Role of Combined Sentinel Lymph Node Biopsy and Axillary Node Sampling in Clinically Node-Negative Breast Cancer

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Abstract Axillary lymph node status is a prognostic marker in breast cancer management, and axillary surgery plays an important role in staging and local control. This study aims to assess whether a combination of sentinel lymph node biopsy (SLNB) using patent blue dye and axillary node sampling (ANS) offers equivalent identification rate to dual tracer technique. Furthermore, we aim to investigate whether there are any potential benefits to this combined technique. Retrospective study of 230 clinically node-negative patients undergoing breast-conserving surgery for single T1–T3 tumours between 2006 and 2011. Axillae were staged using a combined blue dye SLNB/ANS technique. SLNs were localized in 226/230 (identification rate 98.3 %). Three of one hundred ninety-two patients with a negative SLN were found to have positive ANS nodes and 1/4 failed SLNB patients had positive ANS nodes. Thirty-four of two hundred twenty-six patients had SLN metastases and 11/34 (32.4 %) also had a positive non-sentinel lymph node on ANS. Twenty-one of twenty-four (87.5 %) node-positive T1 tumours had single node involvement. Nine of thirty-eight node-positive patients progressed to completion axillary clearance (cALND), and the rest were treated with axillary radiotherapy. Axillary recurrence was nil at median 5 year follow-up. Complementing SLNB with axillary node sampling (ANS) decreases the unavoidable false-negative rate associated with SLNB. Appropriate operator experience and technique can result in an SLN localization rate of 98 %, rivalling a dual tracer technique. The additional insight offered by ANS into the status of

non-sentinel nodes has potential applications in an era of less frequent cALND.

Keywords Sentinel lymph node biopsy · Breast cancer · Axillary node clearance · Axillary node sampling

Introduction

The status of the axillary lymph nodes is a crucial prognostic marker in breast cancer management. Consequently, axillary surgery plays an important role in both staging and local control.

Traditionally, a complete axillary lymph node dissection (cALND) constituted the gold standard in axillary surgery; however, associated morbidity and the emergence of sentinel lymph node biopsy (SLNB), as a validated staging investigation in breast cancer, have led to reservation of cALND as a follow-on therapeutic procedure for patients with positive sentinel lymph nodes (SLNs).

Following the acceptance of SLNB as a standard of care, increased research has been conducted to consider the significance of a positive SLNB, whether this be macrometastases, micrometastases or isolated tumour cells and the likelihood of further positive axillary nodes. Predicting the likelihood of further positive SLN would allow an individualized approach by targeting patients who will benefit from further therapeutic axillary interventions in the form of surgery or radiotherapy. Various prediction models have been described as well as novel imaging techniques. These have not been translated into routine clinical practice. A new question under consideration is whether there is sufficient evidence to implement a change towards non-surgical management and avoid the use of cALND in cases of ‘early’ clinically node-negative breast cancer who have low nodal disease burden on SLNB.

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Background

Sentinel lymph node biopsy is generally regarded as being a safe and accurate technique for axillary staging. A number of cohort studies and subsequent randomized control trials have demonstrated a comparable overall survival, disease-free survival and locoregional recurrence with routine axillary dissection [1, 2]. The false-negative rate of SLNB has been shown to range from 0 to 10.7 %; however, decreasing rates have been reported with increased operator experience [3]. Experience can reduce the false-negative rate, but some are intrinsically related to lymphatic anatomy and/or its response to neoplastic disease burden [4]. Both the American Society of Clinical Oncology (ASCO) and the National Institute of Health and Clinical Excellence (NICE) recommend using a minimally invasive approach with SLNB in staging clinically negative axillary lymph nodes, preferably using a dual tracer (blue dye and radio isotope) technique [3, 5].

Axillary four-node sampling (4-NS) is another less invasive axillary staging technique, which comprises identification via direct palpation and excision of four nodes from level 1 [6, 7]. Fewer studies have been conducted to evaluate axillary sampling in clinically node negative early breast cancer; however, the technique is popular in centres where blue dye is not always commercially available or equipment/training to allow radioisotope SLN localization is lacking [7–9]. Low cost is paramount in some centres; however, the technique need not be inferior; ANS detection rates can be comparable with single tracer techniques [9].

This study aims to assess whether a combination of SLNB using patent blue dye and axillary node sampling (ANS) offers equivalent identification rate to dual tracer technique. Furthermore, we aim to investigate whether there are any potential benefits to this combined technique.

Methods

The study group comprised 230 consecutive patients treated with breast-conserving surgery (BCS) performed by a single surgeon between 2006 and 2011. All patients presented with clinically node-negative, single tumour, breast cancers stage T1a to T3. Axillae were assessed with a combination of clinical and ultrasound examination. Ultrasound-guided fine needle aspiration cytology of lymph nodes was introduced in 2010. Both palpable and impalpable breast lesions were included; impalpable tumours were identified pre-operatively via fine wire localisation and/or US black dot marking. Most procedures were performed as day cases (patient preference and co-morbidity allowing). Neither breast nor axillary drains were used.

A single tracer technique was used to identify the SLN. Following induction of general anaesthesia, 2 mL of blue tracer dye (sodium patent blue V 2.5 % injection,

Laboratoire Guerbet, Villepinte, France) was injected under the dermis of the areola in the quadrant corresponding with the tumour location. The area was briefly massaged for approximately 1 min. Ten minutes following injection (i.e. time for preparation of aseptic operative field and surgical scrub), the axilla was accessed using a low axillary skin crease incision. All blue-stained lymph nodes were excised and labelled as sentinel nodes. Identification and excision of further lymph nodes from level 1, via direct palpation or visualization, comprised the axillary sampling (ANS), until a minimum of four nodes (including the sentinel nodes) were excised.

Histopathological examination of specimens was performed according to RCPATH UK guidelines. Specimens were embedded and processed in 2-mm-thick slices with haematoxylin and eosin staining. Conventional microscopic examination of haematoxylin and eosin (H&E)-stained tissue sections was performed. Immunohistochemistry to detect isolated tumour cells was not routinely performed.

Each case was subsequently discussed at the weekly multidisciplinary team meeting. Although regional guidance prior to 2011 for the study unit was to consider cALND with any evidence of micro- or macrometastases following SLNB, cALND was usually reserved for patients with positive nodal disease and T3, grade 3, ER-negative or HER2-positive tumours. Adjuvant radiotherapy was given within 6–8 weeks following surgery in accordance with dosage recommendations provided by the North of England Cancer Network [10]. Patients requiring no therapeutic axillary intervention received isocentric 3D planned tangential field whole breast irradiation of 40 Gy in 15 divided fractions over 3 weeks. Women under the age of 40 or >40 years old with a resection margin of <3 mm were given a tumour bed boost of 10 Gy in five fractions over a week. Titanium clips were placed at the time of surgery in the excision bed to ensure accurate delivery of the radiotherapy boost. Patients with one or two positive sentinel or axillary sampling nodes (micro- or macrometastases) were given levels I and II axillary field as well as whole breast irradiation. This consisted of 50 Gy in 25 fractions over 5 weeks. Adjuvant endocrine therapy in the form of letrozole 2.5 mg once daily was given in ER-positive cases. Adjuvant anthracycline containing polychemotherapy was given if indicated. Tools such as Adjuvant Online were used to guide the decision process. All patients with HER2-positive breast cancer with tumour size >1 cm were referred to the medical/clinical oncologist for discussion of adjuvant chemotherapy followed by trastuzumab (Herceptin).

Results

All 230 patients were women aged 32–83 years old (mean 60.2, median 61, SD 8.59); 187 patients were identified by

the NHS Breast Screening Programme (NHSBSP) and 43 patients were symptomatic referrals to the outpatient clinic. Table 1 illustrates patient demographics.

One hundred eighty-eight tumours were stage T1, 36 T2 and 6 T3 (Table 1). SLNs were localized in 226 patients; therefore, the sensitivity of blue dye for SLNB is 98.3 %, which is equitable to the identification rate of 97 % shown by the AMAROS trial using a combination approach of blue dye and radioisotope [11]. Three of one hundred ninety-two patients with a negative SLN were found to have positive macrometastatic axillary sampling nodes (Table 2). This equates to a false-negative rate of 8.1 % and negative predictive value 98.4 %. One of four patients who failed SLN localization had positive macrometastatic axillary sampling nodes. Axillary sampling improved staging accuracy in 7/230 patients: 3 patients with negative SLNB had positive axillary sampling nodes and 4 patients who failed SLN identification were still able to undergo axillary staging.

The mean number of SLNs harvested was 1.9 (median 2, range 0–7); mean number of axillary sampling nodes was 4 (median 4, range 0–9) and mean number of total nodes—sentinel and sampling—excised was 5.9 (median 6, range 4–9). The mean number of total nodes excised was higher than

intended probably because more than one node can be present in a specimen.

Thirty-four of two hundred twenty-six patients with successful SLN localization had SLN metastases (Table 3). Eleven of thirty-four (32.4 %) of these patients were also found to have a positive axillary sampling node. In 23/34 (67.6 %) patients with positive SLN, further axillary sampling did not show any additional axillary disease.

No positive SLN was found in tumours <5 mm (T1a). A positive SLN was present in 3 tumours 5–10 mm in size (T1b), 20 tumours 10–20 mm in size (T1c), 7 tumours 20–40 mm and 4 tumours >40 mm in size (Table 4). Considering 38/230 patients with node positive disease, 28/38 (74 %) had only one node involved. Twenty-one of twenty-four (87.5 %) of node-positive T1 tumours had single node involvement.

Nine of thirty-eight node-positive patients progressed to cALND, and only 3/9 were found to have further positive axillary nodes (Table 5). The remaining 29/38 were treated with additional levels I and II axillary field irradiation. In January 2014, after a median follow-up of 5 years, a review of outcomes of lymph node-positive disease patients treated with axillary radiotherapy was conducted: 2 patients had a same-side local tumour recurrence within 12 months, and 1 patient developed contralateral disease. No patients developed axillary or distant metastatic recurrent disease.

Table 1 Population demographics/tumour characteristics

Age	
30–40	3
41–50	25
51–60	82
61–70	105
71–80	12
80+	3
Tumour grade	
Grade I	58
Grade II	102
Grade III	68
Mixed/ungraded	2
Tumour stage	
T1a	13
T1b	70
T1c	105
T2	36
T3	6
Hormone receptor status	
ER positive	184
ER negative	44
Unrecorded	2
HER2 status	
HER2 positive	37
HER2 negative	188
Unrecorded	5

Discussion

Axillary treatment is evolving due to early evidence that cALND may no longer be necessary in clinically node-negative T1 or T2 tumours with less than three positive sentinel lymph nodes [12]. The 2013 St. Gallen consensus supports avoidance of cALND in clinically node-negative patients with 1–2 macrometastatic sentinel nodes operated with breast conservation and receiving tangential field adjuvant radiotherapy [13].

The American College of Surgeons Oncology Group Z0011 trial provides indication that cALND may no longer be clinically justified in T1-2 breast cancer, as low locoregional recurrence rates were demonstrated with breast-conserving surgery, breast radiotherapy and adjuvant systemic therapy alone [14]. Use of cALND in micrometastatic disease has also been questioned [14, 15]. The study, which randomly assigned patients with SLN-positive breast cancer to SLN biopsy and ALND or to SLN alone, reported that ALND was not associated with any survival benefit and that both groups had an extremely low regional recurrence rate (0.9 % for SLN alone and 0.5 % for ALND). This was despite the fact that 27.3 % of the patients who received ALND had additional positive non-sentinel lymph nodes. Issues with the Z0011 trial have been well documented and encompass the statistical design, statistical interpretation, failure to accrue adequate

Table 2 Pathological findings in patients with nodal disease but negative/non-identifiable SLN

	Stage	Grade	ER	HER2	No. of negative sentinel nodes	No. of non-sentinel nodes	No. of positive non-sentinel nodes
Patient 1	T1b	2	Positive	Negative	1	3	1
Patient 2	T2	3	Negative	Negative	1	5	2
Patient 3	T2	3	Negative	Positive	2	8	5
Patient 4	T2	2	Negative	Positive	0	5	3

patients and missing data [16, 17]. It is noteworthy that low accrual was a consequence of a lower than expected event rate in both arms. The time necessary to accrue the patients in order to fulfil the power calculation would have taken many years, rendering the trial impractical [17]. Another concern pertains to the type of irradiation patients received and difficulties in ascertaining homogeneity across the group. Whilst direct nodal irradiation was forbidden, the irradiation field could be modified to include low axillary regions in patients who did not have cALND. This could represent a source of bias and explain the low regional recurrence rate in the SLNB group. Axillary nodal disease burden was also low with 40 % patients having micrometastatic disease or isolated tumour cells (the exact breakdown is not given).

The IBCSG Trial 23-01, a non-inferiority trial, compared axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases. It randomized 931 patients with tumours less than 5 cm and one or more micrometastatic (<2 mm) SLN into axillary and no axillary dissection. Low accrual and lack of statistical power was again noted; however, results have to be interpreted within the confines of real-world clinical practice. The primary tumour was treated with either mastectomy or breast-conserving surgery, with 91 % of patients undergoing BCS. Patients undergoing BCS received a combination of ELIOT intra-operative tumour bed irradiation (27 %) or post-operative tangential field whole breast irradiation. Twelve percent of cALND patients had at least one further positive node. Twenty-two percent of patients who did not receive cALND either did not have any radiotherapy (3 %) or received ELIOT partial breast irradiation which does not irradiate the axilla (19 %), henceforth does not ‘treat’ potential residual nodal disease. In spite of this discrepancy, results showed no significant difference in either disease-free

(DF) or overall survival (OS) at a median of 5 years follow-up [18, 19]. Higher morbidity was observed in the cALND group consistent with previous findings.

A recent systematic review proposed to assess the role of axillary interventions in breast cancer treatment with regard to recurrence of axillary node metastases, mortality and morbidity [13]. It comprised 17 randomized controlled (RCTs) and non-randomized trials that reported on oncological outcomes after axillary surgery or radiation for breast cancer. RCTs needed to have at least 2 years follow-up; non-randomized trials needed to have at least 2 years follow-up in at least 50 % of patients. Most studies were conducted in patients with clinically impalpable axillary nodes. Treatment modalities varied and included mastectomy, breast-conserving therapy, axillary lymph node dissection, whole breast irradiation and tamoxifen. cALND in patients with no palpable lymph nodes compared with sentinel node biopsy gave no survival benefit and was associated with a 1 to 3 % reduction in recurrence of axillary node metastases but an increased risk of lymphoedema (14 % compared to 5 to 7 % for biopsy). The authors concluded that there was little evidence of benefit from surgical cALND compared with SLNB alone in patients with clinically node-negative breast cancers <3 cm who had up to three positive SLNB. It was recommended that physicians should tailor axillary lymph node interventions to maximize regional disease control and minimize morbidity. The papers were not quality assessed and included non-

Table 3 Distribution of number of positive sentinel lymph nodes

Number of positive sentinel nodes	Number of patients
1	27
2	6
3	1
Negative	192
No. of SLN	4

Table 4 Tumour characteristics in patients with positive SLNB

Grade I	6
Grade II	15
Grade III	13
T1a	0
T1b	3
T1c	20
T2	7
T3	4
ER positive	28
ER negative	6
HER2 positive	6
HER2 negative	27
Unrecorded	1

Table 5 Pathological findings in patients who underwent cALND

	Stage	Grade	ER	HER2	No. of SNs (positive/total)	No. of axillary sampling nodes	No. of nodes on cALND
Patient A	T3	II	Positive	Negative	1/1	0/4	1/3
Patient B	T1c	II	Positive	Negative	1/1	1/4	0/6
Patient C	T1c	II	Positive	Positive	1/1	0/5	0/24
Patient D	T3	III	Positive	Negative	1/1	4/6	0/9
Patient E	T3	III	Positive	Negative	1/3	0/5	0/unknown
Patient F	T2	II	Positive	Negative	2/3	0/4	2/18
Patient G	T1b	III	Negative	Positive	3/3	1/4	0/7
Patient H	T3	III	Positive	Negative	2/2	5/5	11/12
Patient I	T2	III	Negative	Negative	0/1	2/5	0/8

randomized studies. A meta-analysis was not undertaken although it may have been possible to do so with inclusion of subgroup analyses for the different interventions. The lack of quality assessment and of statistical pooling renders the conclusions uncertain.

Although the findings of the abovementioned studies have not been adopted into routine clinical practice, the evidence does have important clinical implications [16, 17]. Whilst these studies are open to criticism due to either study design, lack of statistical power, potential for bias or other mitigating factors such as heterogenous adjuvant chemo- and radiotherapy regimens, the presence of limiting factors cannot simply discredit the purported concept and emergence of increasing evidence that a subset of patients with SLN metastases may do well without cALND [20]. The issue is how best to target such cases. Several predictive nomograms have been devised but are not accurate enough to warrant clinical application [21–24]. Novel imaging techniques (e.g. nanoparticle MRI) have not reached clinical maturity [25]. The UK Positive Sentinel Lymph Node: Observation vs Clearance (POSNO) trial will be a logical sequel to Z0011 and IBCSG trial. It will randomly assign to observation only or cALND both patients who undergo breast-conserving surgery and those who undergo mastectomy with one or two sentinel lymph nodes containing macrometastases.

In the meantime, the right conclusion to draw from current studies is not that early T1–T2 breast cancer patients with low axillary nodal burden (1–3 positive nodes) do not need further treatment; rather, in such patients, it appears that a combination of systemic and axillary irradiation as part of the tangential field breast radiotherapy adequately ‘treats’ remaining nodal disease, therefore rendering cALND unnecessary. Axillary nodal disease is only a (potentially crude) surrogate marker for tumour behaviour which may be superseded by molecular and DNA profiling in the near future [26, 27].

Our data—which predates the publication of the cited studies—shows that avoidance of cALND in patients with early (T1–T2) breast cancer with 1–2 positive SLN, who are treated with BCS and whole breast/axillary radiotherapy, is safe.

None of our patients had axillary recurrence at a median follow-up of 5 years.

Post-mastectomy (PMRT) and supraclavicular fossa radiotherapy (SCFRT) depend on nodal status (>4 macrometastatic nodes). A recent report highlighted the potential risk of understaging patients who only have SLNB. In a case series of 38 clinically node-negative predominantly T1–T2 breast cancer patients who had positive SLN biopsy and went on to cALND, SLNB alone was shown to understage axillary disease and would have led to denial of PMRT and SCFRT in 23.7 % of patients [28]. A combination approach of blue dye sentinel lymph node biopsy and axillary node sampling (SLNB/ANS) is a potentially useful investigation to estimate the risk of additional positive nodes [7, 8]. Using ANS as an adjunct to SLNB provides additional insight into the status of the non-sentinel axillary lymph nodes and increases confidence in the safety of non-surgical management of axillae with positive SLN and, as a consequence, may be useful in preventing axillary understaging.

Appropriate injection and surgical technique using blue dye alone can ensure high detection rates which equal that of large series using dual tracer which has positive implications for countries where radioisotope is not generally available.

Limitations

The data set is from a single surgeon consecutive case series, although this does have added strength in terms of technical consistency. The single tracer SLN localization is higher than average; therefore, the ability of this study to compare a combined SLNB/ANS technique with a dual tracer technique is limited. However, 3 % of our study population had their axillary status upstaged or confirmed following failed or negative SLNB; therefore, if future multicentre/operator studies demonstrated a lower single tracer SLN identification rate, more concordant with previous evidence, perhaps the usefulness of ANS would be enhanced.

Previous studies have demonstrated clinically significant lymphoedema rates of 18 % at 5 years following cALND compared to 5 % following ANS [29]. Furthermore, non-surgically managed node-positive axillae received axillary radiotherapy, which has the potential for morbidity, although this is lower than cALND [30]. Data regarding health-related quality of life outcomes as a result of the combined SLNB/ANS technique remains observational, with no evidence of increased morbidity compared to sentinel node biopsy alone. An additional study of this patient group is underway to consider these outcomes more objectively. Further evidence (i.e. POSNOC trial), verifying the safety of treatment algorithms proposed by the Z0011 and IBCSG trials, may prove that axillary radiotherapy as well as cALND is an unnecessary overtreatment. However, as our data predates the publication of cited trials, non-surgical management with axillary radiotherapy of patients with 1–2 positive nodes seemed a cautious approach at that time.

Conclusion

Appropriate operator experience and technique can result in an SLN localization rate of 98 %, rivalling a dual tracer technique. Complementing SLNB with axillary node sampling (ANS) decreases the unavoidable false-negative rate associated with SLNB and may prove beneficial for less experienced operators. Also, the additional insight offered by ANS into the status of non-sentinel nodes has potential applications in an era of less frequent cALND.

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