a later date with the increased burden on resources that this entails (readmission, requirement for theatre space, potentially longer surgery, hospital stay etc). Recent data has suggested that the omission of intraoperative sentinel node analysis in T1a and T1b tumours may be possible to due low incidence of axillary metastasis [19]. Our data indicated that of the 15 tumours less than 1cm in size, no axillary metastases were detected. A further cost advantage may be attainable by omitting intraoperative analysis in these subset of patients but more extensive data is required to change current practice.

Disadvantages

We recognise that our approach to immediate axillary lymph node dissection has some drawbacks, with particular regard to potential false positive reports and the consequences of such a result. Protection of the patient is of paramount importance in our approach. The overall false positive rate in this series was 0% due primarily to the rigorous pathologic examination undertaken for each specimen and the inherent safety of the protocol. It must however be recognised that false positive results can and do

occur. In axillary ultrasound the interpretative error of the fine needle aspirate is the principle cause for false positive results [3,5]. A number of articles examining intraoperative sentinel node analysis have indicated the scarcity of false positive results using this technique [8,20]. A contentious issue is the consenting of patients to the possibility of requiring an axillary lymph node dissection depending on the sentinel node result. It is our experience that patients prefer to undergo as few procedures as possible and to complete the diagnostic/operative process quickly and smoothly.

Technical points

The techniques, as applied, are relatively simple to teach/learn and are neither unduly technical nor overtly time intensive as they are performed in conjunction with other procedures. FNAC for suspicious nodes is performed at the same time as is core biopsy of the primary tumour. Similarly, sentinel node sampling is performed first and excision of the lesion second; therefore time waiting in theatre for the pathology report is reduced to a minimum. Our approach to frozen section analysis reduces the number of sections to review to improve rapidity of reporting. We recognise this approach possibly impedes very high levels of accuracy and sensitivity. By increasing the number of sections taken [21-22], concomitant use of IHC [8] or imprint cytology [14] on the sentinel node the sensitivity and accuracy of the procedure may be improved, particularly in the detection of micrometastasis. However, it is ultimately impractical if the time to report is such, that duration of anaesthesia and operating time is extended for no gain (negative result/false negative result) to the potential detriment of the patient. An emerging technique, intraoperative RT-PCR detection of the sentinel node, detecting the presence of mammoglobin (MG)

and cytokeratin-19 (CK-19) is said to be rapid enough for intraoperative use. The Genesearch Breast lymph node assay test (BLN) can be performed within 35 – 40 mins of excision, to a very high degree of accuracy [23-25]. Major advantages of this technique were portended to reduce the workload of pathologists involved in intraoperative analysis of pathology specimens and provide accurate rapid results to the operating surgeon [23]. Evidence also suggested that it could predict additional, non sentinel node metastases [26]. A contentious issue raised however, was the loss of tissue, as part or the entire sentinel node was required to be homogenised to perform the assay. Veys *et al* had demonstrated that sampling 50% of the node for BLN and the remainder for standard histology did not impair the high sensitivity of the test and this was thought to assuage concern for tissue loss going forward with this technique [23]. This technique was recommended to be used only in conjunction with routine pathological techniques until equal or superior prognostic outcomes were evident in clinical trials. This technology has of late been withdrawn due to failure of the technique to supersede other intraoperative techniques, indicating the strength and reliability of frozen section analysis of the sentinel node.

Conclusion

In conclusion, these data provide persuasive evidence that the application of axillary ultrasound ± fine needle aspiration and intraoperative frozen section analysis of the sentinel node can provide sufficient, high quality information regarding the state of the axilla so that immediate axillary lymph node dissection, where required, can be undertaken at the time of primary oncological procedure. Ultimately, 95.7% of cases

were triaged correctly in the perioperative period so that no delay was encountered in determining final stage and adjuvant therapy requirements for that case.

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Table 1: Patient and tumour characteristics

Characteristic	***n***
Age (years)	
Median	55.5
Range	25-98
Menopausal status	
Post menopausal	118
Pre menopausal	70
T stage	
T1 *a*	5
T1 *b*	10
T1 *c*	70
T2	86
T3	17
Tumour histology	
Ductal	142
Lobular	22
Other	24
Breast surgery	
Wide local excision	107
Mastectomy	81
Hormone receptors	
ER positive	141
PR positive	111
Her2 positive	26
Axillary status	
Positive	93
Negative	95
No. SLN per procedure	
Median	2
Range	1-9

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Table 2: Individual accuracy and sensitivity of axillary ultrasound ± FNAC, frozen section analysis of the sentinel node, and combination of techniques in 188 patients.

	Node +ve	*False -ve*	*False +ve*	*Sensitivity (95% c.i)*	*Accuracy (95% c.i)*
Ax US ± FNAC	59	34[a]	0	63.4 (52.8-73.2)	81.2 (78.5-81.9)
FS SN	26	8	0	76.5 (58.8-89.3)	93.8 (89.6-98.0)
Overall	85	8[b]	0	91.4 (83.8-96.2)	95.7 (92.7-98.7)

Footnote: a) Confirmed positive cases at FS SN and FFPE
b) 8 cases in total required delayed axillary clearance.

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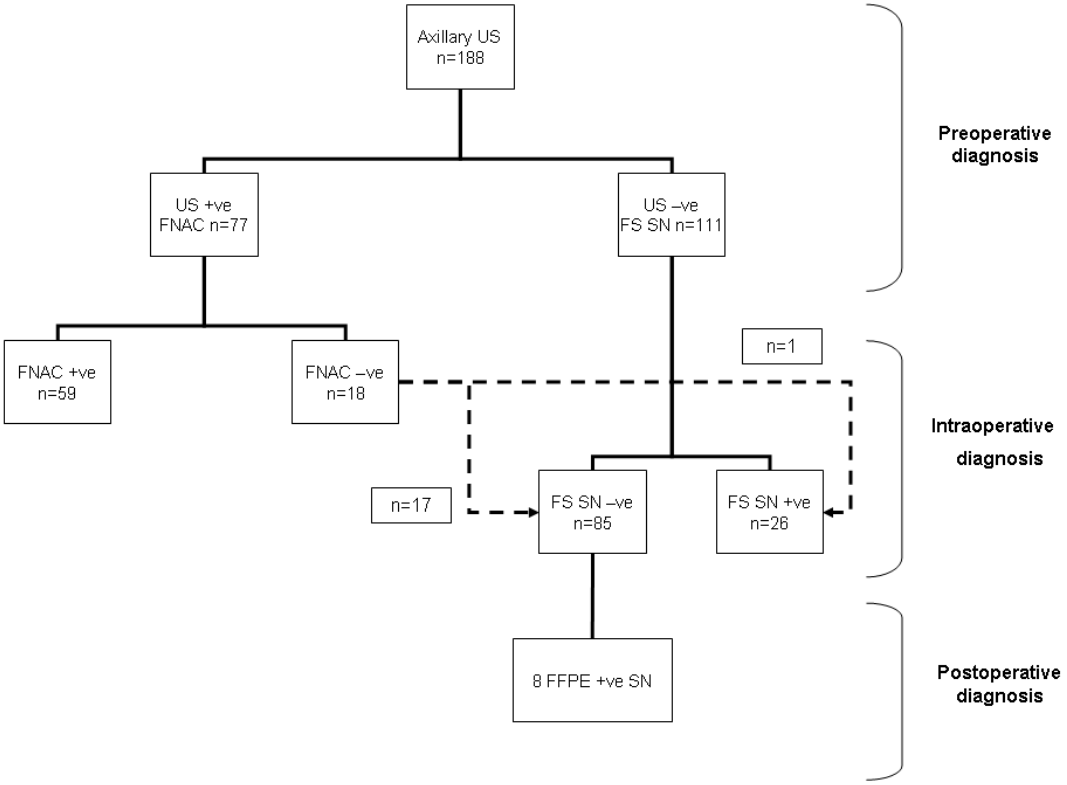

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