

# Sentinel Node Mapping in Early Breast Cancer: A Randomized Comparison of Fluorescein Guided All India Institute of Medical Sciences, Anurag's Technique with Technetium-99 m Sulfur Colloid Plus Methylene Blue

## Abstract

**Purpose:** Evaluation of fluorescein along with blue dye as an affordable tracer for sentinel node biopsy in comparison with technetium + methylene blue. A randomized trial was conducted with the following objectives: (1) to demonstrate that the identification of sentinel lymph node by fluorescein + methylene blue is not inferior to the identification by Tc-99 m sulfur colloid + methylene blue and (2) to evaluate the cost-effectiveness of sentinel node biopsy by above two tracers. **Subjects and Methods:** One-thirty patients above age 18 years presenting with early breast cancer T1, T2, N0 breast carcinoma were randomized to undergo sentinel node biopsy by either fluorescein + methylene blue or Tc-99 m sulfur colloid + methylene blue. **Results:** The sentinel lymph nodes were identified in 89% in Fluorescein + methylene blue group and 90.9% with Tc-99 m sulfur colloid + methylene blue group. The trial demonstrated noninferiority of fluorescein + methylene blue as compared to isotope + methylene blue with effect size = 1; 95% confidence interval- 9.54 to + 11.54. The fluorescein + methylene blue was more cost-effective than isotope guided sentinel node biopsy. **Conclusion:** Fluorescein-guided sentinel node biopsy is noninferior and more cost-effective than isotope-guided sentinel node biopsy.

**Keywords:** Breast cancer, cost-effectiveness analysis, fluorescein, noninferiority hypothesis, randomized trial, sentinel lymph node biopsy

## Introduction

NCCN and other guidelines recommend axillary evaluation in women with early breast cancer by sentinel node biopsy by a combination of isotope and blue dye. The facility for isotope guided sentinel node biopsy is not available in many low- and middle-income countries.

Indocyanine green (ICG) is an alternative to the isotope-guided sentinel lymph node biopsy. ICG requires very expensive infrared light source for excitation and an infrared camera for capturing the fluorescence. Fluorescein sodium is widely used in medicine and ophthalmology. It is very safe and requires low-cost blue light for excitation. On excitation with blue light of 480 nm wavelength (absorption maxima), it emits green fluorescence with a peak wavelength of 520 nm (excitation

maxima) which can be seen by the naked eye [Figure 1].

Dan *et al.* described the initial use of fluorescein in sentinel node biopsy in patients with colon cancer.<sup>[1]</sup>

Srivastava *et al.* developed the technique of sentinel node biopsy in breast cancer by fluorescein at Tata Memorial Hospital Mumbai, India, and refined the technique at the All India Institute of Medical Sciences (AIIMS) New Delhi India.<sup>[2,3]</sup> The present work describes the identification rate and cost-effectiveness of sentinel lymph node biopsy in patients with early breast cancer with clinically and sonographically negative axilla.

## Study setting

The department of Surgical Disciplines, and Department of Nuclear Medicine, AIIMS, New Delhi. The AIIMS is a tertiary care Government Teaching Hospital.

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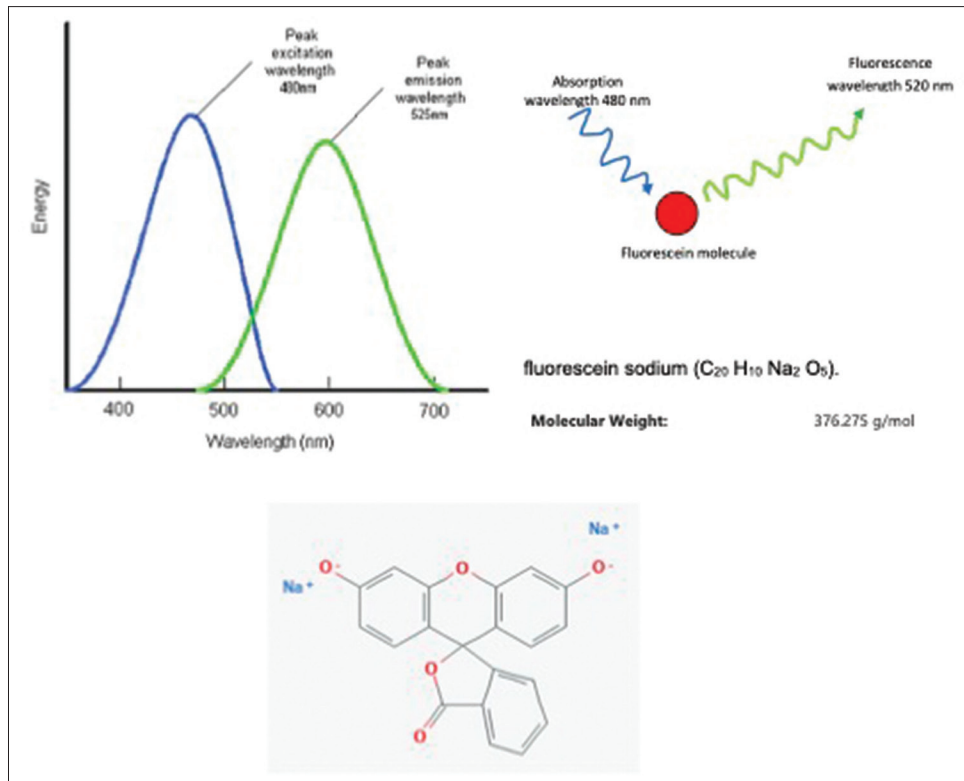


Figure 1: Fluorescence from Fluorescein excited by blue light of 480 nm wavelength (absorption maxima) emitting green fluorescence with wavelength 520 nm (emission maxima)

### Study design

Two arm parallel design randomized controlled trial with noninferiority hypothesis.

### Research question

- Question 1. Can the combination of fluorescein plus methylene blue identify the same proportion of sentinel nodes as identified by isotope (Tc-99 m sulfur-colloid) plus methylene blue in early breast cancer?
- Question 2. Is “fluorescein plus methylene blue” guided sentinel node biopsy more cost-effective than “isotope Tc-99 m sulfur colloid plus methylene blue” guided sentinel node biopsy?

### Primary objectives

To demonstrate that the identification rate of sentinel nodes by combination of “fluorescein plus methylene blue” is “not inferior” to the identification rate of combination of “Tc-99 m sulfur colloid plus methylene blue.”

### Secondary objectives

1. To record the cost in performing sentinel node biopsy with fluorescein plus methylene blue and with Tc-99 m sulfur colloid plus methylene blue and to perform a cost-effective analysis
2. To record the adverse events due to sentinel node biopsy.

### Study population

Patients with histologically confirmed early breast carcinoma with clinically and sonographically node-negative axilla; T1, T2, N0 disease.

### Sample size consideration

The sample size has been computed based on the following assumptions:

The identification rate of sentinel lymph node with technetium-99 m sulfur colloid plus methylene blue has been assumed as 97%. The identification rate of fluorescein and methylene blue has been assumed to be 90%. Our previous validation study in AIIMS demonstrated an identification rate of 92% for Fluorescein. We chose a noninferiority margin of 10% with an alpha error of 0.05 and power of 90%. The sample size required = 71 patients per arm of the trial.

### Ethical approval

The trial was approved by Ethics committee of AIIMS, New Delhi.

### Method of randomization

A computer-generated randomization schedule with an allocation ratio of 1:1, (on nQuery software, licensed by AIIMS Biostatistics Department) was created. The randomization codes were entrusted with a person other than principal investigator and the guides. They were

concealed in a brown opaque sealed envelope and handed over to the principal investigator. The envelope was opened 1 day before the procedure since the radioisotope (if allocated), had to be given by the nuclear medicine doctor a day before the sentinel node biopsy.

### Blinding

The resident evaluating the outcomes and the statistician doing data analysis were blinded to the allocation groups. The patients were told about the group, isotope or fluorescein because in isotope group they had to be shifted to the Department of Nuclear Medicine for injection of Tc-99 m sulfur colloid. The surgeons were not blinded as they had to explain the specific technique of surgery to patient and arrange a gamma probe in the operation theatre for isotope-guided sentinel lymph node biopsy.

## Subjects and Methods

### Inclusion criteria

1. All patients with histologically confirmed early breast cancer T1, T2 on TNM (AJCC 8<sup>th</sup> Edition), attending the departmental breast clinic
2. Clinically and sonographically node-negative axilla N0 disease
3. No multifocal and multicentric disease
4. No known allergy to methylene blue and fluorescein.

### Exclusion criteria

1. Refusal to sign consent
2. Palpable axillary lymph nodes
3. Patient with distant metastasis
4. Pregnant and lactating mothers (relative contraindication for isotope injection)
5. Patients with prior surgery to breast or axilla, scarring in axilla due to burns, trauma, and tuberculosis
6. Previous radiotherapy and or chemotherapy.

### Technique of sentinel lymph node biopsy

Patients with histologically confirmed early breast carcinoma (T1, T2, N0, M0) with clinically and sonographically negative axilla were recruited in the study. The eligible patients were randomized to one of two groups either Tc-99 m sulfur colloid plus methylene blue (T + MB) or fluorescein plus methylene blue (F + MB). In general, the procedure was performed under local anesthesia. However, for obese patients, those with comorbidities (hypertension, heart disease, and diabetes) and very apprehensive patients, the sentinel lymph node biopsy was performed under general anesthesia along with the surgical removal of primary breast tumor.

### Technique of Tc-99 m sulfur colloid plus methylene blue-guided sentinel lymph node biopsy

The Tc-99 m sulfur colloid injection was prepared fresh and injected at the Department of Nuclear Medicine, AIIMS, New Delhi.

### Site of injection of Tc-99 m sulfur colloid

Lower inner quadrant intra-dermally at the edge of areola away from axilla to avoid “shine through” effect.

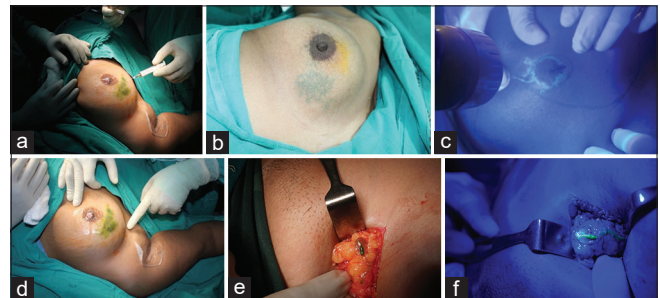
### Dose of isotope

1000 microcurie, unfiltered, was injected 1 day before if the patient was scheduled as first case in the morning. For other patients, the isotope was injected, 2 h before surgery (filtered, 500–700 microcurie).

### Methylene blue injection

In operation theater, 1 ml of 1% methylene blue, diluted in 4 ml saline was injected with a 23 g needle; half of the volume at multiple sites intra-dermally in periareolar region in the direction of axilla, and half deep to areola. Figure 2 illustrates the operative steps of sentinel node biopsy [Figure 2a-f].

The breast tissue was gently massaged towards the axilla to facilitate the passage of dye into the lymphatics and axillary nodes. The axillary crease was incised after 5 min of massage, at the site of maximum gamma-ray count detected by gamma probe. The subcutaneous fat was gently teased away with the help of cotton sponge swab (Jatoi’s technique) till the axillary fascia was exposed. This fascia was incised and using blunt and sharp dissection an effort was made to identify the blue stained lymphatics. The sentinel node was identified with the help of gamma probe and blue color. The node connected to the blue lymphatics was also considered a sentinel lymph node. The nodes (s) was checked for radioactivity using a gamma probe. The node emitting the highest gamma-ray count was considered as sentinel node following rule of 10, i.e., a gamma-ray count more than 10 times the background count on a remote part of body, for example, if background count on leg or towards the ceiling, is zero, then a count of ten or more) was taken as a definition of a “hot node.” The nodes emitting at least 10% of the 10 s count of first (hottest)



**Figure 2: Operative illustration of fluorescein guided sentinel node mapping.** (a) Injection of combined tracer fluorescein 0.125 ml plus methylene blue one ml diluted in 4 ml of normal saline, injected half in intradermal plane and half in subareolar plane. (b) Dermal lymphatic plexus delineated with blue and yellow dyes seen on white light. (c) Fluorescent lymphatics shining with blue LED light (480 nm wavelength). (d) Incision along lateral mammary skin crease. (e) Greenish blue lymphatics and lymph node seen with white light. (f) Fluorescent lymphatic duct and lymph node shining with blue LED light

sentinel node was considered as second “hot” sentinel node (s) and was also harvested. These nodes were marked as sentinel nodes and sent for histopathological examination by frozen section if the operation was done under general anesthesia and in formalin for paraffin fixed hematoxylin-eosin histological examination if sentinel lymph-node biopsy was done under local anesthesia.

### Technique of Fluorescein and methylene blue guided sentinel lymph node biopsy

Initially, we used 0.25 ml of fluorescein diluted in 4 ml saline (first 60 cases), but later our physicist found out that the fluorescence increases by diluting the fluorescein, therefore we later changed the dose to 0.125 ml in 4 ml saline for the last 70 cases to increase the fluorescent activity.

We injected 0.125 ml (measured with a Tubercular syringe) of 10% Fluorescein sodium and 1 ml of 1% methylene blue dye, diluted in 4 ml of normal saline in a 5 ml syringe. This mixture was injected at multiple sites with a 23 gauge needle, half of the volume intradermally towards the axilla, and half of the volume in the sub-areolar region. The breast tissue was gently massaged in the direction of axilla for 5 min and an incision was made on the lateral mammary skin crease. Fluorescent or blue dye-stained lymphatics were visualized by dissection of axillary tissue. Fluorescent green lymphatics were identified with the help of blue LED lamp (wavelength = 480 nm) and traced to the sentinel node. These nodes were marked as sentinel nodes and sent for histopathological examination. If no hot, blue, fluorescent, or palpable lymph node was found after 20 min of dissection, the procedure was considered as failure of sentinel node biopsy. In such cases, an axillary sampling was carried out by Dr. RA Badwe’s technique.

### Dr. RA Badwe’s technique of axillary sampling (Tata Memorial Hospital technique)

The axillary adipo-glandular tissue contained in the lower level I axilla bounded by lateral border of pectoralis major anteriorly, anterolateral border of latissimus dorsi posteriorly and inter-costo-brachial nerve superiorly was removed and sent for pathological evaluation.<sup>[4]</sup>

### Statistical analysis

Basic demographic characteristics were analyzed in two groups. Continuous variables were plotted in graph to assess the normal distribution and a normality check was performed. The results of two groups (Isotope and fluorescein), were compared by Student’s *t*-test for normal and Mann–Whitney U-test for nonnormal continuous data. The categorical data were analyzed by Chi-square test or Fisher’s exact test as deemed suitable.

The primary outcome of interest was “identification of sentinel nodes” by a particular tracer. Effect size and its 95% confidence interval were computed. The decision

to assess noninferiority was based on 10% noninferiority margin decided *a priori*. Both “intention to treat” and “per protocol analyses” were performed.

### Economic evaluation

A “societal perspective of economic evaluation” was considered.

The direct cost was computed for each patient in the two groups.

The direct cost was defined as the sum total of: cost of tracer + cost of manpower + cost of equipment + operation theatre cost.

The equipment cost of the gamma-ray detection probe in our institute was Rs 2 million INR. It is assumed that one set of gamma-ray detection unit will serve the sentinel lymph node biopsy for 7 years.

Thus, the cost of the gamma-ray detection probe would be Rs 285714.28 per year. In 2019 a total of 57 cases of sentinel lymph node biopsy were done using this equipment. Assuming the same number of sentinel lymph node biopsy every year the cost of equipment (gamma probe) for one sentinel lymph node biopsy would be Rs. 5012.53.

The blue LED light of 480 nm was purchased for Rs. 400 INR. We assumed that it will last for 7 years and 57 sentinel lymph node biopsy by methylene blue and fluorescein could be performed by this LED light in 1 year, Hence, the cost of blue LED light for one sentinel lymph node biopsy would be Rs. 1.00025 INR.

### Operation theatre [OT] cost

These costs had been calculated by the Department of Hospital Administration at our Institute and the average cost of OT time open surgery, considering inflation over the years (India Inflation rate was 4.17% by April 2016), these costs for the year (2020) would be Rs. 60.41/min for open surgery. The indirect cost (wages lost + travel cost) was not added in cost analysis as the distance traveled by patients and the wages varied enormously amongst different patients.

Cost-effectiveness for the two types of tracers (two arms of randomization) was calculated separately by dividing the total cost incurred in one group divided by the total number of successfully performed sentinel lymph node biopsy in that group.

## Results

### Baseline characteristics

The baseline characteristics among the two groups, namely, age, body mass index, menstrual status, side and site of breast cancer, T staging of cancer, and immunohistochemical status of estrogen and progesterone receptor and Her 2 Neu receptor, were similar [Table 1].



**Table 1: Baseline characteristics**

Baseline characteristics	T + MB (n=66)	F + MB (n=64)	P
Age (years), mean (SD)	53.18 (10.66)	52.5 (11.43)	0.72
BMI (kg/m <sup>2</sup> ), mean (SD)	24.73 (4.60)	25.22 (3.54)	0.49
Menopausal status, n (%)			
Postmenopausal	44 (66.6)	44 (68.7)	0.80
Premenopausal	22 (33.3)	20 (31.2)	
Side of breast cancer, n (%)			
Right side	27 (40.9)	31 (48.4)	0.38
Left side	39 (59.0)	33 (51.5)	
Site of breast cancer, n (%)			
UOQ	29 (43.9)	28 (43.7)	0.94
LOQ	9 (13.6)	6 (9.3)	
UIQ	7 (10.6)	7 (10.9)	
LIQ	9 (13.6)	11 (17.1)	
Retro areolar	12 (18.1)	12 (18.7)	
T staging, n (%)			
Tis	4 (6.0)	3 (4.6)	0.87
T1	14 (21.2)	12 (18.7)	
T2	48 (72.7)	49 (76.56)	
Estrogen receptor, n (%)			
Positive	46 (69.7)	45 (70.3)	0.93
Negative	20 (30.3)	19 (29.6)	
Progesterone receptor, n (%)			
Positive	44 (66.6)	30 (46.8)	0.02
Negative	22 (33.3)	34 (53.1)	
Her 2 Neu receptor, n (%)			
Positive	14 (21.2)	17 (26.5)	0.50
Negative	52 (78.7)	47 (73.4)	

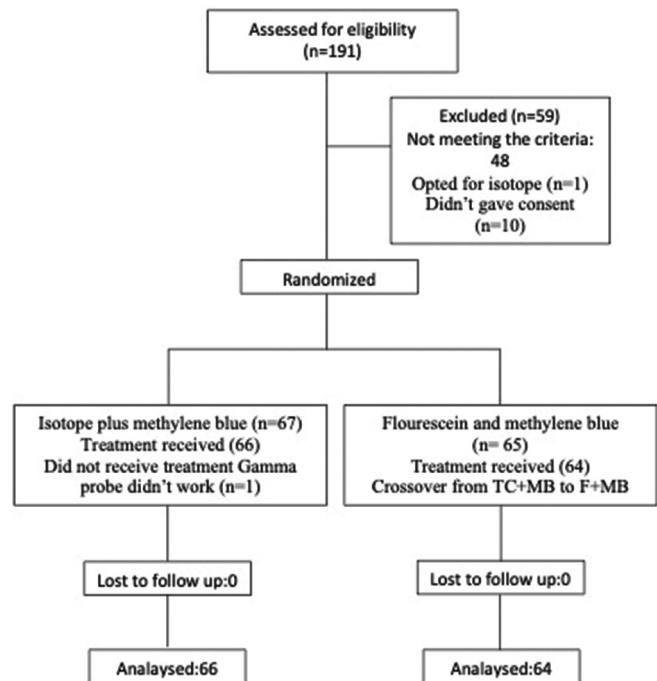
Values expressed as mean and SD or Frequency and (%). SD: Standard deviation, BMI: Body mass index, Her 2: Human epidermal growth factor receptor 2, F + MB: Fluorescein plus methylene blue, T + MB: Technetium+Methylene Blue, UOQ: Upper outer quadrant, LOQ: Lower outer quadrant, UIQ: Upper inner quadrant, LIQ: Lower inner quadrant

The CONSORT flow diagram is presented in Figure 3. Sixty-six ladies were analyzed in the isotope + methylene blue group and 64 ladies in the methylene blue + fluorescein group.

One patient crossed over to methylene blue plus fluorescein group as gamma probe was not working after randomization on the day of surgery. There was no drop out of any patient after randomization and no loss to follow up in the study. Gamma probe did not work intra-operatively after injection of tracer in other 3 patients. Blue nodes were identified in one patient leading to successful identification of sentinel node. In one patient axillary sampling was done as the node was not identified with blue dye. In another patient, there was intense radioactivity throughout the axillary region and no hot or blue node could be identified. Hence, in these patients, axillary sampling was performed.

**Primary Outcome: Identification of sentinel nodes**

The identification rate of fluorescein + methylene blue = 89% and in Tc-99 m sulfur colloid + methylene blue = 90.9%, with effect size of one and 95% confidence



**Figure 3: CONSORT flow diagram**

interval between - 9.54 and + 11.54. Thus, our study demonstrated that the identification rate of sentinel nodes using fluorescein + methylene blue is “not inferior” to that of Tc-99 m sulfur colloid + methylene blue.

The criteria for noninferiority was as follows: lower limit of the 95% confidence interval of effect size should not include the decided noninferiority margin, i.e., -10 or 10%. There was no difference in intention to treat and per-protocol analyses. Figures 4 and 5 depict the conclusion from noninferiority trial for whole data (130 cases) and in the last 70 cases. The median number of sentinel nodes harvested was 3 in both the groups.

The analysis of the last 70 cases on “intention to treat” analysis, revealed the identification rate of fluorescein + methylene blue = 94.2% with effect size three and 95% confidence interval between -9 and + 15 (P = 0.588). The “per protocol” analysis revealed similar results [Table 2]. The data on Table 2 and Figure 5 prove the “noninferiority” of fluorescein + methylene blue, compared to identification with isotope + methylene blue (identification rate = 91.4%).

**Secondary outcomes**

*Cost-effectiveness analysis*

A societal perspective was considered for cost evaluation as AIIMS is a fully funded government hospital and patients did not pay for their sentinel node biopsy procedure. We performed the cost-effectiveness analysis of the sentinel lymph node biopsy program for the two groups for the last 70 patients [Tables 3 and 4]. The drug cost of methylene blue + fluorescein was less than that of isotope + methylene

**Table 2: Identification rate in two groups**

	T + MB (n=66), n (%)	F + MB (n=64), n (%)	Effect size (95% CI)
Intention to treat analysis			
Identification rate of sentinel lymph nodes	60 (90.9)	57 (89.0)	1 (-9.54-+11.54)
Per protocol analysis			
Identification rate of sentinel lymph nodes	59 (90.77)	58 (89.23)	1 (-9.53-+11.54)

Primary Outcome -Identification rate. CI: Confidence interval, F + MB: Fluorescein plus methylene blue, T + MB: Technetium+Methylene blue

**Table 3: Cost-effectiveness analysis according to all India Institute of Medical Sciences costing**

Costs in INR (Rs.)	T + MB (n=34)	F + MB (n=36)	P
Cost of drug/person (SD)	300 (0)	160 (0)	
Manpower cost (SD)	936.93 (383.3)	1047.72 (541.3)	0.32
Equipment cost (SD)	5012 (0)	1.07 (0)	<0.001
OT cost (SD)	1152.12 (82.50)	1193.09 (82.16)	0.73
Cost/per successful sentinel node biopsy (USD; Euro)	8118.38 (109; 91)	2543.18 (34; 28)	<0.001*

\*Z test, Values are expressed as mean and SD. SD: Standard deviation, OT: Operation theatre, F + MB: Fluorescein plus methylene blue, INR: Indian rupee, T + MB: Technetium+Methylene blue

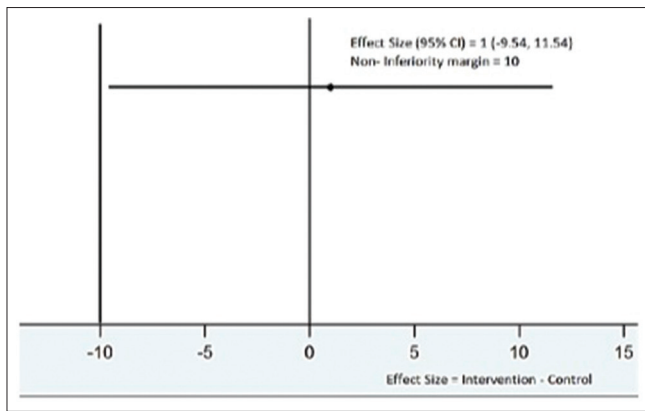


Figure 4: Conclusion from noninferiority trial (130 patients)

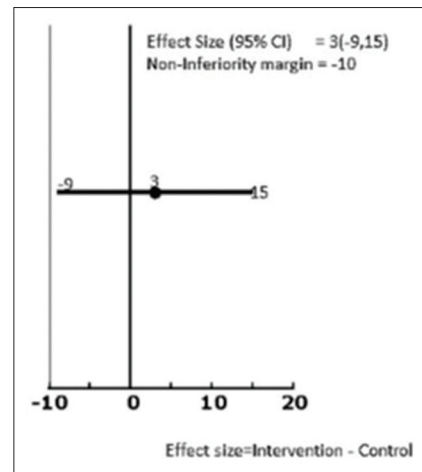


Figure 5: Conclusion from noninferiority trial (last 70 cases)

blue. The manpower cost in both the groups was similar and was not different statistically. The cost of drug and equipment was higher in the Tc-99 m Sulfur colloid group. AIIMS is a heavily subsidized government hospital, hence, the cost of Tc-99 m Sulfur colloid in our hospital is much less than the market price in private hospitals. Therefore, we analyzed the data with both market cost and the cost at AIIMS. Cost per successful sentinel node biopsy in Tc-99 m Sulfur colloid group was Rs 8118.38 (US Dollars = \$109.04) on AIIMS price and Rs 13273.22 (US Dollars= \$178.27) using market price. The cost per successful sentinel node biopsy in fluorescein + methylene blue group was Rs. 2543.18 (US Dollars = \$34.16) both in AIIMS pricing as well as on market price. It is quite evident from this study that the dual tracer, “fluorescein + methylene blue” offers a highly cost-effective alternative to the isotope-based sentinel node biopsy. When sentinel lymph node biopsy was done at AIIMS, the price is very low as the cost of radio-tracer is less (Rs 200), however, if the same procedure is done in a private hospital the cost rises significantly. Total cost according to AIIMS costing in T + MB = Rs 251669.99 for whole group, and in

fluorescein + methylene blue group = Rs. 86468.23 rupees for the whole group.

Figure 6 demonstrates the costing data as box and whisker plot as the cost data were not normally distributed.

Time taken in sentinel node biopsy: The mean time spent for the sentinel lymph node biopsy was 26.69 min (standard deviation [SD] = 10.64) in Tc-99 m sulfur colloid + methylene blue and 26.23 min (SD = 9.93) in methylene blue + fluorescein group. The difference in time between the 2 groups was not significant statistically with  $P = 0.79$ .

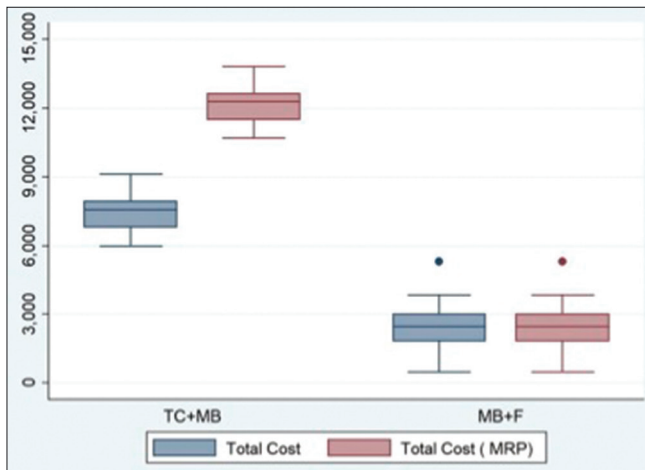
The mean length of incision was 4.0 cm (SD = 0.95) in the Tc-99 m sulfur colloid + methylene blue group and 4.1 cm (SD = 1.14) in the methylene blue + fluorescein group. The difference in the incision length was not significant  $P = 0.71$ .

The number of metastasis positive sentinel lymph nodes = 15/66 (22.7%) in the Tc-99 m sulfur

**Table 4: Cost-effectiveness analysis with market price of isotope**

Costs in INR (Rs.)	T + MB (n=34)	F + MB (n=36)	P
Market price of drugs (SD)	5000 (0)	160 (0)	
Manpower cost (SD)	936.93 (383.36)	1047.72 (541.3)	0.32
Equipment cost (SD)	5012 (0)	1.07 (0)	<0.001
OT cost (SD)	1152.12 (82.50)	1193.09 (82.16)	0.73
Cost/per successful sentinel node biopsy (USD; Euro)	13273.22 (179; 149)	2543.18 (34; 28)	<0.001*

\*Ztest. SD: Standard deviation, INR: Indian rupee, OT: Operation theatre, F + MB: Fluorescein plus methylene blue, T + MB: Technetium+Methylene blue

**Figure 6: Box and Whisker plot of cost data in last 70 cases**

colloid + methylene blue group and 15/64 (23.4%) in the fluorescein + methylene blue group, the difference being nonsignificant at a  $P = 0.9$ .

### Adverse effects

One patient receiving an injection of the methylene blue dye with Tc-99 m sulfur colloid developed adverse effect in the form of epidermal necrosis [Figure 7]. No patient in the fluorescein + methylene blue group developed any side effect. No severe adverse event was observed.

### Discussion

We compared the standard technique of SLNB (Tc-99 m sulfur colloid plus methylene blue) with fluorescein plus methylene blue for the identification of the sentinel node.

The sentinel lymph node technique using Tc-99 m sulfur colloid with blue dye is expensive and resource-intensive. It needs a dedicated in-house radiopharmaceutical laboratory. Even in developed countries, only about 60% of the patients can afford a sentinel lymph node biopsy. We thought about an affordable alternative to replace the standard isotope technique. Fluorescein is used widely in ophthalmology (for retinal angiography and corneal ulcer staining) and brain tumor surgery.

We present the first randomized controlled trial exhibiting the “noninferiority” of fluorescein + methylene blue compared to the standard isotope-based technique.

**Figure 7: Skin necrosis following methylene blue injection**

In the last 70 cases, our identification rate increased to 91.4% in Tc-99 m sulfur colloid + methylene blue and 94.2% in the methylene blue + fluorescein group. This suggests a learning curve in performing sentinel lymph node biopsy by a particular technique and surgeons gain competency as they repeatedly perform a complex task.<sup>[5,6]</sup>

Valiveru *et al.* has validated our results with 95.4% identification and 6.3% false-negative rate with fluorescein + methylene blue.<sup>[7]</sup> Similar encouraging results of sentinel node identification have been reported by several authors with very high identification rate ranging from 94% to 100%.<sup>[8-10]</sup> The false-negative rate with fluorescein ranges from 6.3% to 7.5%.<sup>[7,9]</sup>

ICG has been used for fluorescence-based sentinel node biopsy by a number of authors with very high identification (96% to 100%), sensitivity up to 100% and a false-negative rate of zero to 3%.<sup>[11]</sup> ICG is more expensive than fluorescein. Moreover, the near-infrared light source (wavelength = 780 nm) and the infrared capturing device needed for ICG are very expensive. The blue LED light source needed to excite fluorescein is very economical. No special device is needed to capture the green fluorescence of fluorescein since it falls in the visible range of human eye and can be seen with naked eye.

In most centers in Asia and Africa, surgeons either perform complete axillary lymph node dissection or a single tracer technique of SLNB using methylene blue alone. The axillary dissection is a morbid procedure and its complications like lymphedema, shoulder pain, sensory

loss impair the quality of life.<sup>[5,12]</sup> The lymphedema can lead to significant morbidity and even mortality (due to septicemia). The cost and resources needed for fluorescein are much less compared to isotope-based sentinel node biopsy. The Tc-99 m sulfur colloid-based sentinel lymph node biopsy is resource-intensive, it requires the establishment of nuclear medicine department, installation of cyclotron, and availability of in-house trained radiopharmaceutical chemist to prepare the Tc-99 m sulfur colloid. It also requires a gamma-ray detection probe in the operation theater costing about US Dollar= \$33,678\$/Euro = 28,228. There is an increased risk of radiation exposure to both patient and the operating team. This fact needs to be appreciated where patients, doctors, or nurse are pregnant. On the other hand, fluorescein-based sentinel lymph node biopsy can be performed even in the small surgical set-up, as no expensive tools/workforce is required. Fluorescein and methylene blue are readily available and cheap. Fluorescein costs only Rs 60 rupees = \$0.8 US Dollar, for 3 ml ampoule (one patient needs only 0.125 ml) and methylene blue costs only Rs 100 rupees = \$1.34 US Dollar for 10 ml ampoule, one patient needs only 1 ml. The cost of LED blue light (Rs. 100-500; \$1.34-6.69 US Dollars) is significantly lesser compared to handheld gamma probe. There are very few studies in the literature describing cost-effectiveness of sentinel node biopsy.<sup>[13]</sup>

The escalating health care cost mandates cost containment in the health care especially so in the “post-COVID-19 world.”

Fluorescein is safe to administer even intravenously and is approved by the Food and Drug Administration for use in medical field.

We offer a simple, easy to learn and perform, affordable technology available even in the remotest village of Himalayas or anywhere else in the world.

We implore the surgeons taking care of sisters and mothers with breast cancer to adopt this fluorescent approach with blue light and shine their life with improved quality of life and save scarce resources.

### Limitations and future directions

We did not validate the competence of surgeons performing the procedure. In our department, earlier almost all sentinel node biopsy procedures were performed by a senior faculty. Since, January 2017 the specialty training in MCh Breast and Endocrine Surgery was started. Since then these specialist breast senior residents receive mentoring by a senior professor and learn the technique of sentinel node biopsy. Once, they have assisted about 30 cases, these breast residents perform the sentinel node biopsy under supervision of a faculty. There is a need to formally validate the surgical outcomes of young trainees. It has been shown that with the experience of the surgeon, the identification rates improve.<sup>[6]</sup>

### Conclusion

The identification of sentinel lymph node with fluorescein + methylene blue was not inferior to the identification by Tc-99 m sulfur colloid + methylene blue. Moreover, fluorescein-guided sentinel node biopsy is a more cost-effective and easily available alternative to Tc-99 m sulfur colloid. Fluorescein + methylene blue tracer can be adopted worldwide for the identification of sentinel lymph node biopsy for women with early breast cancer.

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### Conflicts of interest

There are no conflicts of interest.

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