The identification and biopsy of sentinel lymph nodes using intradermal microbubbles and CEUS in Pre-operative Breast Cancer Patients

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Maidstone and Tunbridge Wells Breast Unit
The Axilla
Optimise Axillary Management

ALND

SNB

No Axillary surgery
Microbubbles the story

Sentinel lymph nodes in a swine model with melanoma: contrast-enhanced lymphatic US.
Goldberg BB, Merton DA, Liu JB, Thakur M, Murphy GF, Needleman L, Tornes A, Forsberg F

Preoperative localization of sentinel lymph nodes using intradermal microbubbles and contrast-enhanced ultrasonography in patients with breast cancer.
What are Microbubbles?

- Ultrasound contrast agents are made up of a dispersion of microbubbles.
- Each microbubble acts as a reflector of the ultrasound beam.
- Provided enhanced imaging of tissue microvasculature in many organ systems.
Method – After a normal grey-scale ultrasound (+/- benign biopsy of morphologically abnormal LN)
Biopsy of SLN

Contrast pulse sequencing image
Practicalities

- Ultrasound machine
- Grey-scale and contrast pulse sequencing (CPS) software.
- Contrast (Sonovue, Bracco imaging).
- Core biopsy equipment

- Approximately £50 per procedure for consumables.
- Procedure takes 20-30 minutes.
- Safe
- Only 1 significant haematoma since 2008!
A test to identify SLN Metastases and avoid a ‘futile’ sentinel node biopsy

Microbubble and CEUS SLN Biopsy

B2

Surgical SLN biopsy (blue dye and isotope)

B4/B5

ANC

Action following biopsy Results
Maidstone Breast Clinic – Prospective data collection (EJSO 2014)

SLN clearly visualised in 605 patients (93%)
Successful core biopsy in 555 patients (85%)

<table>
<thead>
<tr>
<th>Invasive Disease</th>
<th>Axillary Surgery</th>
</tr>
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<tbody>
<tr>
<td>Microbubble and biopsy result</td>
<td>LN mets</td>
</tr>
<tr>
<td>Positive (B4/5)</td>
<td>68</td>
</tr>
<tr>
<td>Negative (B2)</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>128</td>
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- Sensitivity: 0.53
- Specificity: 1
- Prevalence: 0.23
- Positive Predictive value: 1
- Negative Predictive value: 0.88

Likelihood ratio for a negative result = 0.47
Post-test probability that, given a negative SLN biopsy, the patient has axillary LN metastases = 12%
Axillary Conservation
Axillary Conservation

- American College of Surgeons Oncology Group Z0011 trial (published 2010)
- Phase 3 non-inferiority trial. Patients were women with clinical T1-T2 invasive breast cancer, no palpable adenopathy, and 1 to 2 SLNs containing metastases.
- Patients with limited SLN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival.
Results of the test and volume of axillary metastases

Interpretation of data in the era of ‘axillary conservation’

What does a positive (B5) result tell us?

What does a negative (B2) result tell us?
Maidstone Breast Clinic Data (all patients with invasive disease and normal grey-scale ultrasound n=654)

- 93% SLN identified
- 85% successful core biopsy
- Prevalence of LN metastases 23%
- Sensitivity 53% (CI 44, 62%)
- Specificity 100% (CI 99, 100%)
- Negative predictive value 88% (12% were false negatives)
- Only 2% of patients with an initial benign SLN biopsy had 2 or more LN metastases at the end of surgical treatment. 52% of patients with a malignant SLN biopsy had 2 or more LN metastases at the end of surgical treatment.

Annals of Surgical Oncology 2015
Tunbridge Wells Breast Clinic – Retrospective data collection (Feb 2011-Sept 2014)

SLN clearly visualised in 291 patients (85%)
Successful core biopsy in 270 patients (79%)

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Sensitivity 0.53
Positive Predictive value 0.91
Specificity 0.98
Negative Predictive value 0.85
Prevalence 0.27

Likelihood ratio for a negative result = 0.52

Post-test probability that, given a negative SLN biopsy, the patient has axillary LN metastases = 16%
Tunbridge Wells Breast Clinic – Retrospective data collection

• 15% of benign SLN core biopsies were false negatives
• 5% were ITC/ micrometastases
• 6% had 1 LN macrometastasis
• 4% had 2 or more LN macrometastases
Can some patients avoid axillary surgery?
Tumour <30mm and normal grey-scale ultrasound (n=436)

- Prevalence of LN metastases 17%
- Sensitivity 41%
- Specificity 100%
- Negative predictive value 89%
- False negatives 11%
- 1.7% of patients with an initial benign SLN biopsy had 2 or more LN metastases at the end of surgical treatment.
Post-menopausal Invasive ductal Breast Cancer
Unifocal tumour Suitable for BCS

Normal Grey-scale axillary U/S

Benign core biopsy of SLN identified with CEUS

Randomization

Molecular test ? oncotype

Surgical SLN biopsy +/- completion ALND

No further axillary surgery

Adjuvant treatment

Adjuvant treatment

This is a randomised, multicentre, non-inferiority trial with 5 year follow up
BUBBLE 2 vs Grey-Scale U/S alone

• SLN core biopsy objective and grey-scale U/S subjective.
• Grey-scale and CEUS SLN biopsy may combine to give an ‘acceptable’ false negative rate (FNR). Surgical SLN biopsy using blue dye and isotope has FNR of 6-10%.
• Does FNR matter?

• **Issues to resolve**
  - Recruitment (tumour size, phenotype)
  - What to do with malignant SLN core biopsy patients
  - Tumour molecular analysis required to help guide adjuvant therapy?
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