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Sentinel lymph node biopsy experience in Taranaki: a prospective audit in a provincial New Zealand hospital

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Abstract

Aim Sentinel lymph node biopsy has been rapidly incorporated into the management of early stage invasive breast cancer. The aim of this study was to review the adoption of sentinel lymph node biopsy at a provincial centre in New Zealand and compare markers of performance against established standards.

Methods The Taranaki Breast Database was created in 2002 and prospectively records data from all breast cancer patients in the Taranaki area. Data on all patients undergoing sentinel lymph node biopsy were retrieved and the results reviewed.

Results Between October 2002 and August 2007, 152 sentinel lymph node biopsies were undertaken in 151 patients. The initial 49 patients (training set) also underwent routine axillary clearance as part of an initial audit on the accuracy of sentinel lymph node biopsy. A sentinel node was identified in 97% of patients (93% including the training set) and a mean of two nodes per biopsy were removed. Metastatic nodal disease was identified in 40 of 152 (26%) of biopsies of which nine were micrometastases. In the training set there was a false negative rate for nodal spread of 5% (two of 40) and a 92% negative predictive value.

Conclusions The performance of sentinel lymph node biopsy in Taranaki is comparable to international centres. Adoption of this technique as routine may spare many Taranaki women the morbidity of axillary clearance, without jeopardising safety.

Axillary lymph node status is considered the most important prognostic factor for patients with early stage breast cancer.[1] While axillary clearance is accepted as the gold standard in detection of metastatic nodal disease, sentinel lymph node biopsy (SLNB) is increasingly adopted as an alternative approach. Early research suggests that SLNB is a reliable method of predicting lymph node status, and may spare women the morbidity associated with axillary clearance.[2,3] Nonrandomised studies of SLNB followed by axillary clearance have demonstrated that one or more sentinel lymph node can be identified in more than 90% of patients with invasive breast cancer, with a false negative rate of less than 10%.[4,5]

In an era of increasing centralisation of surgical services, little published data exists on adoption of SLNB in peripheral centres. In Taranaki, a provincial New Zealand centre, SLNB techniques have been employed since 2002. This study aims to provide a prospective comparison of SLNB in Taranaki with established standards.

Methods

Eligibility and study design—All patients in the Taranaki region, with early stage operable breast cancer, confirmed histologically or radiologically, and requiring axillary staging as part of their surgical management are eligible for SLNB. Major exclusion criteria include tumour size greater than 5.0 cm in diameter, palpable axillary lymph nodes, failure to give consent, and previous axillary surgery. The initial training set (49 patients) has provided information about outcome measures. These 49 patients were included in the final data analysis (152 SLNB). Written informed consent was received from all patients prior to surgery.

Surgery and patient management—Sentinel node identification was performed by either the blue dye or scintigraphic techniques, or a combination, depending on surgeon preference and available equipment. All patients preparing for sentinel node biopsy received a Technetium 99 antimony colloid subcutaneous injection either the day of, or the day prior to surgery. The time between injection and surgery was at least 3 hours. Nuclear medicine staff identified the sentinel node on lymphoscintiscan and marked its location on the skin. In the operating room, 2 ml of patent blue dye in 0.5 ml aliquots were injected immediately after the induction of anaesthesia.

Prior to June 2006 four peritumoural injection sites were used both for technetium and blue dye injections (51 patients). Since June 2006, injection sites have been periareolar. SLNB was performed prior to tumour resection or mastectomy, and nodes that were hot (at least 10 times background activity), or blue were removed. Wide local excision or mastectomy was then performed in the usual manner. In a single case, the sentinel lymph node was sent as a frozen section for immediate cytological examination. This patient underwent immediate axillary clearance for a positive SLNB. If no sentinel lymph node was identified, an immediate axillary clearance was undertaken.

Patients in the training set underwent immediate axillary clearance (level I and II nodes). Patients in the non-training set underwent axillary clearance only if the SLNB was positive or not obtained. All patients were otherwise treated identically.

The Taranaki Breast Cancer Database—This computerised database was established in 2003 as a collaborative effort of the specialist breast care nurse, general surgical consultants, and information systems staff. It is a data storage system which categorises data on patient characteristics, risk factors, diagnostic methods, tumour characteristics, axillary status, surgical procedures, and adjuvant therapy. All patients in Taranaki with histologically or cytologically confirmed breast cancer are entered into the database on a prospective basis. Confidentiality is maintained at all times.

Pathological aspects—Each sentinel LN is submitted in its entirety in approximately <5 mm portions per cassette. Each cassette specimen is then sectioned into five levels (3 micron width) to be examined. One of these levels is stained with a pancytokeratin AE1/AE3, the others with haematoxylin and eosin (H&E).

Results

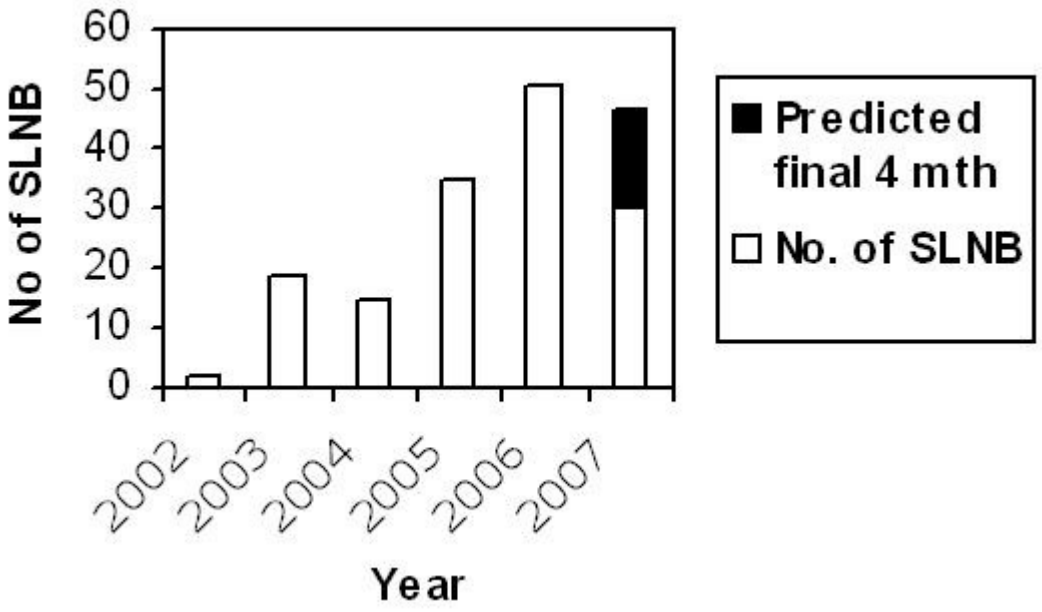
Between October 2002 and August 2007, 152 SLNB were undertaken in 151 patients. Of these, almost half were performed by one surgeon (Table 1).

Table 1. Sentinel lymph node biopsy (SLNB) by surgeon between October 2002 and August 2007

Surgeon	Number of SLNBs	Proportion of SLNBs
A	78	48%
B	48	29%
C	20	12%
D	18	11%

From initiation in 2002, the number of SLNB performed per year has steadily increased. This trend seems to have reached a plateau in 2006, with around 50 SLNB per year (Figure 1).

Figure 1. Number of SLNBs per year performed in Taranaki



The overall identification rate for SLNB was 92.7%. When analysed separately, the identification rate for non-training cases was 97.1%, and for training cases was 83.7%, indicating a sharp increase in identification rates pre and post training. An average of 2.0 nodes per SLNB were removed, with a range of 0–15.

In 70 (46%) cases, surgical technique involved preoperative lymphoscintigraphy and intraoperative use of the gamma probe alone. In 8 (5%) cases blue dye alone was used. These cases occurred when a functional gamma probe was not available, or when nuclear medicine staff were unavailable to perform lymphoscintigraphy. In 74 (49%) cases both blue dye and lymphoscintigraphy with intraoperative use of the gamma probe were employed.

Of the 152 SLNBs attempted, 141 were successfully identified with 11 failures (7.2%). Of the 141 successful biopsies, 40 (26.3%) were positive and 100 (65.8%) negative for nodal malignancy. The positive biopsies can be further subdivided into 9 biopsies positive for micrometastases only, and 31 positive for macroscopic malignancy. One specimen was lost prior to histological examination.

The test performance measures for SNB are available for the training case data and are summarised in Table 2. They indicate a sensitivity of 75% (6 of 8), a false negative rate of 5% (2 of 40) and a negative predictive value of 92% (23 of 25). Individual surgeon test performance is demonstrated in Table 3. The lost SLN was picked up from theatre, but never arrived at the labaratory. An internal investigation was conducted but failed to locate the node.

Table 2. Test performance measures for sentinel lymph node biopsy in Taranaki (training cases only, n=40)

Sentinel node status	Axillary lymph node status		
	Cancer	No Cancer	Total
Positive	6	9	15
Negative	2	23	25
Total	**8**	**32**	**40**

Table 3. Individual Taranaki surgeon test performance

Surgeon	A §	B	C	D
Training cases †	18	20	10	1
Mentored cases ‡	–	5	4	4
SLNB identification rate	89%	75%	90%	100%
SLN not identified	2	5	1	0
SLN lost	1	0	0	0
No. of false negatives	1	1	0	0
Positive axillary clearance	4	3	0	0
False negative rate (% of positive axillae)	25%	33%	0%	0%
False negative rate (% of total cases)	5.5%	5%	0%	0%

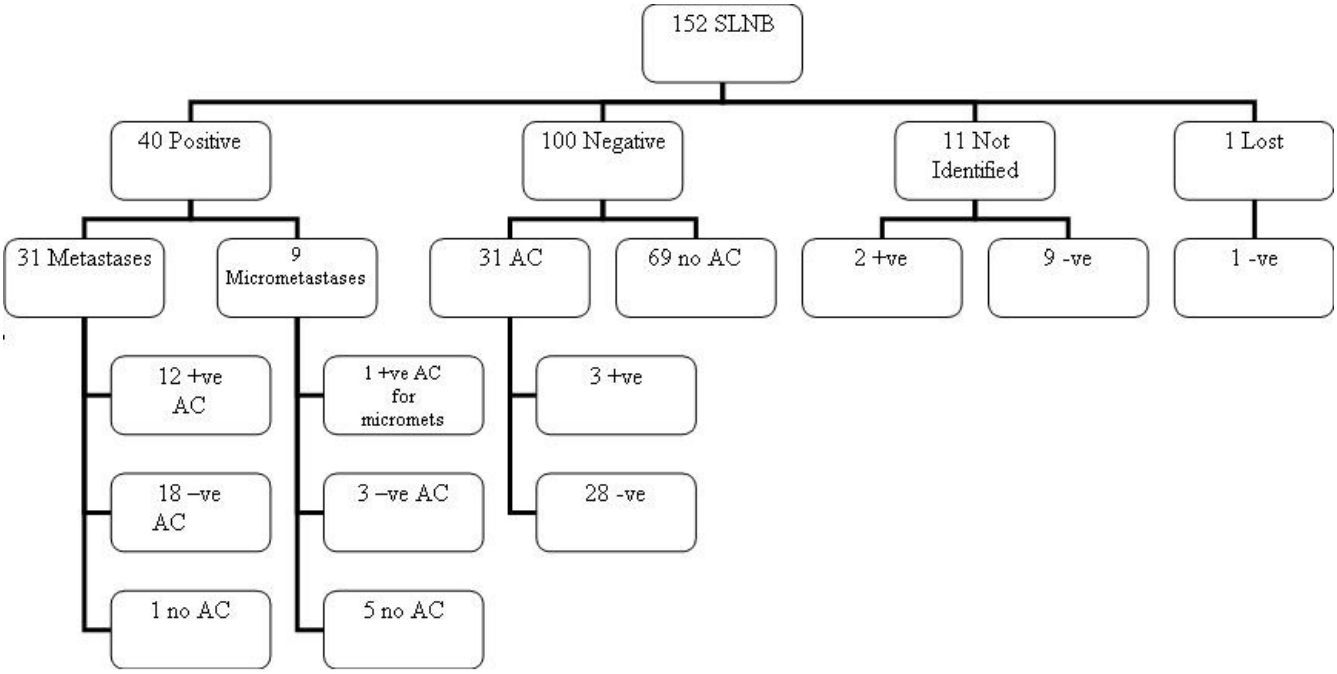
† Cases where SLNB was combined with routine axillary clearance; ‡ cases performed under mentor guidance from Surgeon A; § surgeon A attended a formal training course in 2002; SLNB=sentinel lymph node biopsy; SLN=sentinel lymph node.

Of the 152 cases of SLNB, axillary clearance was performed in 77 (50.7%). This includes the 49 training cases who underwent routine axillary clearance. The indications for axillary clearance are summarised in Figure 2. An average of 13 nodes were removed (range 1–25) with an average of 5 positive nodes (range 0–17).

Eighteen (23.4%) of 77 axillary clearances were positive: 1 for micrometastases only and 17 for invasive metastases. Results are summarised in Figure 2. One patient had a positive SLNB (two of six nodes) but declined further surgical treatment.

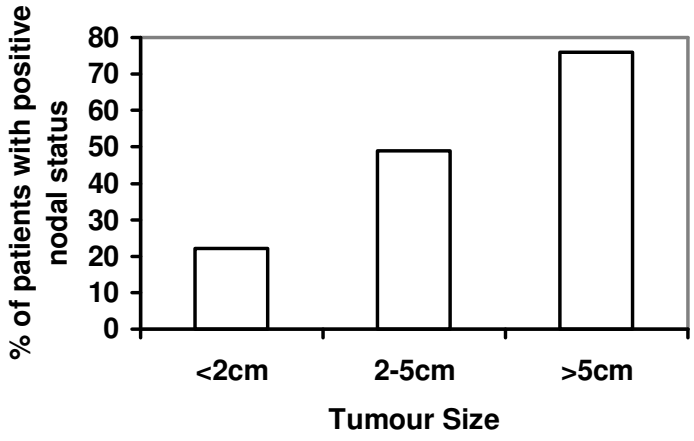
Average tumour size was 2.8 cm. 86 patients (59%) had tumours ≤2.0 cm, 57 patients (39%) had tumours >2.0cm but ≤5.0cm, and 4 patients (3%) had tumours >5.0 cm. Of the four patients with tumours >5.0 cm, all were reported to have tumours estimated at <5.0 cm in preoperative radiological reports. Increasing tumour size correlated with an increased likelihood of positive nodal status (Figure 3).

Figure 2. Indication and results for axillary clearance performed following SLNB in Taranaki between 2002 and October 2007



AC=Axillary clearance; SLNB=sentinel lymph node biopsy; micromets=micrometastases; +ve=positive; –ve=negative.

Figure 3. Predicting nodal status based on tumour size



Histology results showed a predominance of invasive ductal cell carcinoma, with or without an *in situ* component, (n=114 cases [81%]). Invasive lobular carcinoma was diagnosed in 16 (12%), ductal cell carcinoma *in situ* alone in 9 (6%). Single cases of

adenomyoepithelioma, medullary carcinoma, and invasive papillary carcinoma were also reported.

Using the modified Bloom-Richardson cytological grading system, tumour grade was reported for 147 cases. Of these, 65 (44%) were diagnosed as grade 1 tumours, 44 (30%) grade 2, and 38 (28%) grade 3.

Of the nine patients with SLNB positive for micrometastases only, six had micrometastases >0.2 mm, two had micrometastases ≤0.2 mm and one did not have size stated in the pathology report. Management of micrometastases is summarised in Table 4.

Table 4. Management of micrometastases in Taranaki compared to American Society of Clinical Oncology (ASCO) guideline recommendations[6]

Patient	Size of micrometastases (mm)	Axillary clearance performed	Axillary clearance recommended
1	1.5	Yes	Yes
2	0.9	No	Yes
3	0.5	No	Yes
4	1.5	Yes	Yes
5	<0.2	No	No
6	0.28	Yes	Yes
7	0.6	No	Yes
8	Size not stated	Yes	–
9	0.2	No	No

Note: For patients 2 and 3, management decisions were made prior to the publication of ASCO guidelines. For patient 7, the decision not to proceed to axillary clearance was multifactorial, and included patient age, comorbidities, and reluctance for further surgery.

Ten patients who underwent SLNB had ductal carcinoma *in situ* (DCIS) alone on final histology results. Of these 10 patients, 6 underwent mastectomy. Of the remaining 4, 2 underwent wide local excision (WLE) for known DCIS with a possible invasive component on biopsy, and 2 underwent WLE for DCIS only on biopsy.

Discussion

Taranaki is a provincial New Zealand centre staffed by four general surgical consultants, who serve a population of just over 100,000. All four surgeons regularly perform SLNB as part of management of patients with early stage breast cancer.

151 patients underwent 152 SLNB over a period of almost 5 years. The numbers of SLNB increased steadily over the first 3 years after introduction of the technique, and now seems to be levelling off at around 50 procedures per year. This equates to one SLNB per 2000 population.

Initial patient accrual was slow, with potential patients being managed by any of the four general surgeons who adopted the technique at differing dates throughout 2002 and 2003. The introduction of SLNB at Taranaki followed the attendance of one general surgeon, Surgeon A, at a formal SLNB training course in 2002. Adoption of the technique by the remaining three surgeons was mentored by Surgeon A.

None of the remaining three surgeons attended a formal course in the technique as recommended by the ASCO Guidelines for SLNB in early stage breast cancer.[6] However, prior research has failed to identify a statistically significant difference in false negative rates among surgeons who have undertaken a formal training course and those who have not.[7]

The use of mentoring, proctored cases and formal training in accredited continuing medical education courses is thought to reduce the personal case experience necessary to achieve optimal results, but this effect has yet to be quantified.

Accumulated data from many multi-centre trials continues to support the need to perform 20 cases of SLNB in combination with axillary dissection, or to perform 20 SLNB procedures with mentoring, as being necessary to minimise the risk of false-negative results.[5,7]

Among the four surgeons at Taranaki, the number of SLNB in combination with routine axillary clearance (AC) performed as test cases was highly variable (Table 3). Surgeons C and D, who performed fewer training cases, and did not attend formal training, are shown to have higher identification rates and lower false negative rates. However, this may represent a biased figure due to the small numbers of cases and of positive axillae for these surgeons.

There are two key parameters to successful SLNB: the successful identification rate and the false negative rate. Identification rate is defined as the proportion of patients in whom a SLN is identified and removed. For SLNB to be a useful test, it is essential that a SLN is identified in the majority (>90%) of patients. The overall successful identification rate in Taranaki is 93%. In non-training cases, the successful identification rate is 97%. This exceeds acceptable standards. It also identifies an expected initial learning curve.

The false-negative rate is defined as the proportion of patients with axillary nodal metastases who have a negative SLN biopsy. An acceptable false negative rate has been previously defined as 10% or less.[4,5] However, there is a problem with this calculation when a predetermined false negative rate of 10% is set, as there is no way of predicting the percentage of node positivity. If 25% of 40 cases are node-positive (10 cases), then a surgeon with only 1 false negative would have a false negative rate of 10%. However, a surgeon who has 50% node positivity in 40 cases (20 cases) will have the same false negative rate (10%) with 2 false negative cases.

To remove this bias, the false negative rate can be calculated as a percentage of the total number of patients rather than as a percentage of the positive axillae. This issue was addressed in the statement from the Consensus Conference Committee in Philadelphia.[8] This method of calculating false negative rate as a percentage of total cases was used in the ALMANAC trial validation phase, which assessed whether surgeons were competent to proceed to the randomisation phase.[9]

The false negative rate in Taranaki is 5% when calculated as a percentage of total cases. If calculated as a percentage of positive axillae, the false negative rate is 25%. The latter is an unacceptably high false negative rate, however (as explained above) it may represent significant bias.

A recent meta-analysis including more than 8000 patients showed that the reported false negative rate ranged from 0.0% to 29.4% across studies.[10] The false negative rate was significantly lower in the 23 studies that included >100 patients compared with the 46 studies that included <100 patients (p=0.007). Twenty-one studies (36.2%) reported a false negative rate >10%.

Janis, P et al[11] show that unobtainably large numbers of SLNB cases are required to make any reliable conclusions regarding the quality of SLNB. They calculate that it will take 750 patients with 300 tumor-positive basins to establish with 95% certainty that a surgeon who has a nonidentification rate of 5% and a false-negative rate of 5% indeed has these capabilities within a range of 0% to 7%. Therefore Taranaki's high false negative rate when calculated as a percentage of positive axillae may be secondary to bias due to small sample size and a small number of positive axillae.

We have chosen to accept the false negative rate of 5% as a percentage of total number of SLNB as a more accurate indicator of patient safety. This false negative rate is within established acceptable standards.

The inclusion and exclusion criteria for consideration of SLNB used in Taranaki may have affected test performance. In Taranaki, patients with tumour diameters up to 5.0 cm, including those with multifocal or multicentric disease, are included for SLNB. Many of the seminal reports on SLNB, including the recent Australasian Sentinel Lymph Node versus Axillary Clearance I (SNAC I) trial, only included patients with tumours <3.0 cm diameter and excluded patients with multicentric or multifocal disease.[12]

Currently accepted test performance standards, against which Taranaki's test performance measures have been compared, were set based on results from these early reports. Increasing evidence suggests that SLNB for tumours up to 5.0cm diameter (including multifocal and multicentric disease) is feasible with similar test performance measures as smaller, unifocal disease.[13,14] Indeed, the SNAC II trial, which follows on from the SNAC I trial has extended its inclusion criteria to include tumours >3.0 cm and those with multifocal or multicentric disease.

Initial reports of SLNB in breast cancer were based on a technique involving peritumoural injection of either radioactive colloid or blue dye. Subsequent experience has shown that subdermal,[15] intradermal,[16,17] and subareolar[18,19] routes of injection are associated with greater success and a comparable false negative rate to that associated with the peritumoural route. If indeed the same SLN is "sentinel" to the entire breast, then this SLN can be identified in cases of multicentric cancer by subareolar or intradermal injection.

Several small nonrandomised series in which such a approach was evaluated have demonstrated that the test performance of SLNB in multicentric or multifocal disease is similar to that for women with unifocal disease, suggesting that the technique can be applied in this setting.[20–22] Taranaki has chosen to include tumours up to 5.0 cm diameter and those with multifocal or multicentric disease for consideration of SLNB based on current literature. Although this may have affected the test performance measures, evidence suggests that including larger or multicentric tumours should not effect these.

Sentinel lymph node biopsy technique in Taranaki may have also affected both identification and false negative rates. There is now a substantial amount of evidence suggesting that the use of blue dye and radioactive colloid in combination as opposed to either method on its own, increases identification rates while minimising false negatives.[6,23] In Taranaki, the majority of SLNBs were performed using a single method only. Although this does not appear to have adversely affected the identification rate, it may be a contributing factor to the high false negative rate.

It remains unclear whether isolated tumour cells or micrometastases represent an adverse prognostic indicator and whether AC should be carried out on all cases. Likewise, there is insufficient data to determine whether the presence of isolated tumour cells or micrometastases should be a factor in treatment decisions. McCready et al[24] suggest that metastasis is found in nonsentinel nodes in approximately 10% of patients with isolated tumour cells in the SLN and in 20–35% of patients with micrometastases in the SLN.

Some studies have demonstrated an adverse effect on survival in patients positive for micrometastatic disease, others have not.[25–27] The definition of micrometastases and detection methods throughout the literature have varied. There are no clear New Zealand guidelines on the management of axillary micrometastases in patients with early stage breast cancer. ASCO guidelines recommend routine AC in patients with micrometastases >0.2 mm but ≤2.0mm until further studies are completed.[6]

Definitive data from randomised trials is needed to decide if axillary dissection is needed when the SLN is positive. Two large prospective clinical studies, NSABP-32 and American College of Surgeons trial Z0011, are hoped to definitively resolve questions regarding the optimal surgical management of patients positive for micrometastases and isolated tumour cells.[28,29]

In Taranaki, all patients are discussed at a multidisciplinary meeting involving surgical, oncology, radiation therapy, and radiology specialists and further management decisions are made based on current evidence in association with individual patient factors.

Another area of ambiguity is the use of SLNB in patients with a histological diagnosis of DCIS alone. A positive SLN has been reported in 6% to 13% of patients with DCIS.[30] Although it is well established that nodal status for invasive disease is prognostically important, the clinical relevance of a positive SLN in patients with DCIS remains undetermined.

New Zealand guidelines for the use of SLNB in DCIS are inconclusive. ASCO guidelines recommend considering SLNB for patients with DCIS when a mastectomy is indicated or when immediate reconstruction is planned, as axillary staging by SNB is essentially impossible if an invasive tumour is found.[6] Although an invasive component will subsequently be found in 10–20% of cases diagnosed by core biopsy as DCIS alone, they do not recommend SLNB for patients with DCIS undergoing breast conserving surgery. However, some experts argue that SLNB in patients with DCIS undergoing breast conserving surgery will help identify those with unrecognised invasive disease, and suggest that SLNB in those with high grade, or large areas of DCIS is warranted so as to avoid a second operation on the axilla if invasive cancer is found.[27]

Size >4 cm has been shown to be a predictor for invasive breast cancer in patients with an initial diagnosis of DCIS alone.[31] In Taranaki, treatment was in accordance with ASCO guideline recommendations in all but two cases of DCIS who underwent SLNB. In those two cases, the area of DCIS histologically was 40 mm and 50 mm respectively, indicating a high risk of unrecognised invasive disease. Management of both cases was discussed at the multidisciplinary team meeting.

The performance of SLNB in Taranaki is comparable to international centres. This is despite a lack of statutory training requirements. This article highlights the need to adhere to recommended protocols when introducing a new technique in order to provide non-biased test performance measures. In the case of SLNB, this involves at least 20 cases either followed by routine axillary clearance, or with mentor supervision. For cases of micrometastases and ductal carcinoma *in situ*, further evidence is required to determine optimal management.

Adoption of SLNB in early stage breast cancer as routine in Taranaki has been achieved with results equivalent to internationally established standards. This may spare many Taranaki women the morbidity of axillary clearance, without jeopardising safety.

Competing interests: None known.

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