Original article

Isotope-Only Localization for Sentinel Lymph Node Biopsy - Medium-Term Oncological Outcomes

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Abstract

We investigated localization rates and oncological outcomes of single tracer sentinel node localization and biopsy using only radioisotope. Isotope-only SLNB has a comparable localization rate to dual isotope/blue dye SLNB and low axillary recurrence rate, making it a good alternative to dual-tracer SLNB.

Aims: Isotope and blue dye dual localization in sentinel lymph node biopsy (SLNB) gives localization rates of over 98% and is the recommended technique. However blue dye risks a range of adverse reactions. Since 2010, for clinically node negative disease, we have only used blue dye if there is no clear isotope signal at surgery. **Methods:** Electronic records of patients who underwent isotope-only SLN localization between July 2010 and April 2012 were examined. Data were collected on localization and oncological outcomes. **Results:** 426 patients were included. Isotope-only localization rate was 97.4% (415/426). The median follow-up was 63.5 months (IQR: 60.7-70.9). Median age was 57 (IQR: 48-67). Median SLN yield was 2 (range: 1-5). Axillary recurrence rate was 1.4% with median time to recurrence of 39.3 months. In-breast recurrence, distant disease and contralateral breast cancer rates were 2.8%, 7%, and 1.9% respectively and 15 (3.5%) patients died of metastatic breast cancer. **Conclusion:** Isotope-only SLNB has a comparable localization rate to dual isotope/blue dye SLNB and can spare the risk of blue dye adverse reactions. The low axillary recurrence rate, maintained to more than 5 years, confirms that isotope-only SLNB is a feasible and safe alternative to dual blue dye/isotope localization.

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Introduction

Lymphatic mapping for sentinel lymph node biopsy (SLNB) was first described by Morton et al. in 1992 in patients with malignant melanoma.[2-4] Since then SLNB has emerged as the technique of choice for axillary staging of early-stage breast cancer with a clinically and/or radiologically negative axilla.[5-8] It provides an accurate assessment of the axilla, with a low false negative rate (FNR)[9,10] and a significant reduction in surgical morbidity, especially Americanized to lymphedema when compared with axillary lymph node clearance (ALNC).[11] Sentinel lymph node (SLN) localization can be achieved by using many different tracers. Blue dye and radioisotope (technetium-99m labelled nanocolloid), or a combination of the 2 methods are the most common. Others include indocyanine green and superparamagnetic iron oxide particles.[12,13] All methods have been reported to have high rates of SLN detection, sensitivity, accuracy and have acceptable false-negative rates.[14]

The combined technique (blue dye and radio-isotope) of SLN localization is the method recommended by the Association of Breast Surgery[15] and has been shown to have significantly higher localization rates (95%-100%) than blue dye alone (82-86%).[14,16] Blue dye carries a risk of adverse reactions. Anaphylactic reactions to Patent Blue V have been noted since 1966 and the incidence of such reactions is reported to be 0.6% to 2.8% with a mean of 1.8%.[17-21] Although rare, Patent Blue V remains one of the most common drugs causing severe anaphylaxis in the operating theatre environment.[22,23] In addition, blue dye stains the breast for several months, obscures the oncoplastic plane for superficial dissection and following the blue lymphatics in the axilla requires more dissection compared to removal of the hot sentinel nodes guided by the handheld gamma probe alone.

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After a retrospective review of the incidence of blue-only positive nodes in our practice, which showed that a change of practice to isotope-only localization would have minimal impact on localization and false negative rates but would spare patients the adverse reactions associated with blue dye, we stopped routine use of blue dye in 2010.[24] We now reserve blue dye for those patients in whom a clear radioactive signal cannot be detected in the axilla at induction and, after 2013, added it back in for SLNB after neo-adjuvant chemotherapy (NACT) for cN1-2 disease that downstages to cN0.[25] The aim of this study was to establish localization rates and oncological safety of isotope-only SLNB in a high-volume cancer center.

Materials and Methods

Consecutive patients with clinically node negative invasive or in-situ breast cancer who had sentinel node biopsy between July 2010 and April 2012 at the Royal Marsden Hospital were identified from electronic medical records. This was a service improvement project, which had appropriate institutional approval (RMH BR109 SLNB) Patients consented to surgery according to standard practice, and consent forms specifically describe the use of radioisotope with blue dye in cases where uptake of isotope is poor, with specific reference to allergic reactions and staining of the skin.

Retrospective data collected included patient demographics (age, body mass index (BMI)), previous breast/axillary treatment, clinical axillary status at diagnosis, cancer pathology (size, grade, type, phenotype, total number of lymph nodes and status) and oncological (neoadjuvant systemic therapy, breast conservation surgery (BCS) and/or mastectomy, final axillary surgery),

Overall and disease-free survival as well as local/regional recurrence, contralateral cancer, distant metastases and mortality rate were calculated.

Statistics were descriptive and performed using Microsoft Excel (2010).

Results

During the 22-month period between July 2010 and April 2012, 426 consecutive SLNB were performed in clinically node negative patients. Of these, 36 (8.5%) patients had previous ipsilateral breast surgery of whom 8 had previous ipsilateral axillary surgery as well. No previous ipsilateral axillary radiotherapy was recorded. 136 (31.9%) patients underwent mastectomy and 290 (68.1%) BCS. The clinico-pathological characteristics are summarized in Table 1.

Isotope-Only Localization Rate

Technetium 99m isotope successfully localized a SLN in 415 patients giving a localization rate of 97.4%. The remaining 11 patients (2.6%) required the addition of blue dye because of no signal or a very weak radioactive axillary signal at induction. During surgery, 2 of the 11 had radioactive as well as blue SLNs. A further 2 patients had neither blue nor radioactive SLNs, with complete failure of SLN mapping, both underwent ALND and pathology revealed heavy disease burden. The remaining 7 patients had blue SLNs only, suggesting a true failure of the isotope-only localization. Of those 7 patients, 2 had previous surgery in the ipsilateral axilla.

One patient had a strong axillary radioactive signal so no blue dye was injected, but no nodes were identified visibly, palpably or on histopathology. This patient had previous level 1 axillary dissection in the ipsilateral axilla. 3 patients had previous ipsilateral breast surgery, 1 mentioned above and 2 with previous surgery for benign lesions. Overall, therefore, the localization rate in this series of isotope with blue dye back-up was 99% (423/426).

SLN Results

SLN yield ranged from 1 to 5 nodes with a median of 2. Intraoperative assessment was performed on 393 (92.2%) women: touch imprint cytology (TIC) in 204 and one-step nucleic acid (OSNA) in 189. The SLNB contained cancer in 111/426 (26%) patients: 74 had macro metastases (>2 mm) of whom 66 underwent completion ALND giving a total of 15.5% (66/426) of all SLNB patients undergoing ALND. SLNB was negative in 314 patients.

Follow Up

At 63.5 months median follow up (range 60.7-70.9 months) axillary recurrence rate was 1.4% (6/426) patients, 2 had a positive SLNB and had proceeded to ALNC at the time of original surgery, and 4 had a negative SLNB (4/426, 0.94%). The median time to recurrence was 39.3 months. Of the 4 patients with negative SLNB and axillary recurrence, 1 received blue dye in theatre. Therefore, in patients with isotope-only localization and negative SLNB the axillary recurrence rate was 0.98% (3/307). All 3 had concurrent distant disease.

The in-breast recurrence rate was 2.8%, distant disease rate was 7% and contralateral breast cancer rate was 1.8%. One patient developed an ipsilateral radiotherapy-induced angiosarcoma. 15 (3.5%) patients died of metastatic breast cancer giving an overall disease-free survival rate of 96.5%. Overall mortality was 7.2%. Two of the 6 patients with axillary recurrence (both with concurrent distant disease) died of breast cancer (Table 2).

Discussion

Sentinel lymph node biopsy is considered standard of care for the evaluation of the axillary nodal basin in clinically node negative early breast cancer.[26] Although dual isotope and blue dye is the standard technique in the UK this reflects the evolution of axillary SLNB, starting with blue-dye only to which isotope was added to boost localization rates. Understanding this evolutionary 'layering' of localization agents is important when considering the value of blue dye to SLN localization rates, particularly when blue dye is responsible for 5% of anaphylactic reactions in the operating theatre.[23] The difficulty now is we cannot conclusively prove the accuracy of isotope-alone SLNB as we cannot repeat the early randomized SLNB trials using isotope-alone as performing confirmatory ALNC for staging of early breast cancer would no longer be acceptable, hence we are, instead, reporting on medium term oncological outcome. Our series of isotope-only SLNB in 426 patients is the largest reported to date.

Localization Rates

Our series of isotope-only SLN has a localization rate of 97.2% which is consistent with other studies of isotope-only SLNB demon-

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Table 1 Characteristics of 426 Patients Undergoing SLNB

Characteristics	n = 426 (%)
Age (years) median (interquartile range)	57 (48-67)
BMI (kg/m^2) median (interquartile range)	25.7 (22.3-29.8)
	n (%)
Men	2 (0.5)
Women	424 (99.5)
SLNB Negative	315 (73.5)
SLNB Positive	111 (26.2)
Only macro	63 (14.8)
Only micro	37 (8.8)
Both	11(2.6)
Type of initial breast surgery	
Wide local excision	290 (68)
Mastectomy	136 (32)
Neo-adjuvant systemic treatment (all clinically N0 at diagnosis)	
Chemotherapy	48 (11.2)
Endocrine	27 (6.3)
Tumour size	
T1	214 (50)
T2	166 (39)
T3	27 (6.3)
pCR	19 (4.5)
Tumour type	
Invasive ductal	332 (77.9)
Invasive lobular	46 (10.8)
Mixed	7 (1.6)
Tumour grade	
Grade 1	63 (14.8)
Grade 2	169 (39.7)
Grade 3	155 (36.4)
In situ	30 (7.0)
High grade	2 (0.5)
Intermediate grade	23 (5.4)
Low grade	5 (1.2)
Other	11 (2.6)

Table 2 Follow Up of All Patients Undergoing SLNB

	n = 426	%	Of Whom NACT n = 48	%
In-breast/local recurrence	12	2.8	4	8.3
Axillary recurrence (3 post ALNC)	6	1.4	1	2.1
Contralateral breast cancer	8	1.9	2	4.2
Distant metastases	30	7	10	20.8
Overall mortality	31	7.2	7	14.6
Breast cancer mortality	15	3.5	7	14.6
Death in patients who had experienced axillary recurrence	2	0.9	0	0

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strating localization rates from 85.6% to 97.6%.[27-33] These studies suggest that the addition of blue dye to isotope does not enhance localization rates and that blue dye can be reserved for the situations where isotope alone does not localize.

Various studies have investigated the variables associated with successful SLN localization by blue dye or by isotope. Obesity, tumor location,[33] subcutaneous isotope injection, negative preoperative lymphoscintigraphy, age >60 years,[34] surgical inexperience and axillary lymph node involvement were associated with SLNB failure during surgery.[35]

In our series all the patients received isotope either on the day of surgery or the day before. In all the cases blue dye was injected after induction of anesthesia and after the surgeon confirmed that the signal in the axilla was too weak. Although some patients had previous surgery in the ipsilateral breast or axilla this was not considered a reason for using the dual technique unless the axillary signal was weak.

Non-visualization of the SLN by preoperative lymphoscintigraphy has been reported by a few studies to be predictive of SLNB localization failure during surgery.[3,35-38] In our series, we achieved a high SLNB localization rate of 97.4% without the routine use of preoperative lymphoscintigraphy, hence we believe it is unlikely to affect the localization rate.

Surgeons' learning curves and lack of experience has been shown to be another predictor of SLNB localization failure during surgery in some studies, although the definition of sufficient experience has been variable.[35,39-43]

Oncological Safety

The false negative rate (FNR) for dual techniques is reported as 5% to 10%.[6,43,44] A systematic review has concluded that although identification is higher with dual tracer, the FNR is the same.[45] This translates to low axillary recurrence rates.[46] Without performing an ALNC we could never establish if the FNR for isotope-only SLNB is better, worse or equal to that for dual technique. However, axillary recurrence rates and disease-free survival are the clinically relevant end points and high localization rates are likely to be a surrogate for low FNR.[47]

We have, therefore, reported on oncological outcome with a median follow-up of more than 5 years (63.5 months) and shown a low axillary recurrence rate for the isotope-only patients (3/353, 0.84%) comparable to similar large studies of SLNB.[48-51]

Dual technique is standard practice for SLNB post-NACT but the reports advising this were not published until 2013.[25] In our cohort we did not use blue dye in any of the patients and we recorded only 1 axillary recurrence in the 48 NACT patients.

Conclusion

Isotope-only SLNB has a high localization rate and low axillary recurrence rate which suggests that clinically relevant nodal disease has not been overlooked. Our study confirms that isotope-only SLNB is a feasible and safe alternative to dual isotope and blue dye technique and spares the majority of patients the risk of blue dye adverse reactions.

Clinical Practice Points

- Isotope only SLNB has similar localization rates to dual-tracer technique and can spare allergic/adverse reactions associated with administration of blue dye.
- Isotope only SLNB has low axillary recurrence rate, maintained after 5 years of follow up.
- These findings suggest it is a feasible and safe alternative to dual blue dye/isotope localization.

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Disclosure

The authors have no conflicts of interest to report Part of this work has been presented as a poster at the Association of Breast Surgery Annual Meeting, Belfast 2018 and published in abstract form.[1]

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