
^{99m}Tc-Tilmanocept Versus ^{99m}Tc-Sulfur Colloid in Lymphoscintigraphy: Sentinel Lymph Node Identification and Patient-Reported Pain

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Lymphoscintigraphy plays a vital role in sentinel lymph node (SLN) identification in oncologic breast surgery. The effectiveness of SLN localization and the degree of patient pain were compared between filtered ^{99m}Tc-sulfur colloid (^{99m}Tc-SC) and ^{99m}Tc-tilmanocept. **Methods:** A retrospective review of patients undergoing lymphoscintigraphy for breast cancer using ^{99m}Tc-SC (June 1, 2010, to December 31, 2011) or ^{99m}Tc-tilmanocept (June 1, 2013, to January 31, 2014) was performed. SLN appearance time and uptake, SLN pathology, proportion of positive SLNs removed, and pain scores were compared for each radiopharmaceutical using the χ^2 test, Fisher exact test, and unequal variance *t* test, as appropriate. **Results:** In total, 76 patients, with 86 evaluated axillae, underwent lymphoscintigraphy: 29 with ^{99m}Tc-SC and 47 with ^{99m}Tc-tilmanocept. The mean SLN appearance time was 11.0 min for ^{99m}Tc-SC and 19.3 min for ^{99m}Tc-tilmanocept ($P = 0.003$). There was no difference in the mean transit uptake percentage: 2.2% for ^{99m}Tc-SC and 1.9% for ^{99m}Tc-tilmanocept ($P = 0.55$). ^{99m}Tc-tilmanocept identified a greater proportion of intraoperative blue nodes than did ^{99m}Tc-SC ($P = 0.03$). There was no significant difference between ^{99m}Tc-SC and ^{99m}Tc-tilmanocept in the number of SLNs removed, number of patients with positive SLNs, or pain score. **Conclusion:** ^{99m}Tc-SC use in lymphoscintigraphy is an acceptable alternative to ^{99m}Tc-tilmanocept for SLN detection in breast cancer, on the basis of the similarity in intraoperative SLN identification and pain scores.

Key Words: tilmanocept; Lymphoseek; sulfur colloid; lymphoscintigraphy

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Sentinel lymph node (SLN) surgery continues to play a vital role in staging of breast cancer. When identifying SLNs, a detection method must have adequate sensitivity to detect nodal metastases while maintaining a specificity

that will minimize removal of benign lymph nodes. SLNs may be identified via injection of blue dye or lymphoscintigraphy. Two popular radiopharmaceuticals used for lymphoscintigraphy are filtered ^{99m}Tc-sulfur colloid (^{99m}Tc-SC) and ^{99m}Tc-tilmanocept. ^{99m}Tc-tilmanocept is composed of a synthetic macromolecule that specifically targets and binds to CD-206 receptors of macrophages found within lymphatic vessels, theoretically targeting SLNs and not migrating to non-SLNs (1). ^{99m}Tc-SC is a radiocolloid particle with an average size of 0.3 to 1.0 μm , which is then filtered to a size of less than 0.22 μm before injection to improve lymphatic absorption. The smaller, more uniform particle size is translocated from the injection site into the lymphatic channels, eventually reaching the SLNs draining the injection site; however, unlike ^{99m}Tc-tilmanocept, the ^{99m}Tc-SC remains unbound and can migrate beyond the sentinel nodes over time (2,3).

Recent studies have shown that the ability of ^{99m}Tc-tilmanocept to identify SLNs in breast cancer was superior to that of ^{99m}Tc-SC, with less pain on injection (4–17). Two clinical trials performed at the University of California–San Diego showed that ^{99m}Tc-tilmanocept exhibited faster injection site clearance and a lower mean number of identified SLNs with a higher concordance than ^{99m}Tc-SC, whereas ^{99m}Tc-tilmanocept and ^{99m}Tc-SC had equivalent SLN uptake (14,16). Similarly, a retrospective study also from the University of California–San Diego showed that ^{99m}Tc-tilmanocept patients had fewer nodes removed while having a greater proportion of positive nodes removed among node-positive patients. This study also found that injection with ^{99m}Tc-SC independently predicted removal of more than 3 nodes, when adjusted for tumor characteristics (4). Finally, significantly more pain was found to be associated with the ^{99m}Tc-SC injection than with the ^{99m}Tc-tilmanocept injection (17).

^{99m}Tc-SC has been standard at Mayo Clinic–Rochester for SLN biopsy; however, ^{99m}Tc-tilmanocept was trialed in a prospective cohort of patients for SLN detection in breast surgery. Both radiopharmaceuticals were evaluated for localization time, transit uptake, ability to intraoperatively localize SLNs, and pain associated with injection. The aim of this

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study was to determine whether the Mayo Clinic–Rochester experience was similar to previously published reports (4–17).

MATERIALS AND METHODS

After approval by the Institutional Review Board and waiver of the requirement to obtain informed consent, a retrospective review of patients undergoing lymphoscintigraphy for breast surgery using either ^{99m}Tc -SC or ^{99m}Tc -tilmanocept was performed. Patient data for the ^{99m}Tc -SC cohort were retrospectively collected for consecutive patients from June 1, 2010, to December 31, 2011. For the ^{99m}Tc -tilmanocept cohort, patient data were collected from June 1, 2013, to January 31, 2014. ^{99m}Tc -tilmanocept was trialed at Mayo Clinic–Rochester during this period for use in lymphoscintigraphy for all breast cancer patients; before that time, use of ^{99m}Tc -SC had been standard. The 18-mo separation between data collection was to allow for a transition between ^{99m}Tc -SC use and ^{99m}Tc -tilmanocept use. In total, 76 patients were included in the study, with 86 axillae evaluated. Each axilla was evaluated independently. We excluded patients who were pregnant or breast-feeding, had received prior radiation therapy, had ipsilateral recurrence, or had undergone previous surgery involving the ipsilateral breast tissue. Ten patients underwent bilateral lymphoscintigraphy for bilateral breast surgery.

SLN Identification

An institution-specific standard SLN injection technique was used on all patients. ^{99m}Tc -SC patients received 4 intradermal, periareolar injections of ^{99m}Tc -SC (0.2- μm filter) in the quadrant of the primary breast tumor. Each syringe contained 3.7–14.8 MBq (0.1–0.4 mCi) of activity in no more than 0.1 mL of saline solution volume. ^{99m}Tc -tilmanocept patients received 2 intradermal, periareolar injections of ^{99m}Tc -tilmanocept (as manufactured by Navidea Biopharmaceuticals) in the quadrant of the breast tumor. Each syringe was calibrated to contain 18.5–37 MBq (0.5–1.0 mCi) of activity with a total volume of less than 0.4 mL per injection. Immediately after injection, which occurred in the same room as the γ -camera, patients in both groups were imaged for SLN appearance.

Dynamic and static imaging was performed with a γ -camera immediately after injection. With the patients positioned supine and arms above their head, anterior oblique views of the injection site were required for all patients until sentinel node visualization. Any additional imaging was acquired as needed. If patients received bilateral injections, static anterior views were acquired in addition to the anterior oblique views required for each side. A ^{57}Co sheet source was used as a transmission source.

Localization time was defined as the elapsed time from radiotracer administration to sentinel node visualization as indicated on patient images by the imaging technologist. A sentinel node was confirmed by the reading nuclear medicine physician or radiologist and was annotated on final patient images. Manual regions of interest (ROIs) were drawn around the injection site and sentinel nodes, as identified by the physician, on anterior oblique images to yield count information. These values were then used for mathematical manipulation to determine the transit uptake percentage using the equation below:

$$\text{Transit uptake (\%)} = \frac{\text{SLN ROI}}{\text{injection ROI} + \text{SLN ROI}} \times 100.$$

During surgery, SLNs were identified using radionuclide activity via a γ -probe with or without the addition of methylene blue dye.

Excised nodes were submitted for pathologic examination. Pathology reports were reviewed for reported blue nodes, number of SLNs removed, and positive SLNs. Patients who did not undergo SLN surgery, because they were undergoing breast surgery for risk reduction or atypia, were excluded from intraoperative SLN identification analyses. The excluded axillae included 1 (from 1 patient) in the ^{99m}Tc -SC group and 18 (from 15 patients) in the ^{99m}Tc -tilmanocept group.

Pain Associated with Intradermal Injection

Only patients who received a topical eutectic mixture of local anesthetic cream before injection were included in the pain analysis, which consisted of 22 women in the ^{99m}Tc -SC group and 47 in the ^{99m}Tc -tilmanocept group. For all patients, the anesthetic cream was applied to the skin and covered with an adhesive patch around the areola in the quadrant of the tumor 30 min before the injections. Intradermal periareolar injections were performed with a 25-gauge needle by the nuclear medicine radiologist using sterile technique. ^{99m}Tc -SC was given with 4 injections per breast, each containing 3.7–14.8 MBq (0.1–0.4 mCi) in no more than 0.1 mL of saline solution volume. ^{99m}Tc -tilmanocept was given with 2 injections per breast, each containing 18.5–37 MBq (0.5–1.0 mCi) in less than 0.4 mL of volume. Patients were asked to give a pain score immediately after the injections using a linear pain scale from 0 to 10 (0, no pain; 10, unbearable pain).

Statistical Analysis

Data were compared between the ^{99m}Tc -SC and ^{99m}Tc -tilmanocept groups using the χ^2 test, Fisher exact test, and unequal variance *t* test, as appropriate. All analyses were completed using JMP statistical software, version 10.0. The α -level for statistical significance was set at 0.05.

RESULTS

SLN Identification

In total, 76 patients, with 86 evaluated axillae, underwent lymphoscintigraphy: 29 with ^{99m}Tc -SC (29 axillae) and 47 with ^{99m}Tc -tilmanocept (57 axillae). The average patient age was 57.0 y in the ^{99m}Tc -SC group and 59.5 y in the ^{99m}Tc -tilmanocept group ($P = 0.22$) (Table 1). In the

TABLE 1
Nuclear Medicine Data

Parameter	^{99m}Tc -SC (<i>n</i> = 29)	^{99m}Tc -tilmanocept (<i>n</i> = 57)	<i>P</i>
Age (y)	57.0 \pm 13.6 (<i>n</i> = 29)	59.5 \pm 12.7 (<i>n</i> = 47)	0.22
Surgery			0.24
Mastectomy	11 (38%)	31 (54%)	
Lumpectomy	18 (62%)	25 (44%)	
No breast surgery	0%	1 (2%)	
Localization time (min)	10.96 \pm 7.36	19.31 \pm 18.06	0.003
Transit uptake (%)	2.20 \pm 2.37	1.86 \pm 2.71	0.55
Number of nodes visualized per patient	1.07 \pm 0.26	1.26 \pm 0.48	0.02

Data are *n* followed by percentage, or mean \pm SD.

^{99m}Tc -SC group, more patients underwent lumpectomy than mastectomy (18/29 [62.1%] vs. 11/29 [37.9%]), whereas more patients underwent mastectomy than lumpectomy in the ^{99m}Tc -tilmanocept group (22/47 [46.8%] vs. 25/47 [53.2%]); this difference was not statistically significant ($P = 0.24$) (Table 1). One patient in the ^{99m}Tc -tilmanocept group did not undergo concurrent breast surgery, because no breast lesion was seen on preoperative imaging and the patient declined a breast operation.

Localization Time

The average localization time for the ^{99m}Tc -SC group was 11.0 min \pm 7.4, versus 19.3 min \pm 18.1 for the ^{99m}Tc -tilmanocept group ($P = 0.003$). Of the 29 axillae in the ^{99m}Tc -SC cohort, 25 (86.2%) had a visible SLN within 12 min from the time of injection, 1 (3.5%) within 18 min, and 3 (10.3%) within 30 min. For the 57 axillae in the ^{99m}Tc -tilmanocept cohort, 37 (64.9%) had a verified SLN appearance within 12 min, and an additional 9 (80.7% total) had a verified SLN appearance when the time was extended to 18 min. Five (8.8%) had a localization time of 30 min, and 6 (10.5%) had a localization time of more than 30 min. Total nodes visualized were 31 (average of 1.1 per patient) for the ^{99m}Tc -SC group and 77 (average of 1.3 per patient) for the ^{99m}Tc -tilmanocept group ($P = 0.02$).

The average transit uptake for the ^{99m}Tc -SC group was 2.2% \pm 2.4%, versus 1.9% \pm 2.7% for the ^{99m}Tc -tilmanocept group ($P = 0.55$).

Pain Associated with Intradermal Injection

The ^{99m}Tc -SC group had a higher mean pain score, at 4.2 \pm 2.3, versus 3.3 \pm 2.6 for the ^{99m}Tc -tilmanocept group; however, this difference was not statistically significant ($P = 0.16$) (Fig. 1). Additionally, the pain score was 5 or higher in 44.4% (4/9) of the ^{99m}Tc -SC patients but in only 20.4% (10/49) of the ^{99m}Tc -tilmanocept patients.

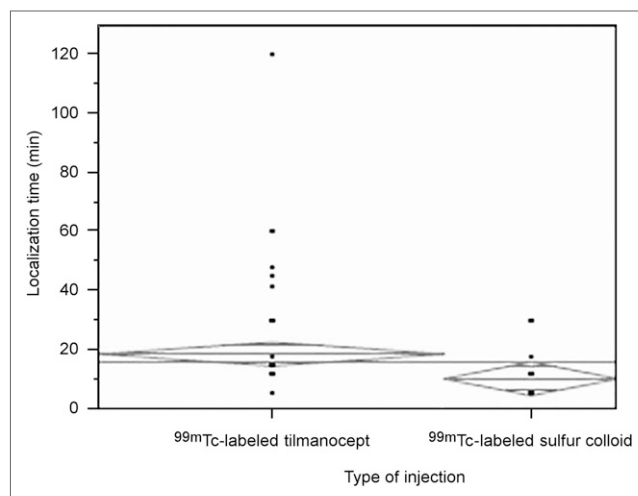


FIGURE 1. Average localization time for ^{99m}Tc -tilmanocept vs. ^{99m}Tc -SC.

SLN Surgery

Of the 29 ^{99m}Tc -SC patients, 28 underwent SLN surgery. All had SLNs identified using a γ -probe. The average number of SLNs removed was 2.6 \pm 1.6 (range, 1–9). Six patients had positive nodes, ranging in number from 1 to 2. Of the 57 breasts injected with ^{99m}Tc -tilmanocept, 39 underwent SLN surgery. The average number of SLNs removed was 2.4 \pm 1.6 (range, 1–8). Five patients had positive SLNs, all with 1 positive node. There was no statistical difference between groups in the average number of SLNs removed, the number of positive nodes, or the proportion of positive nodes excised ($P = 0.66$, 0.89, and 0.72, respectively) (Table 2).

Of all patients injected with methylene blue dye who underwent SLN surgery, 15 of 27 (55.5%) ^{99m}Tc -SC patients had blue SLNs identified, 2 of which were positive for metastasis. In the ^{99m}Tc -tilmanocept group, 22 of 30 (73.3%) patients had blue nodes, 3 of which were positive for metastasis. The proportion of blue nodes identified as SLNs was greater for the ^{99m}Tc -tilmanocept group than for the ^{99m}Tc -SC group ($P = 0.03$) (Table 2).

DISCUSSION

SLN Identification

The localization time for the ^{99m}Tc -SC group was 11 min, versus 19 min for the ^{99m}Tc -tilmanocept group, suggesting that lymphatic transit time may be quicker for ^{99m}Tc -SC than for ^{99m}Tc -tilmanocept with standard use. Additionally, fewer SLNs were identified with ^{99m}Tc -SC than with ^{99m}Tc -tilmanocept, although the difference was not clinically significant. There was no statistical difference in the other evaluated variables, including transit uptake, intraoperative SLN identification, or percentage of positive node identification.

The faster localization time for ^{99m}Tc -SC may be beneficial for institutions that inject intraoperatively, with the surgeon having to wait for the radiopharmaceutical activity to be present in the axilla before proceeding. Additionally, one perceived benefit of ^{99m}Tc -tilmanocept over ^{99m}Tc -SC is that the large size and macrophage-specific receptor binding

TABLE 2
SLN Data

Parameter	^{99m}Tc -SC ($n = 28$)	^{99m}Tc -tilmanocept ($n = 39$)	P
SLNs excised (n)	2.57 \pm 1.64	2.41 \pm 1.56	0.66
Positive SLNs	$n = 6$	$n = 5$	
n	0.28 \pm 0.60 (range, 0–2)	0.13 \pm 0.34 (range, 0–2)	0.89
Proportion	0.12 \pm 0.26	0.08 \pm 0.24	0.72
Blue nodes	$n = 27$	$n = 31$	
n	0.81 \pm 1.00 (range, 0–4)	1.45 \pm 1.72 (range, 1–8)	0.04
Proportion	0.32 \pm 0.36	0.52 \pm 0.43	0.03

Data are mean \pm SD.

of ^{99m}Tc -tilmanocept prevent it from traveling to non-SLNs (1). Our data showed that fewer SLNs were identified with ^{99m}Tc -SC, whereas the percentage of positive SLNs identified in node-positive patients remained statistically equivalent. This finding suggests that the smaller size of ^{99m}Tc -SC and its absence of a specific binding target do not limit its ability to identify SLNs intraoperatively and that ^{99m}Tc -SC remains at least equivalent to ^{99m}Tc -tilmanocept for this purpose.

Previous studies, by Wallace et al., that evaluated the use of ^{99m}Tc -SC versus ^{99m}Tc -tilmanocept in SLN identification showed that SLNs removed from patients in the ^{99m}Tc -tilmanocept group were more concordant with blue dye and that ^{99m}Tc -tilmanocept cleared more quickly from the injection site (14,16). Our study did not evaluate clearance time; however, the ^{99m}Tc -tilmanocept group had a greater number of SLNs identified by imaging and an equivalent number identified intraoperatively. Our study did agree with previous studies in identifying a greater proportion of blue SLNs in the ^{99m}Tc -tilmanocept group. Primary SLN uptake in our study was greater than that reported by Wallace et al. for both groups, but neither study found a statistical difference between the 2 radiopharmaceuticals (16). Reasons for differences between our study and previously published prospective studies may include the larger sample size and the retrospective design of our study.

Baker et al. also performed a retrospective review of 84 ^{99m}Tc -tilmanocept and 115 ^{99m}Tc -SC patients (4). Their study showed that fewer SLNs were identified in the ^{99m}Tc -tilmanocept group than in the ^{99m}Tc -SC group (4). Additionally, they found that both groups had a similar proportion of metastatic lymph node–positive patients; however, the ^{99m}Tc -tilmanocept group identified a greater number of positive nodes among the node-positive patients (4). Collected data in our study suggest that a similar number of SLNs is identified in the 2 groups, with an equal proportion of positive nodes identified in each group. Reasons for the difference between our findings and those of Baker et al. likely include the small sample size and small proportion of patients with positive lymph nodes in both groups in the previously published study.

Pain Associated with Intradermal Injection

Our study found no significant difference in pain between the ^{99m}Tc -SC and ^{99m}Tc -tilmanocept groups. A prior randomized controlled trial found more pain associated with ^{99m}Tc -SC than with ^{99m}Tc -tilmanocept within the first 3 min after injection (17). The topical eutectic mixture of local anesthetic cream was applied preoperatively to all patients in our study, which may have helped to eliminate differences in the injection-associated pain; however, a previous study from Mayo Clinic–Rochester showed that topical anesthetic cream did not help with injection pain (18). Today, these findings may be of limited clinical importance as all patients now receive intradermal lidocaine at the injection sites at Mayo Clinic–Rochester, which has been shown to improve patient tolerance to the procedure (19).

Limitations

Limitations to this study include its retrospective design and modest sample size. Additionally, although patients were injected in the same room as the γ -camera, they were not injected directly beneath the camera with immediate dynamic imaging to ensure the most accurate measurement of transit time. Thus, the time to perform the injections and patient transport time from injection to imaging may have made the times to visualization appear longer than the actual transit times. Also, in the pain analysis, patients injected with ^{99m}Tc -SC had 4 injections, whereas ^{99m}Tc -tilmanocept only had 2 injections. Multiple injection sites were chosen to ensure injection on each side of a tumor or scar to see all possible drainage patterns. Even with the difference in the number of injections between ^{99m}Tc -tilmanocept and ^{99m}Tc -SC, there was only a slightly lower mean pain score for ^{99m}Tc -tilmanocept and no statistical difference was found. Finally, ^{99m}Tc -SC and ^{99m}Tc -tilmanocept could not be directly compared in the same patient. To do so, one would need to inject a patient with one of the agents, wait for radioactivity to decrease to zero, inject the patient with the other agent, and then proceed to surgery. Not only is this unreasonable from a patient standpoint, but no pathologic comparison data would be available, as only one of the injections would be followed by operative intervention.

CONCLUSION

Comparison of ^{99m}Tc -SC and ^{99m}Tc -tilmanocept for lymphoscintigraphy to detect SLNs in breast cancer showed that the former continues to be an acceptable alternative to the latter. This conclusion is based on their similarity in intraoperative SLN identification and in patient-perceived pain.

DISCLOSURE

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