Evolution of sentinel lymph node biopsy for breast cancer patients in a rural setting: 10 years' experience

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ABSTRACT

Sentinel lymph node (SLN) biopsy is the standard axillary staging procedure of early breast cancer. Superparamagnetic iron oxide (SPIO) nanoparticles have been found to be comparable to, while overcoming many of the limitations associated with, the current standard of care for SLN biopsies (dual localisation with radioisotope and patent blue dye). Here, SPIO dual localisation (Sienna+® and blue dye) is compared to blue dye alone for SLN biopsies in a rural centre where radioisotope techniques are not readily available. Sienna+® dual localisation is shown to be more likely to detect nodes (detection rate of 99% compared to 90% when using blue dye alone), and detect more nodes, than blue dye alone. The use of Magseed, a magnetic tracer, was not found to influence node detection. The results from this work show that Sienna+® dual localisation is superior to blue dye alone for detecting SLN, suggesting that it is an excellent alternative to dual localisation of radioisotope and blue dye for small centres lacking easy access to a nuclear medicine department.

Sentinel lymph node (SLN) biopsy is the standard axillary staging procedure for early breast cancer and is undertaken when a patient is clinically and radiologically lymph node negative.[1–4] Dual localisation of SLN with both radioisotope and patent blue dye is superior to single agent and has a lower false-negative rate.[2,5] Its universal uptake, however, is limited as it requires access to a nuclear medicine department or a radioactive licence. Its short half-life (approximately six hours for Tc 99) also reduces its utility for rural patients as they need to travel to a large centre for its administration,[6] making its use impractical for many rural centres within New Zealand.

Superparamagnetic iron oxide particles (SPIO) have introduced an accurate and efficient alternative that overcomes many of the disadvantages of the traditional dual localisation techniques for SLN biopsy.[1,3–5,7,8] Clinical use of SPIO is common for magnetic resonance imaging intravenous contrast injections.[4] The SPIO tracer (Sienna+®) is a dextran coated nanoparticle 60 nanometres in diameter. Once injected subareolarly, it drains into the lymphatic system and accumulates in the sentinel lymph nodes just like radioactive colloid and blue dye. It is detected intraoperatively using a handheld magnetometer. The surgeon detects the location by the audible pitch of the detector and numerical signal range. There have also been reports of lymph nodes found to be stained brown or black.[1,4,5,7,8] When comparing SPIO to dual localisation of radioisotope and blue dye, the identification rate has been found to be comparable,[1,4,8] suggesting that it is an excellent alternative for centres not equipped to use radioactive isotope.

Timaru Hospital is the only facility in New Zealand where all practising breast surgeons use dual localisation of Sienna+® and blue dye for sentinel lymph node biopsies. Sienna+® and blue dye was first used in June 2017, with blue dye alone being used prior. This retrospective study compares the use of both techniques over the last ten years showing their utility in a rural setting.

Materials and methods

Patient population

Data were analysed for all patients who had clinically and radiologically node negative breast cancer and had undergone SLN biopsy for breast surgery (invasive carcinoma or ductal carcinoma *in situ* [DCIS]) at Timaru Hospital, New Zealand between 1 January 2011 and 31 December 2021. Data collated from the electronic health record included demographics, type of surgery, tumour size and type, staging, lymph node status, lymph node detection rate and hormone receptor status. Comparison was made between the patients who

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underwent SLN biopsy using patent V blue dye localisation alone and those using dual localisation with Sienna+® super paramagnetic iron oxide particles and blue dye (Sienna+® dual localisation).

Technique

Single agent blue dye localisation was carried out with a 2ml periareolar subcutaneous injection of patent V blue dye administered after induction of general anaesthesia for surgery. The injection site was massaged for two minutes. Dual localisation Sienna+® dual localisation involved 2ml of Sienna+® injected into the periareolar subcutaneous tissue in clinic approximately a week prior to each operation. Patent V blue dye was injected at induction, as outlined above.

Magseed, a magnetic guide used during surgery when there is no palpable mass, was used to help locate the tumour in some wide local excision (WLE) procedures. After the tumour of interest had been excised and all metal instruments had been removed from the operating field, a handheld magnetometer was used for localisation of the sentinel lymph node. The blue node and/or "hot" (magnetic) nodes were identified and excised for histological analysis. After removal of the sentinel nodes, the axilla was checked with magnetometer probe to ensure minimal residual magnetic count. Non-sentinel nodes may have been sampled at surgeon discretion. Lymph nodes were evaluated by an onsite pathologist using local protocols.

Statistics

Fisher Exact tests was used for demographic comparisons between the two groups and to determine statistical difference between the number of sentinel nodes harvested between groups (Sienna+® dual localisation vs blue dye alone, and Sienna+® dual localisation with and without Magseed).

Ethics

This study was a retrospective clinical audit of patient information from a single unit's practice and therefore was exempt from patient informed consent. Local hospital board ethics committee approval was granted.

Results

Between 1 January 2011 and 31 December 2021, 226 patients underwent SLN biopsy at Timaru Hospital. All patients were female. One patient was excluded due to incomplete documentation detailing their treatment, leaving 129 (57.3%) patients who underwent SLN biopsy Sienna+® dual localisation and 96 (42.7%) using blue dye alone. Demographics, surgical approach and tumour details of the two groups are summarised in Table 1. Sienna+® dual localisation was offered from June 2017. Blue dye alone was used up until March 2020, after which time all surgeons adopted the universal dual tracer technique. The number of patients per technique per year is summarised in Appendix 1.

SLN were successfully harvested in 99% (128/129) of patients using Sienna+® dual localisation and 90% (86/96) of patients when using blue dye alone (p=0.001). Three or more sentinel nodes were detected in 34% of patients (44/129) using Sienna+® dual localisation, and 13% (12/96) of patients when using blue dye alone (p=0.0002) (see Table 2). Non-sentinel nodes were taken from six Sienna+ dual localisation patients, one of which was node positive with isolated tumour cells. In the blue dye group, there were 11 patients with non-sentinel nodes harvested based on the operative decision at the time. All of these nodes were negative. The observed difference was not significant (p=0.0739).

In the Sienna+® dual localisation cohort, no difference was identified for the number of sentinel node harvested between Magseed (n=15) and non-Magseed groups (n=29) (p>0.05) (Appendix 2). No significant differences (p<0.01) were identified between the two cohorts when comparing tumour type, grade and stages, surgery type, age or ethnicity between the treatment groups (Table 1).

Sienna+® tissue staining was recorded in 82% (36/44) of WLE cases, ranging from 5 to 43 months follow-up.

The clinical management of DCIS has evolved at Timaru Hospital in line with its referring tertiary centres' practice and its multidisciplinary meeting reviews. SLN biopsies is still offered for some high-risk patients with DCIS or those undergoing mastectomy for DCIS; however, the decline in the number of DCIS patients treated with sentinel node biopsies over the study period does not reflect a decline in patients presenting with DCIS (Appendix 1).[9]

Discussion

This study shows that Sienna+® dual localisation is superior to blue dye alone for detecting sentinel lymph nodes in rural women with breast cancer, and it is a safe alternative to use where access to radioisotope use is limited by distance required to

Table 1: Patient and tumour characteristics of study cohort.

		Sienna+® dual localisation counts (percentage)		Patent V blue dye counts (percentage)		P-value*
Number of patients		129		96		
Age	**Median (range)**	67	(33–90)	61	(33–87)	
Ethnicity	**NZ European**	107	(83%)	90	(94%)	0.015
	Māori	15	(12%)	6	(6%)	
	Other	7	(5%)	0	(0%)	
Surgery type	**Mastectomy**	85	(66%)	63	(66%)	1.000
	WLE	44	(34%)	33	(34%)	
Grade	**G1**	28	(22%)	29	(30%)	
	G2	61	(47%)	35	(36%)	0.1801
	G3	38	(29%)	32	(33%)	
	Unknown	2	(2%)	0	(0%)	
Stage	**Tis**	10	(8%)	16	(17%)	
	T0	4	(3%)	0	(0%)	0.0302
	T1	82	(64%)	67	(70%)	
	T2	31	(24%)	13	(14%)	
	T3	1	(1%)	0	(0%)	
	Unknown	1	(1%)	0	(0%)	
Side	**Right**	71	(55%)	47	(49%)	0.42
	Left	58	(45%)	49	(51%)	
Tumour type	**Invasive ductal**	95	(74%)	64	(67%)	
	Invasive lobular	10	(8%)	9	(9%)	
	Invasive mucinous	6	(5%)	4	(4%)	0.4889
	Invasive tubular	5	(4%)	2	(2%)	
	Invasive papillary	1	(1%)	1	(1%)	
	Invasive micropapillary	1	(1%)	0	(0%)	
	DCIS	11	(9%)	16	(17%)	

Notes: * Two-sided Fisher Exact tests to calculate difference between two sentinel lymph node biopsy techniques (Sienna+® dual localisation and blue dye alone) with at least one observation in each cell.

Table 2: Number of lymph nodes harvested using Sienna+® dual localisation or blue dye alone.

		Sienna+® dual localisation counts (percentage)		Patent V blue dye counts (percentage)		P-value*
Nodes detected	0	1	(1%)	10	(10%)	0.001
	1	49	(38%)	50	(52%)	0.042
	2	35	(27%)	24	(25%)	0.761
	3+	44	(34%)	12	(13%)	0.0002

Notes: * Two-sided Fisher Exact tests to calculate the difference between two sentinel lymph node biopsy techniques (Sienna+® dual localisation and blue dye alone).

Table 3: Initial set up cost and per patient personal and procedure cost analysis, as estimated by Sreedhar et al. 2021.

			Sienna+	Radioisotope
Setup costs			SentiMag	Gamma probe
			$44,275	$41,400
Personal costs	Travel		-	$130
	Hotel		-	$100
Procedure costs	Magnetic tracer		$557.7	-
	Radioactive colloid injection	Injection	-	$600
		Lymphoscintigraphy	-	$588
Cost per patient*			$558	$1,418
Cost for 100 patients*			$55,770	$141,800

Note: *excluding set up cost

travel. It also highlights that when dual tracers are used, fewer women will require random axillary sampling, as a SLN is highly likely to be found with this technique.

Dual localisation using radioisotope and blue dye has been the gold standard for locating sentinel lymph nodes in breast cancer patients;[1,4,7] however, its utility in rural centres is limited. Smaller centres lack the nuclear medicine department required for the use of radioisotope. The isotope could be administered by a licensed surgeon or clinical nurse specialist without mapping but administration around the use of radioactive materials makes its uptake prohibitive. Additionally, due to its short half-life, surgery needs to occur on the same day or as soon as possible within 24 hours after injection with the radioisotope. For rural women who need to travel

to metropolitan centres with nuclear medicine departments this is made logistically impractical, especially if it needs to be co-ordinated with hook-wire placement with breast conservation surgery.

Timaru Hospital introduced Sienna+® dual localisation for SLN biopsies after SPIO was shown to be as effective as radioisotope and blue dye dual localisation at detecting SLN.[1,4,7,8] All breast surgeons at this centre have adopted this technique and it is now the standard of care. Sienna+® dual localisation detected more nodes than blue dye alone. When both techniques were used, it was unlikely that no SLN would be found. Additionally, a higher number of SLN was found using dual technique. These findings are consistent with previously published work where Sienna+® dual localisation was found to have a 98% detection rate, while blue dye alone was only 86–90%.[4,8,10]

Sienna+® dual localisation provides a good alternative to radioisotope dual localisation. While a formal cost analysis is beyond the scope of this paper, Sreedhar et al. (2021) estimated Sienna+® to be to be the more affordable option to administer in New Zealand, with an estimated cost of $558 NZD per patient. Radioisotope dual localisation costs around $1,188 for the procedure, with patient travel and accommodation costs additional to this sum, indicating that Sienna+® would save approximately $86,000 per 100 patients (see Table 3). This suggests that the up-front costs of the SentiMag machine ($44,275 NZD) would have been covered by its use for only 52 patients after implementing Sienna+® at Timaru Hospital. In addition to the financial benefits, Sienna+® is not a radiation-based procedure and so is not restricted to access to a nuclear medicine facility, making it suitable for use in a rural setting.[6] This means patients do not need to travel out of town for their procedure, while staff and patients are not exposed to radiation. Timing of surgery is also less pressured as Sienna+® injection can be administered by a clinical nurse up to three weeks prior to surgery allowing for flexibility in theatre planning especially if hook-wire placement is also planned.[1,7]

As a magnetic-based procedure, the main limitation of Seinna+® utilisation is the presence of any metalware in the ipsilateral side of the SLN biopsy.[7] Metal retractors and equipment are therefore not able to be used during SLN detection, while patients with metal implants such as pacemakers or orthopaedic metal prostheses need to undergo SLN detection with other non-magnetic techniques. Disposable plastic retractors are available; however, some products can be bulky and brittle making their design inferior to metal retractors for the delicate work required of them.

Conventional dual localisation using radioisotope detects extra-axillary sentinel nodes or high infra-clavicular nodes by lymphoscintigraphy. While SPIO with blue dye is a more targeted approach that focuses solely on detecting the axillary level 2 and 3 nodes, this method is adequate as these nodes are where the most common pathway of metastases are located.[8] No pre-operative mapping is available with SPIO, and while lymphoscintigraphy may show extra-axillary nodes like internal mammary or supraclavicula—few centres would pursue these operatively due to limited oncological benefit and risk of retrieval.

The same SentiMag machine is also used for wide local excision technique for non-palpable lesions as an alternative to hook-wire localisation with its associated timing logistics. While Sienna+® can be used alongside Magseed localisation, it is recommended that care is taken to remove the tumour and the Magseed prior to undertaking the SLN biopsy to limit magnetic interference. Magseed was used *in situ* to locate the tumour in 15 Sienna+® dual localisation patients. No significant difference was found between in the number of nodes detected with or without the use of Magseed. This is consistent with similar studies published in New Zealand and overseas,[6,11,12] suggesting that Magseed can be utilised alongside SPIO SLN procedures without interference. While allergy when using Sienna+® is infrequent,[1,4,8,13] a much more common side-effect is tissue staining. Light brown staining of the breast tissue was detected in 82% (36/44) of women undergoing breast conservation surgery, ranging between 5 to 43 months follow-up. The number of patients that reported staining was similar to what has been reported previously and this staining is known to not be permanent.[14] This light brown staining containing SPIO has been shown to cause void artifacts and potentially obstruct key findings in post operative MRI for up to 25 months. [15] However, none of the women in this study needed MRI scanning after surgery as the threshold is low to obtain an MRI as part of the pre-operative workup.

Conclusions

This is the first study to show that Sienna+® dual localisation is superior to blue dye alone for detecting SLN and is an excellent alternative to dual localisation of radioisotope and blue dye for small centres without good access to a nuclear medicine department. This technique could also be offered in larger centres allowing for more flexible operating list planning.

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COMPETING INTERESTS

Nil.

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Appendices

Appendix 1: Number of DCIS cases where SLN biopsies were performed by year within the study period.

	SIENNA+® dual			Blue dye		
Year	**DCIS cases**	**Total cases**	**% DCIS**	**DCIS cases**	**Total cases**	**% DCIS**
2011	-	-	-	1	5	20%
2012	-	-	-	1	5	20%
2013	-	-	-	1	4	25%
2014	-	-	-	1	11	9%
2015	-	-	-	4	16	25%
2016	-	-	-	1	22	5%
2017	2	13	15%	6	16	38%
2018	4	16	25%	0	8	0%
2019	1	25	4%	0	8	0%
2020	2	33	6%	0	1	0%
2021	1	42	2%	-	-	-

Appendix 2: Number of nodes harvested with and without the use of Magseed for location of impalpable tumours.

Nodes harvested	WLE with Magseed	WLE without Magseed	*P-value
1	7	12	1.000
2	3	6	
3	3	6	
4+	2	5	

Note: * Two-sided Fisher exact tests to calculate the difference between WLE performed with and without Magseed.