RADIOISOTOPE VS DYE USAGE FOR SENTINEL NODE BIOPSY IN A RESOURCE CONSTRAINED ENVIRONMENT ARGUMENT FOR RADIOISOTOPE

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INTRODUCTION

- In the management of breast cancer, the status of the axilla is one of the key factors that determine the prognosis.
- Patients with clinically palpable nodes are generally offered axillary lymph node dissection.
- Clinical examination of the axilla is not always reliable with a false negative rate of up to 45%.

INTRODUCTION

- Despite the advances in technology, imaging modalities such as U/S, MRI and PET scan have also proven to be of limited value in the clinically node negative axilla (cN0).
- Surgical staging therefore remains the gold standard for assessing the axilla in this group of patients.

INTRODUCTION

- Axillary lymph node dissection (ALND) carries a lot of morbidity namely lymphoedema, axillary numbness and shoulder abduction impairment.

- As more patients were diagnosed with early breast cancer, the morbidity of ALND could not be justified. Sentinel lymph node biopsy (SLNB) was then brought to the fore in the management of breast cancer.

INTRODUCTION

- Sentinel node mapping is based on the theory that tumour cells migrating from a primary tumour spread to one of few lymph nodes before involving others.
- This occurs in an orderly and reproducible manner as demonstrated in the 1940s studies done by Gilchrist, Zeidman and Buss. The sentinel lymph node (SLN) is the initial node that drains lymph from a particular organ before draining into subsequent nodes (non-sentinel nodes).

INTRODUCTION

- The identification and assessment of a sentinel lymph node when carried out properly using proven techniques provides an accurate clinical window into the regional basin.
- Sentinel lymph node biopsy (SLNB) was introduced as a technique for nodal biopsy in breast cancer by Giuliano & Krag in 1993 and 1994. It was validated in various trials and shown to positively impact on the quality of life (QOL) without compromising oncological outcomes. It has become the standard of care in patients with early breast cancer and a clinically negative axilla.

Accuracy of sentinel node biopsy in early breast cancer

Trial/author	Year	SLN identification (%)	Sensitivity (%)	False negativity (%)
Veronesi et al. [24]	2003	98.5	91.2	8.8
ALMANAC [25]	2006	98.0	93.3	6.7
Sentinella-GIVOM [26]	2008	95.0	83.3	16.7
SNAC [27]	2009	94.0	94.5	5.5
Canavese et al. [29]	2008	98.6	77.1	9.1
NSABP B-32 [28]	2007	97.3	90.2	9.8

SLN=sentinel lymph node.

Comparison of morbidity outcomes (SLNB vs. ALND)

Trial/author	No. of patients	Arm lymphedema (%)	Axillary numbness (%)	Abduction deficit (%)	Seroma (%)
Veronesi et al. [24]					
SLNB	259	7	1	0	NR
ALND	257	75	68	21	
ALMANAC [25]					
SLNB	478	5	11	Significantly impaired in ALND group	NR
ALND	0476	13	31		
Sentinella-GIVOM [30]					
SLNB	345	OR = 0.48*	OR = 0.51†	OR = 0.55‡	NR
ALND	352				
SNAC [27]					
SLNB	0544	2.8	NR	2.5	17
ALND	0539	4.2	-	4.4	36
NSABP B-32 [32]					
SLNB	2,697	8	8.1	13	NR
ALND	2,619	14	31.1	19	
Purushotham et al. [31]					
SLNB	143	OR = 0.30§	66	No significant change	14
ALND	155		84		21

SLNB=sentinel lymph node biopsy; ALND=axillary lymph node dissection; NR=not reported; OR=odds ratio.

*p=0.01; †p<0.0001; ‡p=0.02; §p=0.004.

Comparison of survival outcomes (ALND vs. SLNB)

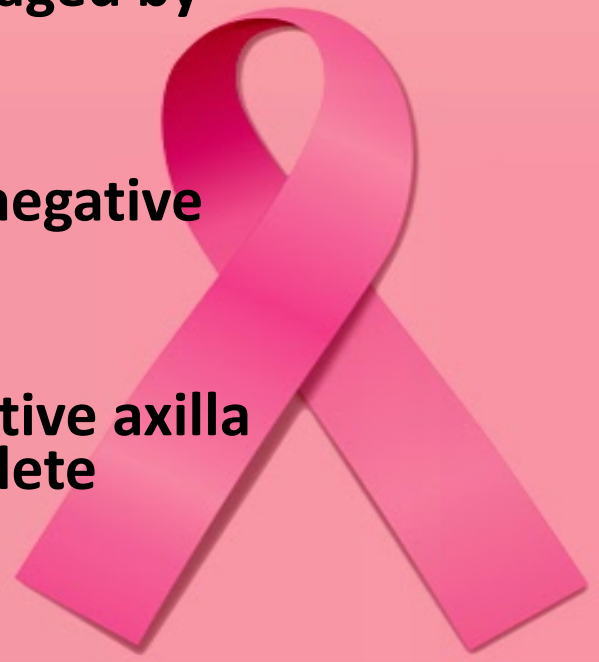
Trial/author	Axillary recurrences (%)	Disease-free survival (%)	Overall survival (%)
Veronesi et al. [33]	0 vs. 0.01	88.8 vs. 89.9 (10 yr)*	89.7 vs. 93.5 (10 yr)†
ALMANAC [25]	0.84 vs. 0.2 (1 yr)	NR	NR
Sentinella-GIVOM [30]	0.05 vs. 0.01	89.9 vs. 87.6	95.5 vs. 94.8
Canavese et al. [29]	0.87 vs. 0.0	89.8 vs. 94.5‡	97.2 vs. 97.2§
NSABP B-32 [34]	0.1 vs. 0.3	82.4 vs. 81.5 (8 yr)	91.8 vs. 90.3 (8 yr)

ALND=axillary lymph node dissection; SLNB=sentinel lymph node biopsy; NR=not reported.

*p=0.52; †p=0.15; ‡p=0.715; §p=0.697.

INDICATIONS FOR SENTINEL NODE BIOPSY

- **Early breast cancer with a clinically negative axilla.**
- **DCIS managed by mastectomy.**
- **DCIS with suspicious features of harbouring invasive cancer managed by lumpectomy.**
- **In the setting of neoadjuvant chemotherapy in a clinically node negative axilla.**
- **Post neoadjuvant chemotherapy in patients with a clinically positive axilla who are rendered negative after chemotherapy i.e. have a complete clinical response.**



CONTRAINDICATIONS

- **Clinically palpable metastatic nodes**
- **T4 tumour**
- **Inflammatory breast CA**
- **If the axillary status is not going to influence the planned treatment**
- **Pregnancy**

SNLB TECHNIQUES

- Proper surgical technique is very important in SLNB to minimize the risk of understaging and undertreating patients as this has a direct impact on survival.
- The technique of carrying out a SLNB involves injecting one or two tracers into the breast skin or parenchyma either in the vicinity of the tumour or under the areolar plexus.
- From the injection site the tracers then enter the lymphatic channels and passively flow into the draining lymph nodes. The first lymph nodes to have the tracer are then identified as sentinel nodes and removed.

SLNB TECHNIQUES

Radioisotope technique

- Technetium Sulphur Colloid/Technetium-labelled serum albumin used.
- Half-life of Technetium is six hours.
- Amount injected depends on the time of the injection relative to the timing of the surgery, usually 0,5mCi to 2,5mCi injected.
- A hand held gamma probe is used to identify the area of maximum radioactivity in the axilla.

SLNB TECHNIQUES

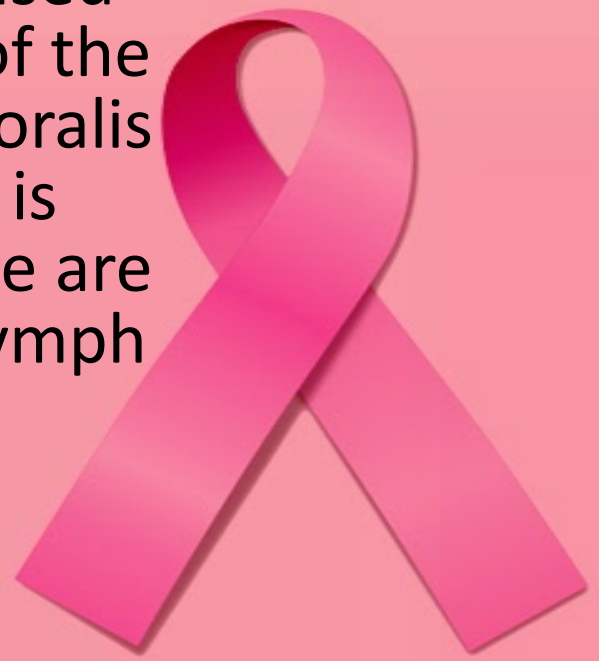
Radioisotope technique

An axillary incision is then made over the hot spot. It is important that this incision is made such that it can be incorporated into the incision of a subsequent ALND if indicated. The lymph node with the most radioactivity as determined by the gamma probe is removed first. An ex-vivo count is then obtained. Nodes with more than 10% of the ex-vivo count of the most radioactive node should also be removed. Usually two to three sentinel nodes should be removed. If four have been removed there is no value in removing more. It is however important to remove all suspicious palpable node even if they don't display any radioactivity as this decreases the false negative rate of SLNB. It is important to avoid the "shine through" effect.

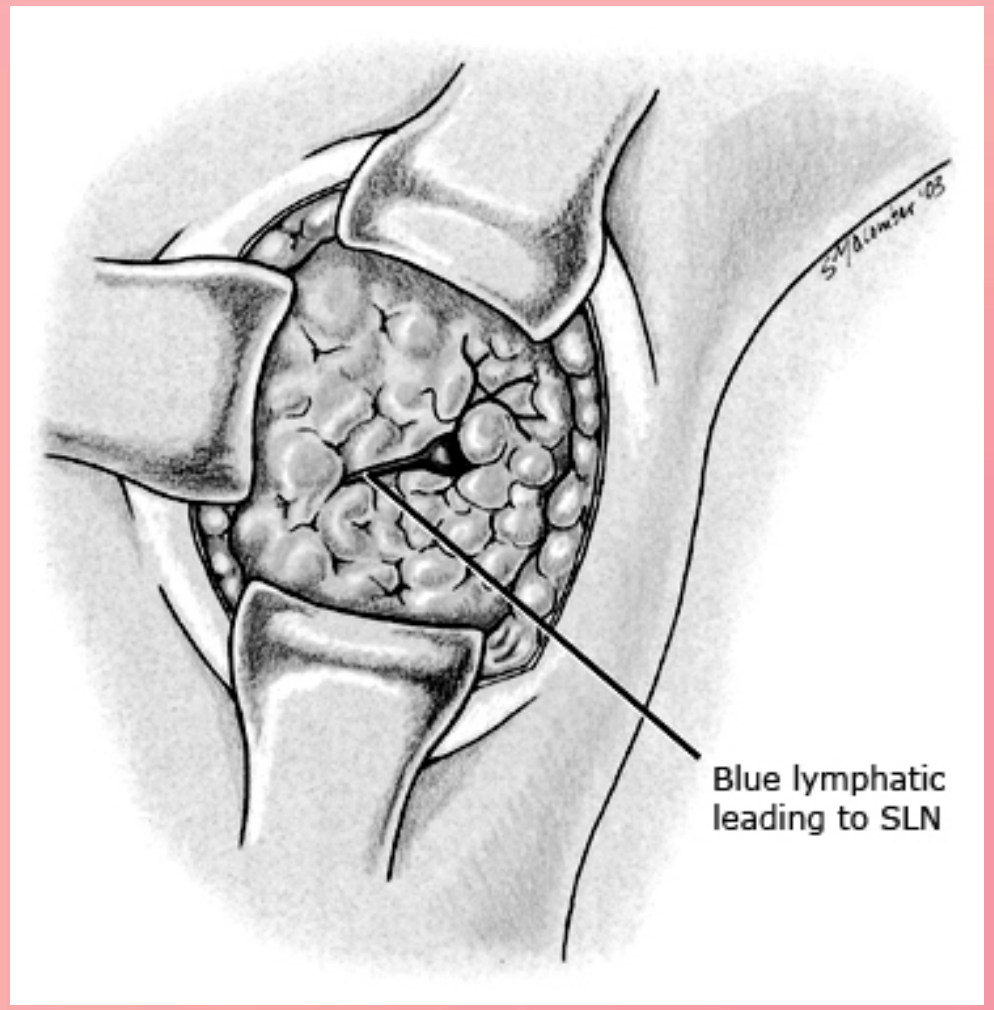
SLNB TECHNIQUES

Blue dye

3 – 5 ml of 1% isosulfan blue/patent blue dye is injected around the tumour periphery or into the subareolar plexus. Methylene blue is an alternative. After the injection the breast is massaged for about 5 minutes to dilate the lymphatics. If the dye is used alone, an axillary incision is then made at the lower edge of the axillary hairline extending to the lateral border of the pectoralis major muscle as for ALND. A careful meticulous dissection is then made looking for blue lymphatic channels. Once these are found they are followed until they lead to a blue-stained lymph node, as depicted in the diagram below.



SLNB TECHNIQUES



SLNB TECHNIQUES

Blue dye

All blue lymph nodes and any lymph node at the end of a blue lymphatic channel are removed as sentinel nodes. It is important to identify the bluest node and the blue node most proximal to the tumour in the axilla as the dye transit time is rapid and this can result in the staining of non-sentinel nodes. The two most common technical errors when using this technique are failure to remove the bluest node, and failure to recognize the node at the end of a blue lymph channel as a sentinel node even if it hasn't taken the dye.

RADIOISOTOPE VS BLUE DYE

Sentinel node mapping in early breast cancer

- There are no large controlled randomized trials comparing the use of radioisotope to blue dye in sentinel node mapping.
- The combined technique is generally accepted as the gold standard as it has consistently been shown to have the lowest false negative rate (FNR).
- Several systemic reviews in patients where the combined technique was used followed by ALND have shown the radioisotope to be superior to the dye i.e. having better identification rates (IR) and lower FNR. All these studies were carried out in patients with early breast cancer and a clinically negative axilla.

RADIOISOTOPE VS BLUE DYE

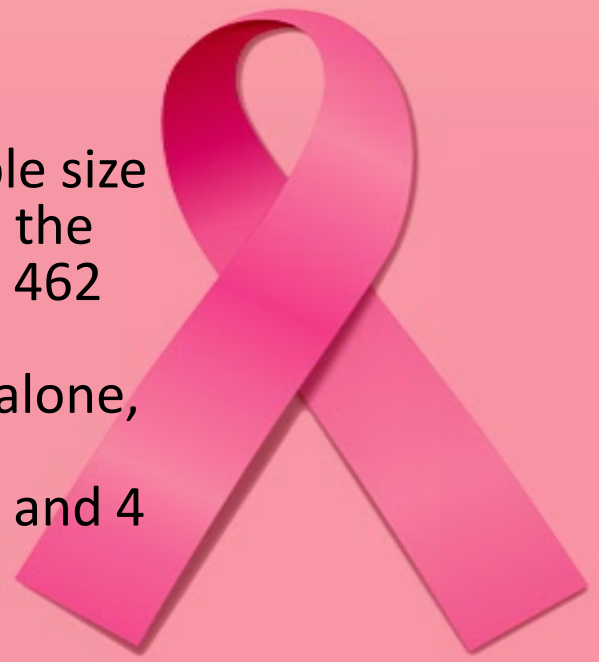
Sentinel node mapping in early breast cancer

- In the NSABP B-32 trial in patients with clinically node-negative breast cancer, both tracers were used for sentinel node mapping.
- 65% of the nodes were both hot and blue
- 24% were hot only
- 5% were blue only,
- 3.9% were neither hot nor blue

RADIOISOTOPE VS BLUE DYE

Sentinel node mapping in early breast cancer

- A number of studies have suggested that with the increased surgical experience in the radioisotope technique, the added value of blue dye over radioisotope alone is minimal.
- Recently a systematic review looking at the combination of blue dye and radioisotope versus radioisotope alone reached a conclusion that the superiority of dual tracers is limited, and it did not lower the FNR.
- 24 studies were included in this meta-analysis. Only studies with a sample size over 100 were included and all retrospective studies were excluded. it is the largest and most comprehensive systemic review, analyzing a total of 15 462 patients. For patients with a positive lymphoscintigraphy no statistically significant difference was found between dual tracers and radioisotope alone, further validating radioisotope over blue dye. Of note is that of the 24 publications, no study reported adverse episodes with the radioisotope, and 4 studies reported allergic reaction to blue dye.



RADIOISTOPE VS BLUE DYE

- Very recently a systemic review and meta-analysis of SLNB mapped with methylene blue dye alone in breast cancer was published.
- The period reviewed was from January 1, 1993 to 31 March 2018. A total of 1559 patients in 18 studies published from 2000 and 2017 were eventually included.
- The identification rate (IR) of methylene blue was found to be 91% but the FNR was unacceptable at 13%. Conclusion drawn from this meta-analysis was that caution is warranted when using methylene blue dye alone as the mapping method of sentinel node biopsy.

RADIOISOTOPE VS BLUE DYE

Sentinel node mapping in the setting of NACT

- In the NSABP – 27 trial, a multicenter study in which a subset of 428 patients underwent SLNB + ALND after NACT.
- SLN identification rate (IR) was 85% and FNR was 11%.
- In this study there was a marked difference in the FNR when comparing the two tracers. The FNR was lower with the radioisotope at 8% compared to the blue dye at 14%.
- In this setting blue dye alone is clearly shown to have an unacceptable FNR and is therefore not recommended.

RADIOISOTOPE VS BLUE DYE

Sentinel node mapping in the setting of NACT

- Recently the results of two trials namely the SENTINA trial and ACOSOG Z-1071 trial which both looked at SLNB in the node positive patients who end up with a pathological complete response (pCR) following NACT were published.
- Both trials showed that SLNB in these patients is feasible but the FNR is too high.
- This is only lowered to acceptable levels if certain conditions are fulfilled. One of the conditions is that dual tracers must be used.
- This therefore disqualifies the use of a single tracer in this setting as too many patients will be falsely declared node negative post chemotherapy.

RADIOISOTOPE VS BLUE DYE

Side effects profile

- Isosulfan blue dye is associated with severe allergic reactions including anaphylactic shock requiring resuscitation in up to 2% of patients.
- It is also teratogenic and cannot be used in pregnant patients.
- Intradermal injection of methylene blue can lead to skin necrosis and intraparenchymal injection can cause induration resulting in severe pain.
- The skin incision needed when using blue dye alone is also much bigger, as the surgeon is not guided by any probe translating to more morbidity.
- All these factors favour the use of the radioisotope tracer, which has negligible side effects at the dosage used for sentinel node biopsy.

CONCLUSION

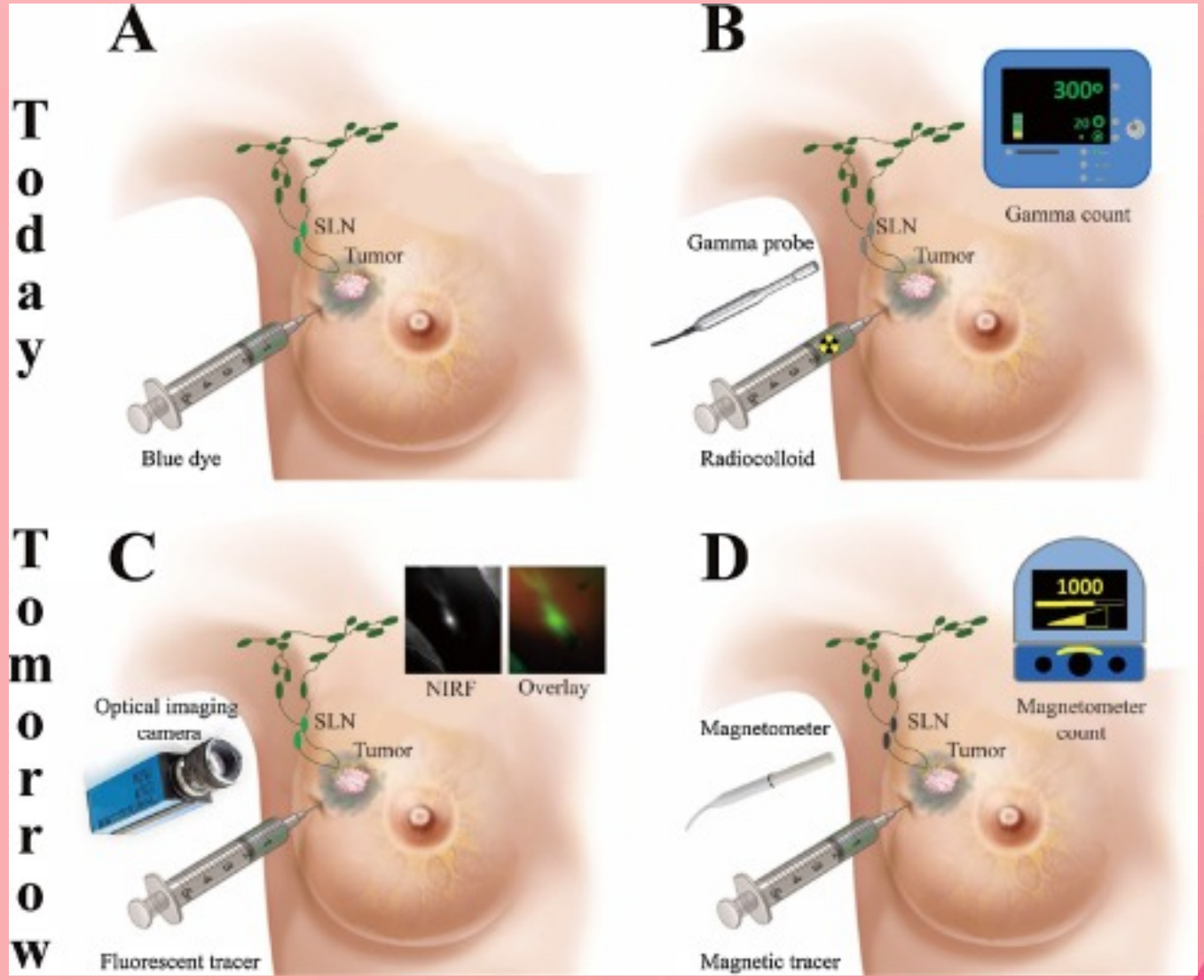
Novel techniques

Indocyanine green

The tracer is injected intradermally or in the subareolar location, and then sentinel nodes are localized using a fluorescent imaging system. A meta-analysis of 12 nonrandomized comparative studies showed this tracer to be equal or better than the radioisotope in localizing tumour positive nodes.

Superparamagnetic iron oxide

The tracer is also injected intradermally or in the subareolar region, and a hand- held magnetometer is then used to localize sentinel nodes. In a meta-analysis of seven randomized trials this technique had an identification rate of 97.1% and a FNR of 8.4%.


Today
Tomorrow
A
B
C
D
SLN
Tumor
Blue dye
Gamma probe
Gamma count
Radiocolloid
Optical imaging camera
NIRF
Overlay
Fluorescent tracer
Magnetometer
Magnetometer count
Magnetic tracer

CONCLUSION

Whilst it is very important to carefully manage resources in a resource constrained environment, oncological outcomes must remain our priority as poor oncological outcomes have far worse adverse effects even on the economy of the country. The use of blue dye alone, though much cheaper has an unacceptable high FNR, rendering it unsuitable for use as a single tracer in SLNB.