

# CLINICAL AND QUALITY EFFICIENCY OF FRACTIONATED NANOCOLLOID KITS IN PRE-OPERATIVE VISUALIZATION OF SENTINEL LYMPH NODES: A COST-EFFECTIVE STRATEGY FOR PUBLIC SECTOR HOSPITALS

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## ABSTRACT

**BACKGROUND:** Sentinel lymph node (SLN) mapping is a crucial diagnostic and staging tool in breast cancer, melanoma, and gynecologic malignancies. In resource-constrained public sector hospitals, high radiopharmaceutical costs, wastage, and unpredictable patient load often challenge the sustainability of SLN services. Fractionating <sup>99m</sup>Tc-nanocolloid kits offers an opportunity to improve clinical efficiency while reducing per-patient cost and minimizing radiopharmaceutical waste. **OBJECTIVE:** To evaluate the clinical, quality, and cost efficiency of fractionated Nanocolloid kits for pre-operative SNL visualization in a public sector tertiary hospital. **METHODS:** This is a cross-sectional study performed in Nuclear Medicine & Theranostics Department of Dow university of Health Sciences. Study included consecutive 51 breast cancer patients undergoing SLN mapping from April to October 2025 using fractionated <sup>99m</sup>Tc nanocolloid aliquots prepared under validated aseptic conditions at 30-45 minutes of imaging after intradermal peri-areolar injection in all four quadrants of mapping breast with mean dose of  $39 \pm 3$  MBq. Clinical efficiency included SLN visualization rate and SLN imaging quality. Nanocolloid cold kit vial was fractionated aseptically and stored in  $-22^{\circ}\text{C}$  for use of four equal fractions in future not beyond 1 month. Radiolabeling of fractionated nanocolloid was performed as per the standard labeling protocol. Quality Control (QC) analysis included Radiochemical purity (RCP), pH, osmolality, and energy spectrum of fractionated <sup>99m</sup>Tc-Nanocolloid were tested. Secondary outcome included cost per patient compared with standard single-batch kit use. **RESULTS:** Fractionated kit use demonstrated high clinical efficacy, with SLN visualization rates of 98%, i.e. node visualization seen in 50 out of 51. Average numbers of node visualizations were  $2 \pm 1$  and 76% (39/51) received Neoadjuvant chemotherapy (NAC). Mean age of patient was  $49 \pm 9$ , 50 female and 1 male patients and almost equal left to right laterality. No evidence of labelling failure seen in visual interpretation. QC analysis was performed on reconstituted fractionated <sup>99m</sup>Tc-Nanocolloid kit of a standard batch. The analyzed results of sample revealed  $\text{pH}=6.7 \pm 0.3$  (6.5-7.5), osmolality 294 mOsm/kg (250 - 350 mOsm/kg), single photo peak= $147.50$  ( $140 \pm 10\%$  keV) on energy spectrum and Retention Factor 99.92% on Thin Layer Chromatography TCL ( $\geq 95\%$ ). **CONCLUSION:** Fractionated <sup>99m</sup>Tc-Nanocolloid kits provide clinically reliable, quality-assured, and cost-effective SLN mapping in public sector hospitals. This strategy enhances sustainability, increases patient access to diagnostic services, and aligns with resource-optimization goals in low- and middle-income health systems. Wider adoption can significantly reduce operational costs without compromising diagnostic accuracy. **Keywords:** Sentinel Lymph Node mapping, Pre-operative SLN visualization, <sup>99m</sup>Tc-Nanocolloid, Fractionated, Cost-Effective

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## Introduction

Breast cancer is the most frequent cancer diagnosed in women worldwide.<sup>1</sup> Accurate detection of SLNs minimizes unnecessary axillary dissections, reduces morbidity, and improves clinical decision-making.<sup>2</sup> Sentinel lymph node mapping has become a standard of care for staging and surgical planning in breast cancer, melanoma, and select gynecologic malignancies.<sup>3</sup> In principle the SLN represents the first lymph node receiving lymph-borne metastatic cells.<sup>4</sup>

Despite its clinical value, the high cost of radiopharmaceutical kits often designed for single-batch use poses a significant challenge for public sector hospitals in low- and middle-income countries (LMICs). Additionally, daily patient volumes frequently fluctuate, resulting in unused doses and increased operational expenditure. Characteristics of the ideal radiotracer for SLN include rapid transit to SLNs combined with prolonged nodal retention. Studies have shown that the success rate in the identification of axillary SLNs is not significantly affected by the particle size of the radiotracer.<sup>5</sup> Thus, choice of radiotracer should be based more on local availability than on differences in the lymphatic mapping features for SLN detection.

Fractionation of <sup>99m</sup>Tc-nanocolloid kits, when performed under validated aseptic and good medical practices, offers an opportunity to reduce wastage, maintain quality, and deliver SLN services at a significantly lower per-patient cost. While several centers internationally have adopted fractionation strategies for costly procedures, study suggested based on quality analysis of a fractionation of tetrofosmin kit for multiple use of a single vial for multiple cardiac imaging patients at different days.<sup>6</sup> However data from LMIC public sector settings remain limited for use of fractionated kit for multiple use.

## Objectives

This study evaluates the clinical, quality, and cost efficiency of fractionated nanocolloid use in a tertiary-care public hospital in Pakistan.

## Material and Method

This was a cross sectional observational study conducted retrospectively at the Department of Nuclear Medicine & Theranostics, Comprehensive Cancer Center

of Dow University of Health Sciences Karachi Pakistan. The study received a due exemption from review by the institutional review board. The study was conducted from April 2025 till October 2025. Retrospective retrieval of 51 patients SLN imaging data was collected retrospectively from departmental patient's logbook. Patient's demographic data and SLN imaging studies were obtained from the hospital Picture Archive and Communication system (PACs) system using Weasis version 4.5.1 against retrieved medical record (MR) numbers. Patient's demographics like age, gender, tumor demographics, history of NAC, dose of <sup>99m</sup>Tc Nanocolloid, imaging sequence were recorded from available SNL imaging. All SLN imaging were independently reviewed by two experienced nuclear medicine physicians, blinded to each other. Image quality and the number of identified sentinel nodes were recorded. SLN visualization success rate was defined as detection of at least one sentinel node. Quality scoring was labelled "1" for acceptable and "0" for non-acceptable. Per-patient cost was calculated for both fractionated and standard kit-labelling methods. Costs of radiopharmaceuticals was compared to determine cost savings and efficiency associated with fractionation.

## Radiopharmaceutical Preparation

Commercially available <sup>99m</sup>Tc-Nanocolloid kits (® Nano-HAS-ROTOP) were aseptically constituted with 4 mL of normal saline in the reagent vial and immediately stored at -22 °C in a radiopharmacy-grade freezer. On the day of the SLN procedure, the frozen constituted vial was thawed to room temperature, and under strict aseptic conditions, a 1 mL fraction was withdrawn and transferred to an empty sterile vacuum vial for radiolabeling with the required activity of <sup>99m</sup>Tc-pertechnetate, following standard labeling protocols. All radiolabeling procedures adhered to institutional standard operating procedures (SOPs) and manufacturer recommendations.

This fractionation approach was successfully utilized for four separate SLN procedures on four different sessions average 1-2 patient and maximum 3 patients/fraction over a one-month period, demonstrating its feasibility and operational efficiency.

## SLN Mapping Procedure

Patients received an intradermal periareolar injection in four quadrants of the mapping breast. The mean

administered dose was  $39 \pm 3$  MBq and volume of  $0.25 \pm 0.05$  ml per injection aliquot. Early static anterior and oblique images were acquired 30-45 minutes post-injection under dual head discovery gamma camera ® GE Healthcare.

### Quality Control (QC) Procedures

An aliquot from the fractionated batch of  $^{99m}\text{Tc}$ -Nanocolloid underwent standardized QC assessment using Elysia-Raytest Quality Control equipment. The RCP was calculated using the MiniGITA TLC scanner, pH was measured with the Quantofix Relax pH meter, osmolality was analyzed using the Knauer Osmometer, and the energy spectrum was verified using MUCHA Nova. All equipment for these QC procedures was operated through the GINA X software by Elysia. The reference acceptance criteria for  $^{99m}\text{Tc}$ -Nanocolloid are as follows: RCP  $\geq 95\%$ , pH 6.5 - 7.5, osmolality 250 - 350 mOsm/kg, and a characteristic technetium-99m photopeak at  $140 \pm 10\%$ .

### Statistical Analysis

Commercially available packages including Microsoft Excel 2016, Medcalc® 2024 version 22.019, and the Statistical Package for Social Sciences (SPSS 19® Armonk, New York, US) were utilized for the study. Statistical significance was established as  $P < 0.05$ . For continuous variables, the mean difference and standard deviation were computed for each parameter. Bland-Altman plots were constructed to illustrate the intra rater agreement in SLN node visualization and Cohen's Kappa inter-rater agreement was calculated on visual quality scoring of SLN imaging between two NM physicians.

## Results

The fractionated kit approach demonstrated high clinical efficacy, achieving a SLN visualization rate of 98%, with successful node detection in 50 of 51 patients. The average number of visualized SLNs was  $2 \pm 1$ , and 76% (39/51) of patients had received NAC. The mean age was  $49 \pm 9$  years, comprising 50 females and 1 male, with an approximately equal distribution of left- and right-sided breast involvement (Tab.1).

Kappa Inter-rater agreement was 0.920, SE=0.035 with 95% CI of 0.851-0.988 on visual quality scoring of SLN

Variable	n=51
Age (years) Mean $\pm$ SD	49 $\pm$ 9
Site of SLN mapping (Left or Right)	26: 25
Female: Male	50:01
Dose of Tc-99m Nano colloid (MBq) Mean $\pm$ SD	39 $\pm$ 02
Volume of per injection aliquot	0.25 $\pm$ 0.05 ml
Number of SLN visualization Mean $\pm$ SD	2 $\pm$ 1
Time of SLN visualization within 45 minutes	99%
Neoadjuvant chemo	39 (76%)
Success rate of SLN visualization (at least one SLN node)	50 (98%)

SD = Standard deviation, MBq = Mega Becquerel, SLN = Sentinel lymph node, SD = Standard deviation

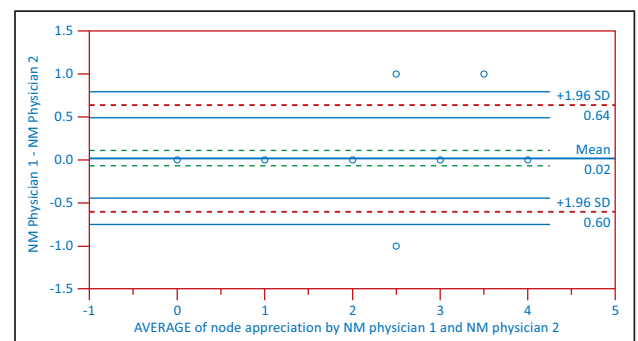
**Table 1:** Study demographics

imaging (Tab.2) and Bland Altman plot revealed very good agreement on number of SLN visualization on imaging between two reading Nuclear Physicians blinded to each other (Fig.1). No evidence of radiolabeling failure was observed on visual image assessment. QC analysis was performed on the reconstituted fractionated  $^{99m}\text{Tc}$ -Nanocolloid vial derived from a standardized batch (Tab.3). QC results demonstrated acceptable radiochemical and physicochemical characteristics, including a pH of  $6.7 \pm 0.3$  (reference range: 6.5 - 7.5), osmolality of 294 mOsm/kg (reference:

Variables	n=51
Weighted Kappa	0.920
Standard Error	0.035
95% CI	0.851 - 0.988

CI = Confidence interval

**Table 2:** Cohen's Kappa Inter-rater agreement on quality of SLN imaging by two nuclear medicine physicians blinded reading protocol.



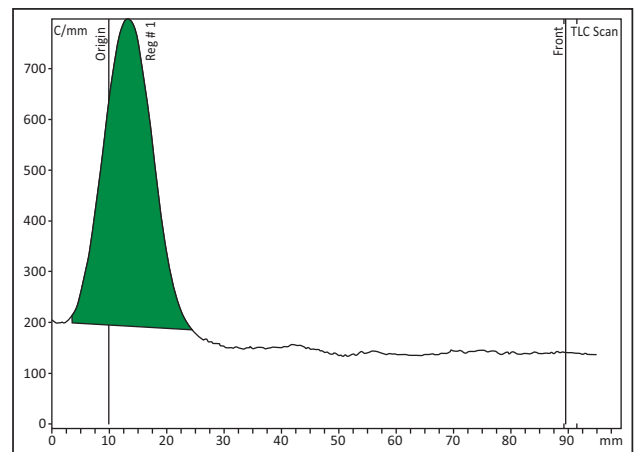
**Figure 1:** Bland Altman's plot for inter-rater agreement in SLN node visualization by two nuclear medicine physicians blinded reading protocol.

250 - 350 mOsm/kg, a single gamma photopeak at 147.5 KeV (acceptable range:  $140 \pm 10\%$ ), and a Retention Factor (RF) of 99% on TLC (acceptable  $\geq 95\%$ ) (Fig.2,3). In addition to maintaining clinical and radiochemical performance, the fractionation strategy substantially reduced radiopharmaceutical wastage and yielded a significant per-patient cost reduction, achieving up to 75-92% cost savings (depending on 1-3 patient/ fractioned kit) compared with conventional single-batch full-kit use (Fig.4).

Variables	Result	Recommended Range
Ph	$6.7 \pm 0.3$	6.5 to 7.5
Osmolality	294 mOsm/kg	250 – 350 mOsm/kg
Energy Spectrum	147.50	$140 \pm 10\%$ KeV
% Total RF factor on TLC	99.92%	$\geq 95\%$

HAS = Human serum albumin, KeV = Kilo electron volt, mOsm/kg = Miliosmolality/Kilogram, RF = Retention factor TLC = Thin layer chromatography

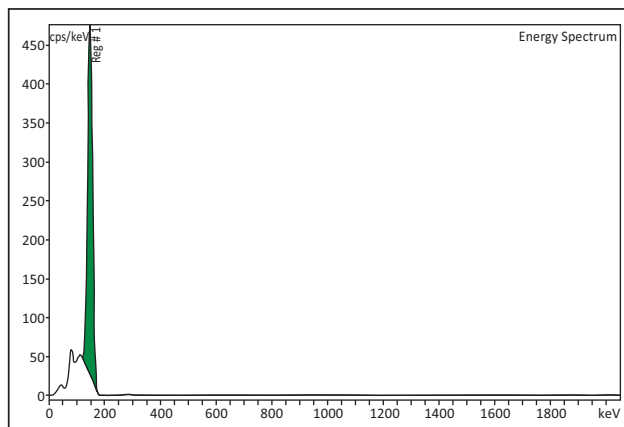
**Table 3:** Quality control analysis of  $^{99m}\text{Tc}$ -Nanocolloid (@ Nano HSA-ROTOP Germany).



**Integration TLC scan**

Substance	R/F	%Total %	Type	Area Counts	%Area %	%Total R/F %
Reg # 1	0.038	70.00	BB(M)	6183.000	100.00	99.92
Sum in ROI	-	-	-	6183.000	100.00	99.92
Total Area	-	-	-	8833.333	-	-
Area (Total) RF	-	-	-	6188.222	-	100.00
Remainder (Tot)	-	-	-	2650.33	30.00	-

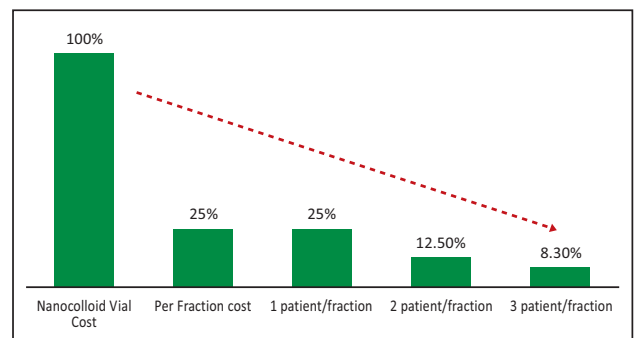
**Figure 3:** Retention factor was analyzed by Thin Layer Chromatography with runtime 480s by Mini Gita Software Version: 10.5, service pack 1, Build 6539.



**Integration energy spectrum**

Substance	R/T keV	Type	Area cps	% Area %
Reg # 1	147.50	BB (M)	9532.898	100.00
-	-	-	-	-
Sum in ROI	-	-	9532.898	100.00
Area (Total)	-	-	14075.376	-
Ext. BKG.	-	-	0.00 cps/k	-

**Figure 2:** Energy spectrum was analyzed by Mucha Nuva Software Version: 10.5, service pack 1, Build 6539.



**Figure 4:** Cost effective analysis of fractioned Nanocolloid average 1-2 patients and maximum 3 patient per fractioned vial of Nanocolloid.

## Discussion

The present study demonstrates that fractionation of  $^{99m}\text{Tc}$ -nanocolloid kits is a clinically robust, quality-assured, and cost-efficient strategy for SLN imaging in breast cancer. The SLN visualization rate of 98%, with successful detection in 50/51 patients, aligns with internationally reported performance benchmarks for SLN imaging typically more than 90% and false negative rate  $<5\%$ .<sup>5</sup> This confirms that fractionated labelling

method is cost effective when performed under standardized radiopharmacy conditions, does not compromise diagnostic efficacy.

Importantly, 76% of our cohort had received NAC, yet SLN detection remained high (on average  $2 \pm 1$  node). Axillary nodal status after NAC is a highly significant prognostic factor and there are no significant differences in the success rate of SLN biopsy post NAC when compared with patients not having received NAC.<sup>7,8,9</sup> Our findings therefore suggest that fractionated nano-colloid kits maintain performance even in post-NAC patients, supporting their reliability in diverse clinical contexts.

Inter-observer agreement between two blinded nuclear medicine physicians was excellent, with a  $k$  value of 0.920, indicating near-perfect concordance. The Bland-Altman analysis further confirmed strong agreement in the number of SLNs detected, demonstrating that fractionated doses yield stable and reproducible imaging outcomes. No radiolabeling failure or particle instability was detected visually, reinforcing the suitability of fractionation protocols in routine practice.

QC analysis confirmed high RCP ( $\geq 99\%$  RF), optimal pH ( $6.7 \pm 0.3$ ), physiologic osmolality (294 mOsm/kg), and a stable gamma emission peak around 147.5 KeV—all within accepted pharmacopeia ranges for <sup>99m</sup>Tc-Nanocolloids. The excellent QC outcomes corroborate the clinical reliability observed in imaging performance. A significant advantage of this study was the substantial reduction in radiopharmaceutical wastage, translating into 75-92% lower per-patient cost. This is especially valuable in public-sector and resource-limited nuclear medicine settings, where fluctuating patient volumes often result in unused residual activity from single-use full kits. Similar studies on other expansive radiopharmaceutical have been tested, shown that Tetrofosmin (MYOVEIW) cold kit fractionation succeeded or six months with the first mode of fractionation<sup>10</sup> and one Tetrofosmin vial can be used in six fractions up to 15 days when stored at  $-20^{\circ}\text{C}$  and  $4^{\circ}\text{C}$  freezer temperature.<sup>6</sup> The current findings add further evidence supporting fractionation as a sustainable, economically efficient workflow, aligned with global recommendations for minimizing radioactive waste and optimizing departmental resources.

Collectively, this study confirms that fractionating <sup>99m</sup>Tc-Nanocolloid kits when accompanied by standardized preparation methods and rigorous QC preserves clinical

efficacy, ensures RCP stability, and delivers major cost savings, making it particularly impactful for high-volume or resource-constrained institutions. Future multicenter studies with larger cohorts would strengthen the generalizability of these results, especially in diverse healthcare environments.

## Conclusion

Fractionating <sup>99m</sup>Tc-Nanocolloid kits is a clinically reliable and cost-efficient strategy for SLN mapping in breast cancer. It reduces radiopharmaceutical waste, ensures quality-assured imaging, and strengthens sustainability in resource-limited public healthcare systems. Broader implementation across LMIC Nuclear Medicine departments can substantially improve access to essential diagnostic services without compromising clinical outcomes.

**CONFLICT OF INTEREST:** None

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