Original Article

A single centre experience in the use of superparamagnetic iron oxide as an alternative tracer in sentinel node biopsy in early breast cancer

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Background: Sentinel lymph node biopsy is now the recognised technique for staging of the axilla in early breast cancer. National Institute of Clinical Excellence, United Kingdom, guidelines advise the use of a dual technique in identifying the sentinel lymph node. However, national restrictions in the supply of Technetium^{99} have created a real problem in delivering this gold standard. We studied an alternative magnetic tracer (Magtrace®, Endolab) to use as an adjunct to Patent Blue dye (Guerbet Laboratories) in axillary staging.

Methods: In 2019–2021 all patients who received magnetic tracer as an alternative were identified using theatre list and unit database records. Retrospective data were collected from pathology reports to identify tumour size, grade, and type; axillary staging and if the nodes identified were: Magtrace® positive, blue or both.

Results: A total of 99 patients were identified using Sienna® (Endolab), Magtrace® and Patent Blue dye in their axillary staging. Complete records were identified in 99 patients. Eleven patients used Sienna® tracer and of these 2 were sentinel node biopsy (SNB) positive and 9 were negative, with all nodes hot and blue. 88 patients received Magtrace®. In combination, the sentinel node identification rate was 97.9% with a false negative rate of 3%. There were 2 cases of failure to identify a sentinel node and the average SNB harvest was 2.1 nodes.

Conclusions: This study suggests Magtrace® as a safe alternative to radioisotope in dual technique SNB in early breast cancer.

Keywords: Breast cancer; sentinel node biopsy (SNB); Magtrace

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Introduction

Sentinel lymph node biopsy using dual radioisotope and Patent Blue dye remains the gold standard in intraoperative assessment of the axilla in early breast cancer (1).

However, difficulties exist in both the worldwide supply of Technetium^{99} (2) and its use in hospitals without an ARSAC license. With recent changes in delivery of breast cancer services, secondary to pressures from COVID-19,

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alternative locations for provision of breast cancer surgery have been necessary.

An alternative to radioisotope has been sought to overcome these difficulties, with promising results in the use of superparamagnetic iron oxide (SPIO) (3). The development of a small volume 2 mL of Magtrace® (with SPIO covered by carboxidextran) provides 56 mg of iron with a diameter of <60 nm. This small size allows for the faster migration to the Sentinel node.

Non-inferiority in both false negative rates and ease of use have been reported with Magtrace® and its predecessor Sienna®. Initial results from the Sunrise study (4) of 135 patients as well as both the SentimagIC trial of 148 and Asian retrospective audit of 328 patients (5) suggest the use of magnetic tracer as a safe alternative.

To confirm its use as a viable alternative, we performed a retrospective analysis of its use in all patients between Jan 2019 and Jan 2021 within a large district general hospital. We hypothesize that Magtrace® localisation is as effective as blue dye in the identification of the sentinel node.

We present the following article in accordance with the STROBE reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-24/rc).

Methods

All patients diagnosed with early breast cancer (T1–3, N0) who underwent a sentinel lymph node biopsy between January 2019 and January 2021 were identified from a unit database.

All patients were assessed with axillary ultrasound preoperatively and discussed as suitable for sentinel node biopsy (SNB) at multidisciplinary team meetings. All procedures were performed by a single surgical team. A review of patient notes including pathology reports and theatre notes was performed to identify all patients where a dual technique of Patent Blue dye and either Sienna® or Magtrace® were used. Pathology reports identified the successful localisation of a sentinel node and its method of identification: whether blue, magnetic tracer positive or both. The SNB was performed in combination with either mastectomy or breast conserving surgery. The intraoperative detection of the sentinel node was performed using Patent Blue dye and either 5 mL of Sienna® or 2 mL of Magtrace®, which were injected subdermally and retroareolar after induction of anaesthesia. Massage was performed for 5 minutes and identification of the sentinel node was performed using Sentimag®. In suitable patients a single incision was performed for both the breast and axillary surgery and the Sentimag® probe was used to assess the axillary bed, after removal of the sentinel node, to ensure all nodes were removed.

Statistical analysis

Data was collated on a Microsoft Excel database and P values were calculated using standard Chi Square and independent *t* test calculators.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval for this study was considered unnecessary by the Ethics Department in our Institution (Southern Health and Social Care Trust) as it was a retrospective study and no patient identifiable data was shared. Informed consent was also waived.

Results

A total of 99 patients were identified in the study; 98 female and 1 male. Eleven patients were administered Sienna® and 88 patients Magtrace® in conjunction with Patent Blue dye. The average age of patients was 59 years with a range from 32–80 years. The average tumour size was 25 mm with a range of 0.3 to 93 mm (Excel Software). Multifocality was present in 19%.

Forty-one patients (41%) had a mastectomy and sentinel node with 3 (3%) having a skin sparing mastectomy and immediate reconstruction. Of those undergoing mastectomy 27 patients (66%) had their surgery after the start of the COVID-19 pandemic and during a timeframe when restrictions were placed on reconstruction. Of the remainder, 5 patients (5%) had a central segmentectomy and 54 patients (54%) had breast conserving surgery with 13 Level 2 therapeutic mammoplasty and 41 level 1 wide local excisions. Of those having breast conserving surgery, 40% had a Magseed® inserted as their method of tumour localisation. Of the 41 mastectomies performed 7 were for ductal carcinoma in situ (DCIS) and 34 for invasive disease. With respect to tumour type, 70% of patients had ductal carcinoma and 19% had lobular carcinoma (see *Figure 1*).

Patent Blue dye was identified in 94.9% of sentinel nodes and magnetic tracer was identified in 91.9%. In combination, the sentinel node was identified in 97.9%

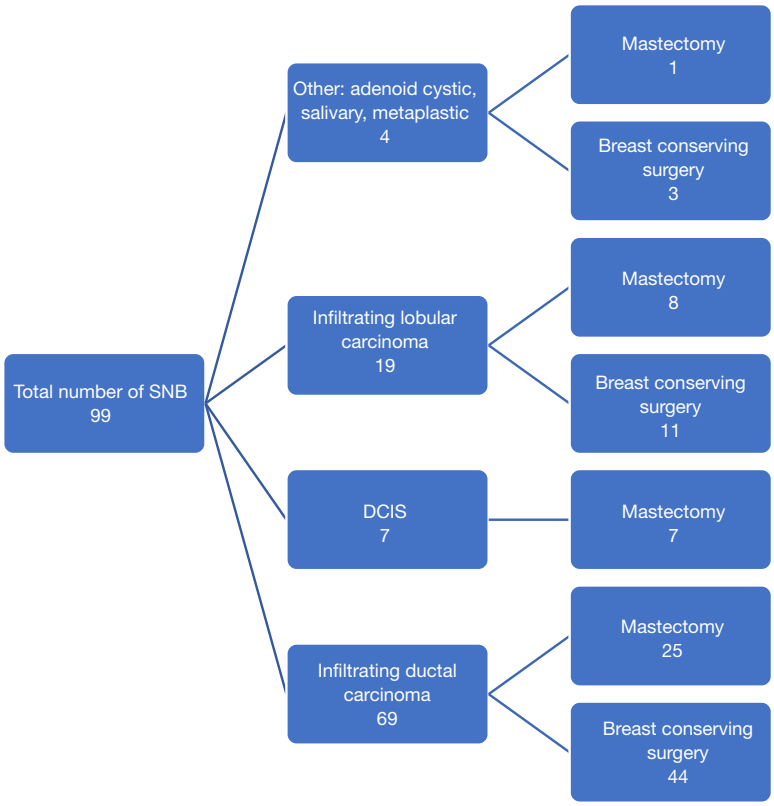

Figure 1 Distribution of excision by histological tumour type. SNB, sentinel node biopsy; DCIS, ductal carcinoma in situ.

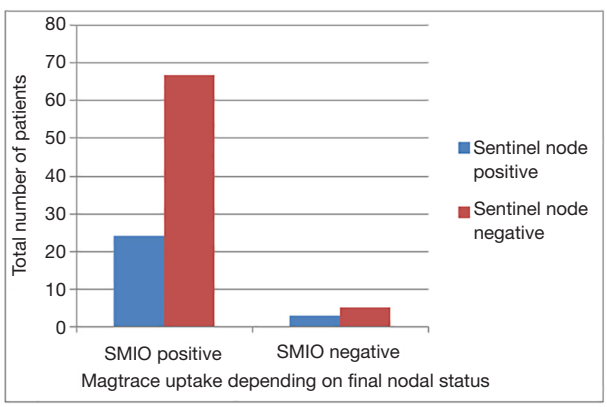

Figure 2 Negative predictive value of SPIO technique. SPIO, superparamagnetic iron oxide.

of sentinel lymph node biopsies. There was a failure to identify the sentinel node in 2.1% of patients. Both these patients had a mastectomy. In one case the axilla had a high nodal burden not picked up on ultrasound. An axillary node clearance was performed at the time of SNB and 12 out of 21 nodes were positive with extranodal extension. In the second case there were multifocal tumours and 2 out of 6 nodes were positive in the nodal sample.

In 3 cases, where the blue dye did not identify the sentinel node, the node was positive for magnetic tracer. In 4 out of a total of 5 cases where blue dye did not travel the SNB was in conjunction with a mastectomy. In only 3 cases the node was negative for magnetic tracer and was involved with cancer spread, giving a false negative rate of 3% (see *Figure 2*).

On average, 2.2 nodes were sampled at time of SNB and 25% of all SNBs were node positive (25 patients). Within the node positive cohort the average tumour size was larger at 32 mm with a range of 10.5–72 mm. The median grade was 2 with 48% grade 2 and 44% grade 3. A basal phenotype, i.e., grade 3 infiltrating ductal carcinoma which was triple negative, was associated with 20% of those positive on sentinel node. Given the incidence of triple negative breast cancers as 15% of all breast cancers (6) this would suggest TNBCs as a more aggressive tumour subtype although P=0.71 (see *Figure 3*).

There were no reported unexpected significant adverse reactions to the combined tracers.

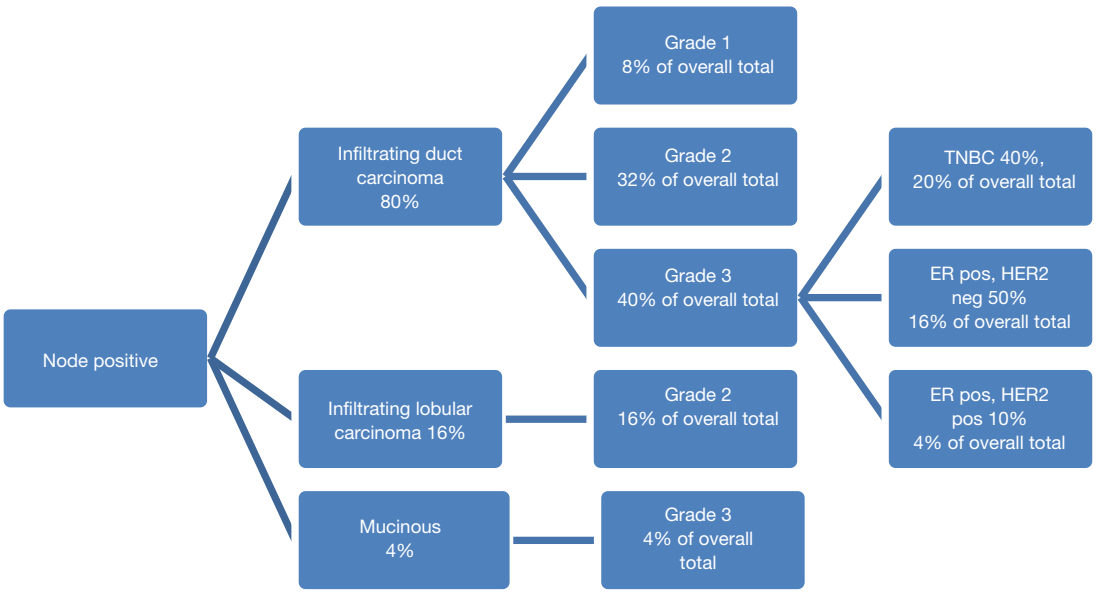

Figure 3 Distribution of node positive cases by tumour characteristic. TNBC, triple-negative breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; pos, positive; neg, negative.

Discussion

The study shows that sentinel lymph node identification using dual modalities is still superior to a single tracer technique with an improvement in sentinel node identification of 3%. The use of dual technique allows a 97.9% identification of sentinel node compared to only 94.9% using blue dye alone. This improvement in localisation highlights the benefit of a dual technique and allows an alternative to radioisotope in a centre where it is not available.

In introducing any new technique, the accuracy and therefore the false negative rate is important. In this series, the false negative rate was 3% for SPIO and 2% for combined dual technique. This is favourable when compared to radioisotope Technetium^{99} studies where a recent meta-analysis of 9,000 patients reported a false negative rate of 7.4% for radioisotope alone and 5.9% for the dual technique (7).

Of the 11 patients where Sienna was used as a tracer they all demonstrated nodes positive for blue dye and tracer. Given the small sample size of this cohort a P value of significance is not possible.

Analysis of the 25% node positive patients demonstrated a significant difference in tumour size compared with the node negative population (32 mm, 25 mm; P=0.0107 *t*-test). This would correlate with the already described prognostic value of tumour size in predicting nodal status (8). This is further supported by the fact that both cases where a SLN was not identified were both in mastectomies with a larger tumour size.

We used a Magseed® in 22% of cases and in 40% of breast conserving surgery. We did not experience any difficulty in the use of Magseed® and Magtrace® concurrently but where the Magseed® was placed in the periareolar region a decision was made preoperatively by the multidisciplinary team, to avoid the use of SPIO tracer.

Previous studies have highlighted skin staining with SPIO and have reported rates of 67% with periareolar injection (4). We certainly found cases where staining was noticeable but did not have this as an endpoint during this study. Further use of patient-reported outcome measures should be utilised to quantify the impact this has on patients. Ongoing studies into peritumoral injection of the SPIO are predicted to address this issue (9).

Use of SPIO intra-operatively along with Patent Blue dye reduces need for interventions prior to surgery, avoids difficulties associated with the handling and disposal of radioactive specimens and facilitates the organisation and fluidity of theatre lists with a potential reduction in delays.

Conclusions

We believe that, given the impact of COVID-19 on the

delivery of breast cancer surgery, the use of SPIO is a safe and reliable technique in the breast surgeon's toolkit to facilitate delivery of service in centres not equipped to utilise radioisotopes.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://abs.amegroups.com/article/view/10.21037/abs-21-24/rc

Data Sharing Statement: Available at https://abs.amegroups.com/article/view/10.21037/abs-21-24/dss

Peer Review File: Available at https://abs.amegroups.com/article/view/10.21037/abs-21-24/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://abs.amegroups.com/article/view/10.21037/abs-21-24/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval for this study was considered unnecessary by the Ethics Department in our Institution (Southern Health and Social Care Trust) as it was a retrospective study and no patient identifiable data was shared. Informed consent was also waived.

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