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Review Article

Techniques with overview of sentinel lymph node biopsy in early breast cancer: a review

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ABSTRACT

The sentinel lymph node biopsy (SLNB) technique has been developed and validated in past three decades. It has been demonstrated to be feasible, accurate, and less morbid than axillary lymph node dissection (ALND), as a standard initial approach in patients with early-stage breast cancer. The techniques and management decision of SLNB in comparison with ALND was carried out by literature search from PubMed, Medline, Clinical key and clinical trials.com, ranging from 2010 to 2025. Despite variability in selection criteria and technique, sentinel lymph node is consistently identified in approximately 96 percent of patients predicting the status of remaining axillar lymph nodes in greater than 95 percent patients. Failure to map in a SLNB eligible patients or with three or more sentinel lymph nodes (SLN) positive should undergo ALND for staging and to maximize local control. There is no one size fits all SLNB technique, but the choice depends upon institutional resources, patient factors, logistics, surgeons experience. Multidisciplinary team approach with quality assurance and auditing to minimize false negative SLN rate (FNR) to achieve better patient outcome.

Keywords: Sentinel lymph node biopsy, Axillary lymph node dissection, Breast cancer, Sentinel lymph node, Breast conserving surgery, False negative rate

INTRODUCTION

The technique of Sentinel lymph node biopsy (SLNB) of the axilla in staging of clinically node negative breast cancer, was introduced by Giuliano and Krag in 1993-94. SLNB identifies those patients needing further axillary treatment, and sparring others from morbidities associated with axillary lymph node dissection (ALND). It is considered as one of the most important prognostic factors in breast cancer, while histological examination of lymph nodes remains the most accurate method for assessing lymph node metastasis. The techniques and management decisions of SLNB with ALND, in breast cancer will be reviewed here. Different Randomized Trials of axillary lymph node management will be discussed in this review in context with SLNB, ALND. SLNB in breast cancer (BC) is indicated in clinically node negative breast cancer and ductal carcinoma in situ (DCIS) requiring mastectomy. Preoperative evaluation of the axilla is essential in this context. ALND is typically for clinically node positive patients, or patients may undergo neoadjuvant chemotherapy (NACT) and require restaging. Proper surgical technique in SLNB minimizes the risk of under staging and undertreating the patients, influencing the outcomes.[1] The ability of SLNB to accurately predict the status of other axillary nodes is being validated in several studies. The NSABP B32 (National surgical Adjuvant breast and bowel project) trial showed that SLNB was equal to ALND in accurately staging the axilla in clinically node negative axilla.

Veronesi et al showed overall survival (OS) was similar between node negative patients undergoing SLNB and ALND group, and 10 years follow up results confirmed no difference in survival between SLNB and ALND, confirming ALND could be avoided in patients with negative SLNB.[2] SLNB begins with either intradermal, subcutaneous, retro areolar or in vicinity of breast tumour with injection of one or two tracers. The tracers enter the lymphatic channels and passively flow to draining lymph nodes. Sentinel lymph nodes (SLN) are identified as those first receiving the drainage of tracer and are removed. SLN location may be variable but usually found within lower axilla, at level 1 (Figure 1).[3]

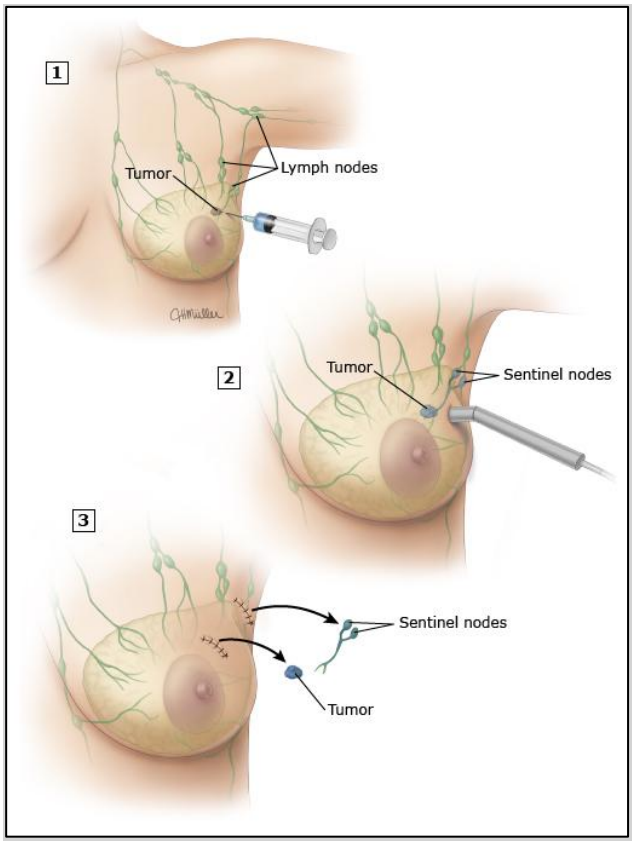

Figure 1: Sentinel node biopsy for breast cancer.

Common methods include using blue dye (BD), radioisotope (RI), superparamagnetic iron oxide (SPIO), indocyanine green (ICG), and combinations of above. BD (Isosulfan blue, patent blue, methylene blue) injected immediately before surgery peri tumour or sub areolar has a 70-90% visualization and pickup rate. False negative rate (FNR) 10-15%. RI like (Tc 99m Sulphur colloid, Nano colloid) with gamma probe picks radio colloid in lymphatics, when injected peri tumour or sub areolar a day before surgery or few hours before surgery. SLN pick up rate is around 92-97% with FNR rate of 5-10%. SPIO tracer is magnetic nano particle tracer detected by handheld magnetometer (Sentimag), injected preoperatively in clinic setting or immediate post induction, peri tumour or sub areolar or peri areolar. SLN is picked up by visual as well as tracer uptake reading by magnetometer. SLN pickup rate is 90-98% with FNR around 5-10%.

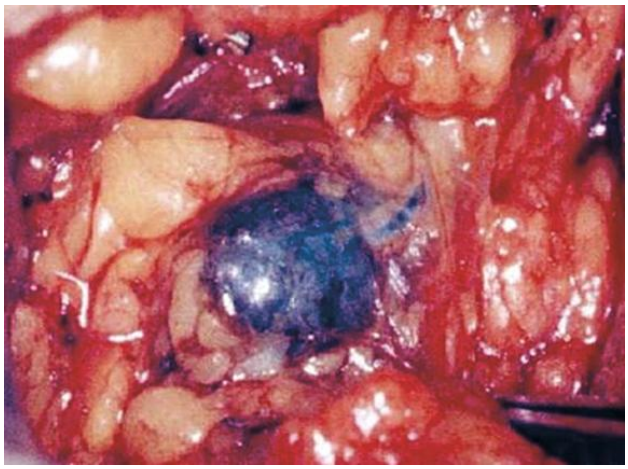

Figure 2: Blue sentinel lymph node, lymphoscintigraphy of early breast cancer.

ICG tracer with near infrared fluorescence (NIR) camera is visualized by NIR, dye is injected immediately preoperative, due to rapid lymphatic transit either peri tumour or sub areolar. SLN pickup rate is around 93-100% with FNR around 5-10%. Hybrid tracer (HT) combination of RI+ICG OR RI+ICG+BD injected as per protocol as above depending upon the tracer used.

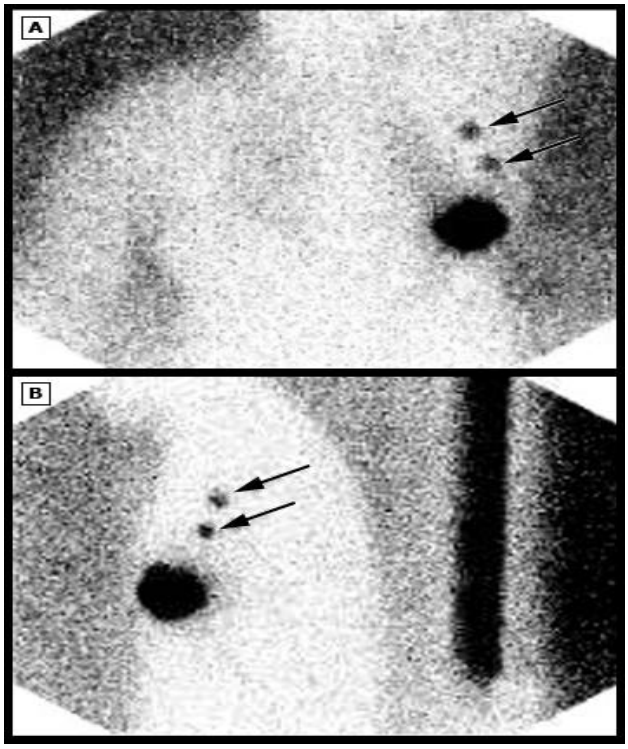

Figure 3 (A and B): Lymphoscintigraphy of early breast cancer.

SLN pickup rate is around > 95 percent with FNR less than 5% (Table 1).[3-5] Tracers are either injected

preoperatively or just before surgery depending upon their half-life and transit time. It is important not to inject the tracer into the tumour because lymphatics can be occluded by tumour or into seroma cavity as it is devoid of lymphatics (Figure 2,3).

A newer technique which is evolving, is highly operator dependent and technically demanding, this is known as Contrast enhanced Ultrasound (CEUS) with microbubbles (MB). MB tracer is injected preoperatively, peri tumour with ultrasound mapping visualization of lymphatics and nodes. SLN pickup rate 70-95% with FNR heterogenous.[6]

Patients with clinically positive axillary nodes undergo ALND or may undergo NACT and restaged afterwards following response. There are absolute contraindications for SLNB, such as inflammatory breast cancer, locally advance breast cancer like skin and chest wall involvement and metastatic breast cancer.

Aim

This current review study was carried out to assess and compare SLN biopsy techniques, in clinically node negative breast cancer, as primary endpoint. The secondary endpoint was to compare SLNB proven metastatic lymph nodes in relation to proceeding to axillary lymph node dissection in clinically node negative breast cancer.

METHODS

Literature search and eligibility

The following databases were searched. PubMed, Medline, clinical key data base, and clinical trials.gov. Studies were included from 2010 to 2025.

Search strategy

Search terms used were ‘Breast neoplasia”, sentinel lymph node biopsy’, axillary lymph node dissection’. Medical subject headings (Mesh) terms were’ Breast neoplasia”, ‘sentinel lymph node biopsy’, ‘axillary lymph node dissection’.

Inclusion criteria

Inclusion criteria for current review were randomised prospective case control trials and research articles, comparing SLN biopsy techniques versus axillary lymph node dissection. Female patients above 18 years of age, clinically and radiologically proven node negative breast cancer (T1-3) were included.

Exclusion criteria

Studies including the following were excluded from literature search. Pregnant, lactating patients, proven axillary metastasis, locally advanced and metastatic breast cancer, hypersensitivity to blue dyes and iodine, intolerance or hypersensitivity to iron or dextran compound, iron overload disease, pacemaker and implantable devices.

RESULTS

Multiple randomised clinical trials have shown SLN detection rate of 97% with low FNR of approximately 5% with dual technique (RI+ Blue dye), considered as standard technique in SLNB. Draw backs of dual technique are handling, disposal of radioactive material with a need of nuclear medicine centre, legislation regarding usage of radioactive tracer, limited access of Technetium Tc99m along with its short half-life of 6 hours limiting its use to only day or on day of surgery. The use of Isosulfan BD is associated with severe anaphylactic reaction in 0.6-1.1% cases, requiring resuscitation. Methylene blue is an alternative to Isosulfan blue dye with lower rate of anaphylaxis (0.06%), but intradermal injection of Methylene blue can cause skin necrosis, induration, erythema and pain. Pulmonary oedema and serotonin syndrome is also reported in patients who take serotonergic medications. This can be minimized by diluting it normal saline in dilution of 1:1 or 1:7.[7,8]

Newer non-radioactive techniques like ICG, magnetic tracer SPIO, and others offer comparable identification rates in many series and may be preferred due to drawbacks of Radioisotope methods (RI, RI+BD, RI+ICG+BD Hybrid method). Multiple RCT for SLNB in clinically node negative breast cancer have shown BD SLN identification rate of 70-90% approximately, with retrieved lymph nodes number being average two. FNR was reported as 10-15%. BD method is simple, low cost with no special equipment required with lower identification rate, skin and soft tissue staining and allergic reaction as limitations. To minimize the limitations dilution of blue dye as described above is recommended. Radio colloid (Technetium TC 99m sulphur/nano colloid) (RI) plus lymphoscintigraphy reported SLN identification rate of 92-97% with average lymph node retrieval averaging 2 -2.5. FNR reported as 5-10%. It has an advantage of preoperative mapping and SPECT/CT localization and well validated. Disadvantages requiring nuclear medicine, radiotracer injection and radiation exposure. Pregnancy requires specialist assessment (Table 1).

Dual technique (RI+BD) considered as standard technique till the introduction of recently validated non-radioactive tracer techniques, showing noninferiority to standard gold standard technique. As name suggested identification perioperatively is by dual method by gamma probe and visual inspection of BD. SLN pickup rate reported as 95-99% with average LN retrieved 2.2 and greater nodes. FNR around 5-7%. Disadvantages as per both techniques described above.

Table 1: Techniques of sentinel lymph node biopsy.

Technique common method	Tracer principle	Injection site and timing	Intraoperative detection method	Approx SLN identification rate	Sensitivity false negative (FNR) rate	Main advantages	Main limitations	Key safety
Blue dye (isosulfan blue, patent blue, methylene blue. BD	Visual staining of lymph nodes with dye	Peritumoral/ subareolar. Injected immediately before surgery.	Visual inspection.	70-90% 1.8-2.0 nodes	FNR variable (10-15%). Higher than radioisotope and dual technique.	Simple, no special equipment and low cost.	Lower identification rate. Skin and soft tissue staining. Allergic reaction.	Risk of anaphylaxis, with isosulfan blue on comparison to methylene blue, skin tattooing. Avoid large volume.
Radio colloid (RI) (TC-99m sulphur colloid or nano colloid) and lymphoscintigraphy with SPECT	RI injected and lymphatic mapping using handheld probe supplemented by lymphoscintigraphy preop.	Peritumoral/subareolar injected 6-12 hours before surgery.	Handheld gamma probe perioperatively. Preop lymphoscintigraphy +/- SPECT.	92-97% 2.0-2.5 nodes.	Generally low FNR (5-10%) depending on centre and technique. High sensitivity.	High identification rate allows for pre-op mapping and SPEC/CT localisation. Well validated.	Requires nuclear medicine. Radiotracer logistics. Radiation exposure. Pregnancy use requires specialist assessment.	Radioprotection and safe disposal of radioactive material. Obstetric input required.
Dual technique (radiocolloid+ Blue dye) (RI+BD)	Combines radio colloid mapping and visual dye uptake	As per radio colloid and blue dye. Blue dye immediately pre-op (duration)	Gamma probe and visual inspection.	95-99% 2.2+ nodes.	Lowest in FNR in many studies (5-7%).	Combine effects of both techniques. Reduce rate missed nodes.	Higher complexity and cost. Requires nuclear medicine.	As above due to constituents. Allergic reaction. Radiation.
Indocyanine green (ICG) and infrared (NIR)	Fluorescent dye visualised with NIR camera. Real time lymphatic mapping.	Peritumoral/subareolar. Injected immediately preop due to rapid lymphatic transit.	NIR fluorescence camera with imaging system.	93-99% (studies compare it to radio colloid) 2.0-2.2 nodes.	FNR reported similarly to radio colloid and dual (<5-10%).	Real time visualisation. High identification rate in obesity. No radioactivity. Rapid.	Requires NIR camera. Rapid transit so time is critical. Limited deep tissue penetration vs radionuclide.	IGG contains iodine, exercise caution in iodine allergy. Rare adverse reactions.

Continued.

Technique common method	Tracer principle	Injection site and timing	Intraoperative detection method	Approx SLN identification rate	Sensitivity false negative (FNR) rate	Main advantages	Main limitations	Key safety
SPIO magnet tracer + handheld sentimag probe	Magnet nano particle tracer detected by handheld magnetometer (sentimag)	Peritumoral/ subareolar. Can be injected in outpatient setting or immediately preop.	Handheld magnetometer probe.	90-98% 1.9-2.1 nodes.	FNR comparable to dual technique in many studies (5-10%).	No radioactivity. Flexible timing. Good identification.	Requires dedicated probe. Injection site discolouration. Cost (?).	Causes MRI artefact in axilla and the injection site for months. Local discolouration. Check MRI scheduling.
Hybrid technique: TC 99m+ blue dye+ ICG radiocolloid (RI+BD+ICG)	Combines radioactive and fluorescent tracers in the formation	As per protocol preop for radio colloid. ICG component allows interop detection.	Gamma probe and NIR camera.	>95%	Low FNR similar to both techniques (<5%).	Best of both, pre-op imaging and interop fluorescence for precise localisation.	Complex and logistics. Cost. Requires both devices.	Constituents radioactive ICG caution.
Contrast enhanced U/S (CEUS) with microbubbles	Peritumoral injection of micro bubble contrast and ultrasound visualisation of lymphatic flow to the nodes	Contrast administered preop during ultrasound mapping.	Ultrasound machine. Marker placement. Skin tattoo or clip.	Variable; 70-95% (operator dependent).	Variable, technically demanding. Evolving FNR data; heterogeneous.	Real time. Non-radioactive. Guided percutaneous localisation and targeted biopsy.	Highly operant dependent. Limited standardisation. Less common in routine practice.	Contrast agent well tolerated. Operator and equipment dependent.

Sentinel lymph node biopsy techniques in early breast cancer and their comparison.BD: blue dye, RI: radioisotope, ICG: indocyanine green, NIR infrared fluorescence, SPIO: super Para magnetic iron oxide, HT: hybrid tracer, CEUS: contrast enhanced ultrasounds: sentinel lymph node, FNR: false negative rate.

ICG plus infrared fluorescence has evolved as replacement for dual technique with SLN pick up rate of 93-99%, with average LN retrieval of 2-2.2 nodes, FNR reported as <5-10%. Advantages include real time visualization with high identification rate in obese patients as compared to other commonly practiced techniques. Disadvantages included NIR camera, rapid transit time of tracer so time is critical factor post injection, limited deep tissue penetration as compared to Radioisotope. It is contraindicated in Iodine allergy.[4]

SPIO, a magnetic tracer also widely practiced as non-radioactive tracer with non-inferiority to Standard dual technique and ICG in various studies shown promise in SLNB procedures. LN pickup rate reported as 90-98% with average LN retrieval rate of 1.9-2.1 nodes. FNR reported as 5-10%. Advantages included availability, easy administration (can be carried out in clinic/ outpatient even two weeks before surgery as it stayed in the system for 30-days. longer half-life, no radioactivity and easy visibility using Sentimag probe. Disadvantages included dedicated Sentimag probe, injection site discoloration, and MRI artefact in breast and axilla.[5]

Hybrid technique (RI+ICG) (RI+ICG+BD) as name suggested a combination of two to three techniques with advantages and disadvantages of all three together. SLN pickup rate mentioned as expected high greater than 98%. FNR reported as <5%. Complex logistics, cost, radioactivity are main issues. Contrast enhanced ultrasound with microbubble contrast (dispersion with sulfur hexafluoride gas) is a new technique which is evolving for SLNB, using ultrasound visualization of lymphatics and nodes after injection of contrast microbubble peri areolar or peritumour. Lymph nodes can be clipped or skin marked / tattoo also preoperatively. LN retrieval rate is operator dependent as required Ultrasound machine, is variable from 64-90%. FNR is heterogenous but reported as 6.6-39%.

Advantages are it is real time, non-radioactive, guided percutaneous localization and targeted biopsies. Disadvantages included highly operator dependent, limited standardization and not in common practice also requiring validation.[6] From the description and Table 1, it is gathered that detection performance of dual technique (RI+BD) is equivalent to nonradioactive ICG and SPIO. While RI alone is superior to BD. Recommendations are post SLNB, no further ALND in following patient groups, one with fewer than three metastatic sentinel lymph nodes on SLNB, undergoing primary breast conserving surgery followed by postoperative whole breast irradiation, mastectomy followed by post mastectomy irradiation therapy.

A completion ALND is required in patients with three or more metastatic SLNs on SLNB. Patients with one or two metastatic SLN not desiring post-surgical irradiation. These recommendations are consistent with American Society of Clinical Oncology (ASCO) guidelines of 2017 and newer data. Completion ALND is performed for staging purposes and to maximise the local control. Timing of axillary procedure whether immediate or delayed does not seem to affect the total lymph node yield or rate of long-term complication like lymphoedema, validated by ASCO 2017 guidelines. The recommendations to omit ALND in patients with one or two positive SLNs who plan to undergo whole breast irradiation but not partial breast irradiation. This has been validated by ACOSOG Z-0011 trial where women received whole breast irradiation, IBCSG 23-01 trial and SENOMAC trial ,90% of women part of axilla is included in treatment field with whole breast irradiation, showing therapeutic effect from radiation to tumour cells in the axilla.

After mapping of axilla surgery or radiotherapy trial (AMAROS), was multi-institutional trial conducted by European organization for research and treatment of cancer (EORTC). The Trial included 4806 patients with T1/T2 primary, unifocal, invasive breast cancer without palpable axillary lymphadenopathy. 1425 patients were found to have positive SLNs by SLNB, while 744 were randomly assigned to ALND and 681 to axillary radiotherapy. Ninety-five percent patients in both groups had 1-2 SLN positive. The 5 years axillary recurrence rate was 0.43% (0-0.9) in ALND group and 1.19% (0.3-2.8) in the axillary radiation group. There were no statistically significant differences in DFS and OS between treatment groups. Lymphoedema was noted significantly more often after ALND than after axillary irradiation at 1,3 and 5 years. The 10 years follow up results of AMAROS trial axillary recurrence remained low compared to ALND group (7/744 patients 0.93%). Axillary radiotherapy group (11/681: 1.82%). Distant metastasis and OS rates were similar. The AMAROS trial showed axillary radiation is acceptable alternative to ALND in patients with positive SLNs.[9] Patients not eligible for SLNB, like clinically node positive, T4 breast cancer and patients not willing to go for post operative radiotherapy require ALND for axillary staging and disease clearance.

DISCUSSION

We discuss few controversial issues related to SLNB techniques. Considering sole technique of RI, BD and dual technique using in combination both tracers. Although excellent results are reported for each technique, but dual technique appear to minimize the FNR in most studies. In a systematic review conducted by expert panel by ASCO, dual technique was associated with significant trend towards fewer false negative results (7 versus 9.9%, p= 0.07). In NSABP B-32, randomized trial of SLNB versus ALND in patients with clinically node negative breast cancer, both BD and RI were used to detect SLNs intraoperatively. Most of the SLNs were both hot and blue (65%), while 24% were hot only and only 5% were blue only. 3.9% were neither hot nor blue, but abnormal palpably (Table 2).[2] Dual technique is

warranted in situations where SLN identification is expected to be low with a FNR high, such as limited experience of surgeon, NACT prior to SLNB, prior breast or axillary surgery and obese patients. American College of surgeons oncology group (ACOSOG Z1071) trial SLN identification rate in NACT patients with BD was 78.6%, RI alone 91.4% while dual tracers' technique reported 93.8%. In previously operated breast or axilla, blocked normal lymphatics causing alternate pathway channels, with high failure rate of localization of SLN with single agent. In such cases preoperative lymphoscintigraphy and dual agents may help ((Table 2).[11]

Table 2: Randomised trial of axillary node management in early breast cancer.

Study name	Study population	Mean follow-up	Comparison	Primary outcome	Additional outcomes	Morbidity
NSABP B32 (2010)[2,10]	5611 women with mostly <4 cm invasive breast cancer	96 months	NSABP B32 (2010)[2,10]	5611 women with mostly <4 cm invasive breast cancer	96	NSABP B32 (2010)[2,10]
Veronesi et al(2010)[26,27]	516 women with <2 cm breast cancer	102 months	1.SLNB	Veronesi (2010) [26,27]	516 women with <2 cm breast cancer	102 months
Z0011 (2011)[11,12,21,22]	856 women with T1-2 breast cancer, and 1-2 metastatic nodes by SLNB	NR	Z0011 (2011)[11,12,21,22]	856 women with T1-2 breast cancer, and 1-2 metastatic nodes by SLNB	NR	Z0011 (2011)[11,12,21,22]
IBCSG 23-01 (2013)[18,23]	931 women with <5cm breast cancer and 1 or more micro metastatic sentinel nodes	60 months	1.ALND	IBCSG 23-01 (2013)[18,23]	931 women with <5cm breast cancer and 1 or more micro metastatic sentinel nodes	60 months
Senomac (2024)[24]	2540 patients with clinically node-negative primary T1-3 breast cancer and 1-2 macro metastatic sentinel nodes undergoing breast conserving surgery or mastectomy	47 months	1.ALND	Senomac (2024)[24]	2540 patients with clinically node-negative primary T1-3 breast cancer and 1-2 macro metastatic sentinel nodes undergoing breast conserving surgery or mastectomy	47 months
Amaros (2014)[9]	4805 patients randomized, 1425 patients had positive sentinel node(s)	NR	Amaros (2014)[9]	4805 patients randomized, 1425 patients had positive sentinel node(s)	NR	Amaros (2014)[9]

Randomized Trials of axillary lymph node management in early breast cancer. ALND: axillary lymph node dissection, DFS: disease free survival, ENE: extra nodal extension, NR: not reported, OS: overall survival, RCT: randomized control trial, SLB: sentinel lymph node biopsy.

In most cases more than one SLN is identified. The maximum number of SLNs to be removed is debateable. Most surgeons that procedure should be terminated after three SLN, because very rarely fourth lymph node involvement is seen (2% in 1000 patients). In another large study of over 144,000 patients' disease specific survival was better in 2 to 3 SLN than patients with one lymph node retrieved. Literature suggests that FNR does not increase with more than 3 to 4 lymph nodes yield. Intraoperative evaluation of sentinel lymph nodes yields one quarter of patients with positive lymph nodes with some requiring ALND. Intra operative evaluation of SLNs allow immediate ALND, instead of second operation in certain patients. Some surgeons defer the SLNB evaluation to permanent pathology and perform a completion ALND, as a delayed procedure, along with

intra operative evaluation. Several techniques like imprint cytology, cell smears, cytokeratin staining one-step nucleic acid amplification (OSNA) and frozen section. All the mentioned techniques have limitations and evaluation. Permanent paraffin section is more accurate.
Average FNR of intraoperative SLN evaluation is 25%. Combination of frozen section and rapid cytokeratin immunostaining decreased the FNR of intra operative analysis of small prospective trials of 100 patients, however cytokeratin staining results in false positive results. Gold standard is the permanent section with paraffin +-Immunohistochemistry (IHC).[12-14]

Table 3: Standard radioisotope technique to SPIO technique.[15]

Authors	Tracer	Number of patients	Mean number of SLN for patient identification	Number of metastatic SLN identified	SLN identification rate
Alvarado et al	SPIO	146	2.4	24	0.94
	RI +BD	146	2.4	24	0.94
Douek et al	SPIO	160	2	23	0.94
	RI+BD	160	1.9	24	0.95
Ghilli et al	SPIO	193	1.8	55	0.98
	RI	193	1.8	56	0.99
Houpeau et al	SPIO	108	2.01	45	0.97
	RI+BD	108	1.94	44	0.95
Karakatsanis et al	SPIO	206	1.83	52	0.98
	RI +BD	206	1.79	53	0.97
Karakatsanis et al	SPIO	183	1.26	24	0.96
	RI	155	1.7	25	0.97
Madrona et al	SPIO	181	1.63	67	0.91
	RI	181	1.55	69	0.86
Pelc et al	SPIO	62	2	5	0.92
	RI	62	3	5	0.92
Rubio et al	SPIO	118	2.21	32	0.98
	RI	118	1.9	32	0.96
Shiozawa et al	SPIO	30	-	-	0.80
	BD	30	-	-	0.77
Tarunto et al	SPIO	210	-	-	0.95
	RI	210	-	-	0.98
Thill et al	SPIO	150	1.9	33	0.98
	RI	150	1.8	31	0.97

SPIO: superparamagnetic iron oxide, RI: radioisotope, BD: blue dye, SLN: sentinel lymph node.

A systematic review of 69 trials of SLNB including 8095 patients, SLN could be identified in 95% patients with FNR of 7.3% (range 0-29%). FNR of SLNB is influenced by multiple surgeon and patient factors. Surgeon experience, previous breast/axillary surgery in relation to lymphatics, number of SLN retrieved, and axillary palpation per operatively.[14]

In a metanalysis of seven homogenous studies comparing standard dual technique to SPIO technique for utility and safety, showed neither standard technique nor magnetic tracer technique are superior or inferior to each other.[15] The newer magnetometer (Sentimag) probe has sleek balanced handling but still require rebalancing and it lacks light source. Moreover, there is interference with surgical instruments and for axillary SLN retrieval plastic instruments are required. The magnetic tracer persists within the breast tissue creating potential artefacts in post operative MRI. The tracer cannot be used in patient with pacemaker or with metal implants or allergy to iron or dextran. Brown skin staining secondary to injection of magnetic tracer has been reported showing regression with time but not complete disappearance. The skin discoloration due to SPIO can be minimized with either diluting Sienna or using smaller dose of undiluted Magtrace that 1ml instead of 1.5 or 2 mls. This lesser volume has no effect on SLN pickup rate. SPIO has a short learning curve as compared to ICG technique and is more cost effective and easy to handle with a luxury of having a long half-life and cut the hospital cost from all angles (Table 3).[15] ICG technique for SLNB has promising results in terms of SLNs detection rate, retrieval rate and FNR in comparison to other methods including standard dual technique and SPIO. ICG technique is not standardised yet.[16] The needed dose to be injected depends upon surgeon's preference, BMI of patient and breast volume. The time between the injection and incision should not be shorter than 10 minutes, but

again due to quick transit time and tissue penetration of contrast carries a fine balance. Iodine allergy is another issue to consider. On the other hand, ICG enables real time visualization of lymphatics from breast to axilla allowing full road map of lymph nodes. It is cheaper than radioisotope and does not require nuclear medicine centre. Data is lacking for the cut off learning curve this technique.[17]

CEUS is an active field of research but cannot be recommended for use at this stage. It has potential to improve the sensitivity of grey scale ultrasound and stage the axilla non operatively. National institute for health and care excellence (NICE) guidelines recommend SPIO (Magtrace and Sentimag) system as an option for locating sentinel lymph nodes, especially in hospitals with limited access to radio pharmacy. This procedure offers flexibility in scheduling procedures and has a broader spectrum encompassing the patients with ductal carcinoma in situ (DCIS) who are at high risk of invasive disease. If radiotherapy is not Planned in these patients, additional factors should be considered such as size of tumour and lymph nodes, extra nodal involvement extension (ENI), size and extent of lymph vascular invasion (LVI). However, these patients undergoing ALND on these grounds in retrospective analysis revealed no reliable clinical benefit in disease free survival or overall survival.[18,19]

Three randomized trials demonstrated that these patients with 1-2 SLNs positive on SLNB. The ACOSOG Z-0011 trial. Designed to address the need for completion ALND for patient with T1 or T2, clinically node negative breast cancer with less than three SLNs positive on SLNB, undergoing breast conserving surgery. All patients were treated with whole breast adjuvant radiotherapy. In comparison SLNB versus ALND group, SLNB alone resulted in similar 5-year OS rates (91.9% versus 92.5%). DFS rates (82.2% SLNB versus 83.9% ALND) and recurrence events (4 SLNB-2 ALND). The trial has been criticised for premature study termination, protocol noncompliance and high percentage of patients lost to follow up (20%).

Around 70% patients in trial had T1 tumour was another point raised. Despite all this ACOSOG Z-0011 trial widely changed the practice. With a median follow-up of 9.3 years, the 10-year OS was 86.3% for SLNB and 83.6%. ALND and DFS (80.2% SLNB versus 78.2% ALND). These were like five years rate mentioned. Additionally, the incidence of ipsilateral axillary recurrence at 10 years in SLNB group was 1.5% (5 patients) and in ALND group 0.5% (2 patients). Incidence of Locoregional recurrence in SLNB group was 5.3% and 6.2% in ALND group.[21,22] The IBCSG 23-01 trial (international breast cancer study group) randomly assigned patients with primary tumour less than 5cm in size with clinically negative axilla assigned to ALND and no axillary surgery, postpositive SLNB. Only one to two SLNs were positive in 85% patients. All patients had nodal metastasis less than 2mm in size, 67 percent had micro metastasis less than1mm.90 percent patients had BCS and 10% had mastectomy. A similar proportion of patients in each group received adjuvant radiotherapy, hormonal therapy and chemotherapy. 90% patients in both groups received whole breast radiation. At 5 years there was no statistical difference in DFS rate (84% ALND group versus 88% without ALND) with OS rates (98% versus 97.6%). The trial was closed prematurely due to low enrolment and low event rates.[23]

The SLN in breast cancer, omission of completion axillary lymph node dissection trial (SENOMAC) randomly assigned 2540 patients with T1 to T3 breast cancer with one or two SLNs containing macro metastasis (>2 mm) to either ALND or No ALND. Most patients both groups received radiation including nodal target volumes. Median follow up of 46 months; the recurrence free survival was not different (ALND 88.7% versus 89.7%). Compared to earlier trials this trial enrolled more patients, more older patients, excluded micro metastasis and included T3 tumours. Patients with extra nodal tumour extension and those underwent mastectomy which were underrepresented in previous trials were also considered.[24]

The AMAROS trial examined the role of ALND in managing axillary disease in patients with early stage clinically node negative breast cancer in the light of first two randomized trials and other studies, so called “Z-0011 eligible” group.[19] ASCO expert panel updated the guideline published in 2025 (literature review January 2016- May 2024).

The following recommendations were made.[25] Clinician should not recommend routine SLNB in select patients who are post-menopausal and are 50 or more years of age with negative findings on preoperative axillary ultrasound for grade 1-2, small < 2cm, hormone receptor positive, human epidermal growth factor receptor 2 (Her2) negative, undergoing BCS, clinicians may offer post mastectomy radiation (RT) with regional nodal irradiation (RNI) and omit ALND in patients with clinically node negative invasive breast cancer equal to or less than 5cm who received mastectomy with finding of 1-2 positive sentinel nodes.

Clinicians may offer SLNB in patients who have T3-T4 tumours or multicentric tumours, clinically node negative or DCIS, treated with Mastectomy, obese, male or pregnant or had prior breast or axillary surgery. Clinicians should not recommend ALND for patients with early-stage breast cancer who do not have nodal metastasis, or who have one or two sentinel lymph nodes metastasis receiving BCS and adjuvant RT to whole breast with or without RNI (Figure 4).[25] Patients with three or more SLNs involved should undergo completion ALND for staging purposes and to maximize local control. There is no data to support the omission of ALND in these patients. The timing of the procedure

either immediate or delayed does not seem to affect the total lymph nodes yield or rate of long-term complications like lymphoedema. There are no trials to compare the radiation versus radiation plus ALND in this group of patients (AMAROS trial revised guidelines) (Figure 4).

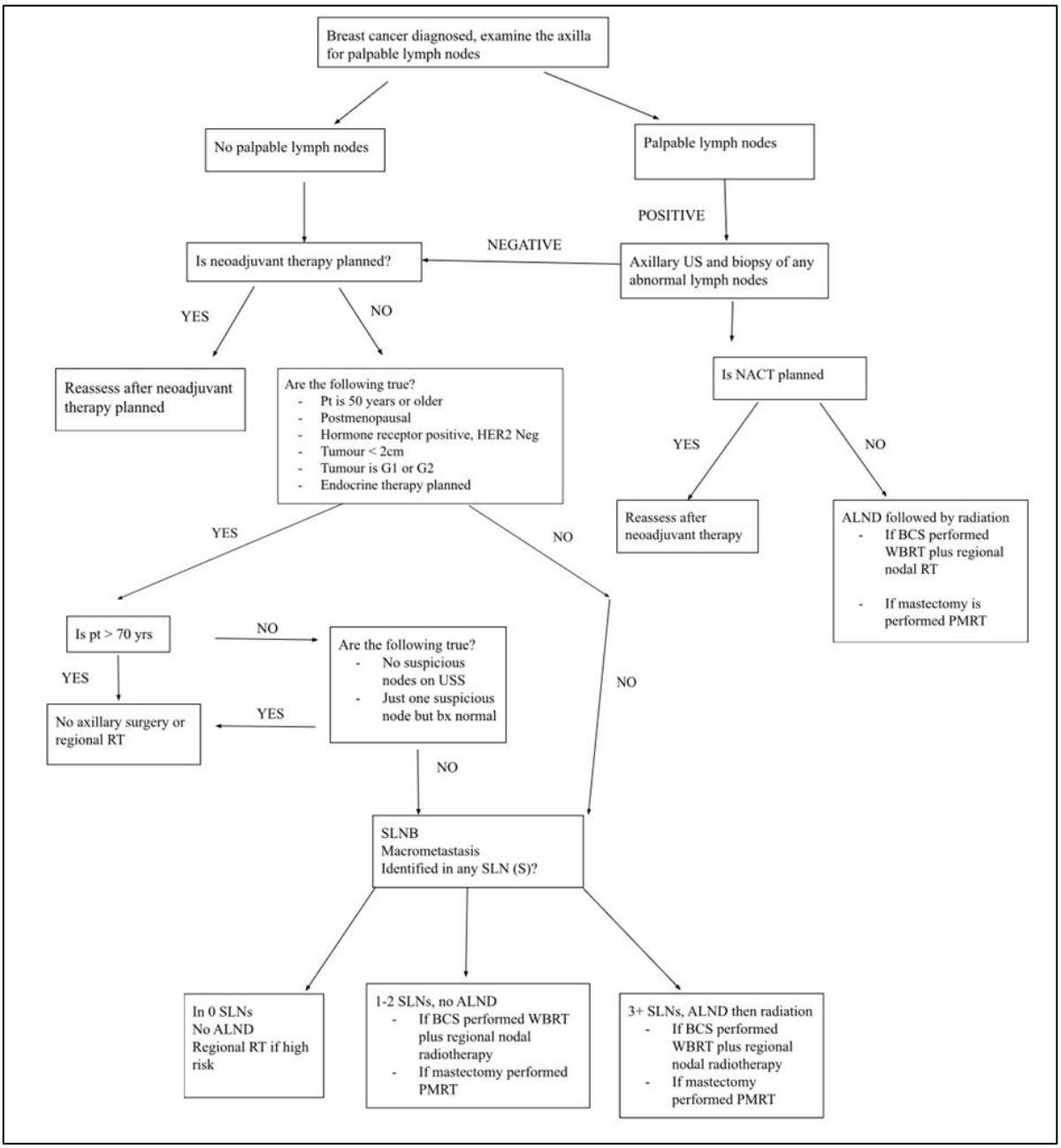

Figure 4: Axillary management of breast cancer.

NACT: Neo adjuvant chemotherapy, HER2: Herceptin 2 receptor, G: grade, ALND axillary lymph node dissection, BCS: breast conserving surgery, RT: radiotherapy, PMRT: post mastectomy radiotherapy, USS: ultrasound, BX: biopsy, SLNB: sentinel lymph node biopsy, SLN: sentinel lymph node, WBRT: whole breast radiotherapy.

CONCLUSION

To conclude there is no one size fits all technique. It depends upon institutional resources, patient factors, logistic and surgeon experience. Dual technique (RI+ BD), the most researched one with a long record of accomplishment with strong excellent credentials. ICG and magnetic tracer (SPIO) are non-radioactive and effective alternate to dual method. Whichever technique is used adherence to best practices like patient selection, MDT discussion preoperatively, team approach, proper injection technique, appropriate retrieval with adequate number of lymph nodes, quality assurance and auditing all minimize FNR and a better patient outcome. CEUS technique is still considered investigational, comparative studies with standard technique are required to validate this technique. A German Trial (Intergroup-sentinel-mamma (INSEMA) 2024-2025, has published the non-

inferiority of omission of surgical axillary staging to SLNB with a median follow up of 6 years. This comparison needs more research studies to validate the non-omission of axillary intervention at all in clinically node negative early breast cancer.

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