# Radiopharmaceuticals in sentinel lymph-node detection – an overview

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**Abstract.** Biopsy of the first tumour-draining lymph node (sentinel node, SN) is bound to become the procedure of choice in regional staging of melanoma and breast cancer patients. Several radiopharmaceuticals have been developed for lymphoscintigraphy. In this paper we review the most frequently used radiopharmaceuticals for their appropriateness in the sentinel-node procedure. We conclude that accurate localization of SNs is demonstrated using technetium-99m-sulfur colloid ($^{99m}$Tc-SC), $^{99m}$Tc antimony trisulfide colloid ($^{99m}$Tc-ATC) [10] and $^{99m}$Tc nanocolloidal albumin ($^{99m}$Tc-CA). $^{99m}$Tc-Ca and $^{99m}$Tc-SC are both available in Europe. In the United States $^{99m}$Tc-SC is the only registered tracer for lymphoscintigraphy

*Key words:* Sentinel node – $^{99m}$Tc-sulfur colloid – $^{99m}$Tc-antimony trisulfide colloid – $^{99m}$Tc-colloidal albumin – Radiocolloids

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## Introduction

Recently, multidisciplinary interest in lymphoscintigraphy emerged primarily because of recent validation of the sentinel node (SN) concept in patients with cutaneous melanoma and breast cancer. The availability of intraoperative gamma probes and the positive reports from surgeons who have used the hand-held probe to localize and excise previously radiolabeled sentinel lymph nodes, have strengthened the excitement. There is no golden standard in the performance of the sentinel-node procedure yet. Differences exist between the route of administration, time to scintigraphy, use of vital dyes and the radiopharmaceutical used.

Numerous radiopharmaceuticals have been used for lymphoscintigraphy, including technetium-99m-labelled dextran, [1], $^{99m}$Tc hydroxy ethyl starch [2], $^{99m}$Tc human serum albumin (HSA) [3–5] and several labelled colloids, including gold-198-colloid [6], $^{99m}$Tc stannous phytate [7], $^{99m}$Tc sulfur colloid ($^{99m}$Tc-SC) [7–9], $^{99m}$Tc antimony trisulfide colloid ($^{99m}$Tc-ATC) [10] and $^{99m}$Tc colloidal albumin ($^{99m}$Tc-CA) [11, 12].

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Among these agents only $^{99m}$Tc-CA and $^{99m}$Tc-SC are available as commercial products in Europe and licensed for use in lymphoscintigraphy.

There is no consensus regarding the optimal methods for lymphoscintigraphy. The intra lymphatic kinetics of presently available lymphoscintigraphic radiopharmaceuticals are not well understood. The ideal tracer should combine rapid and predictable transport towards the sentinel node (SN) with persistent retention. These properties are highly dependent on colloid particle size and stability because the radiopharmaceutical has to be absorbed by peripheral lymph receptors to gain entrance into the lymphatic system [8, 9, 11, 13, 14]. Uniform dispersion of small particles (<100 nm) is necessary for the colloid to translocate from the interstitial injection site to lymphatic channels and nodes. Large particles (500–2000 nm) remain trapped at the injection site and are unsatisfactory [15]. Particles smaller than 4–5 nm have been reported to penetrate the capillary membranes and therefore may be unavailable to migrate through the lymphatic channel [16].

The particle size of a colloid can be determined by electron microscopy, photon correlation spectroscopy and ultracentrifugation. It should be realized that most particles are not regularly shaped. Dependent on the method of analysis the size is expressed as a projected diameter for microscopic techniques or the Stokes' diameter, which describes an equivalent sphere undergoing sedimentation/ultracentrifugation at the same rate as the asymmetric particle. Figure 1 summarizes the particle-size ranges of the different colloids.

In melanoma the colloid is administered intradermally or subcutaneously [10]. Different administration techniques of the colloid have been reported in breast cancer: intratumoral [17], peritumoral [12, 18–20] and subcutaneous [21, 22]. Most authors favour peritumoral injection. No studies have been published yet comparing both injection methods in the same patients. Focal accumulation of the radioactivity after peritumoral injection seems to correspond with the accumulation after sub- or intracutaneous injection. Owing to the high intradermal pressure the intradermal administration technique may cause contamination. This is the result of aerosol forming after the needle is withdrawn [23]. This can be overcome by covering the injection site while retracting the needle. On the following pages the tracers that are mostly used will be described.

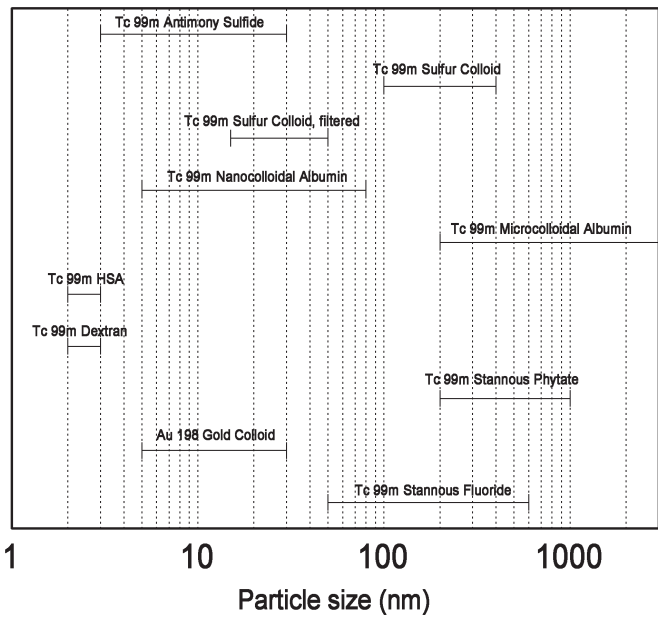


**Fig. 1.** Particle size range of colloids lymphoscintigraphy

## $^{99m}$Tc Sulfur colloid ($^{99m}$Tc-SC)

In principle, there are two methods to prepare $^{99m}$Tc sulfur colloid. Initially, sulfur colloid was produced by leading hydrogen sulfide gas through an acidic pertechnetate solution. Oxidation of the solute hydrogen sulfide produces a colloidal sulfur solution. It results in very small particles. Nowadays a preparation based on the reaction of thiosulphate with acid is common. Acidified pertechnetate solution is added to thiosulphate in the presence of a stabilizing compound. This can be gelatin, polygeline or mannitol. Essentially all technetium is incorporated in the sulfur colloid. Forming of the colloid is enhanced by heating the solution 5–10 min on 100°C. Typical particle sizes are 100–1000 nm [8]. Shortening the heating time and utilizing $^{99m}$Tc pertechnetate, which has a longer ingrowth of $^{99m}$Tc pertechnetate, produced a formulation which has the largest percentage of particles smaller than 30 nm [24]. The colloid is neutralized with a phosphate buffer. Disodium edetate can be added to bind aluminium ions from the eluate and prevent aluminium phosphate precipitation. The final preparation can be filtered through a 0.1–0.2 µm filter to obtain the small particle fraction [8, 25].

Besides this preparation from sodium thiosulphate, preformed and freeze-dried sulfur colloid with a particle size of ±80 nm is available. This colloid consists of a precipitate of stannous(II)sulfide, stabilized with polyvinylpyrrolidone or gelatin. Pertechnetate is reduced by the stannous(II), and reduced technetium binds to the preformed colloid.

Table 1 summarizes the characteristics of $^{99m}$Tc-SC. After intradermal injection of a volume of 0.2–0.5 ml, 0.2 µm filtered, $^{99m}$Tc-SC, the median transit time to the SN is 11 min. At 30 min 2.09±1.94 visible nodes are demonstrated, and 3.82±3.11 (range 1–14) after 2–4 h [26]. After two intracutaneous injection of 5–10 MBq non-filtered $^{99m}$Tc-SC in 0.15 ml saline uptake in the SN is 0.51%ID/g lymph node [27].

After intradermal administration of 0.1 µm filtered $^{99m}$Tc-SC, the absorbed dose was estimated [µGy/MBq]: whole body, 4.9; liver, 9; lymph nodes, 900; injection site, 31,000 [8].

Mudun et al. [28] studied the influence of lymphoscintigraphic and intraoperative gamma probe findings

**Table 1.** Comparison of $^{99m}$Tc sulfur colloid (SC), $^{99m}$Tc colloidal albumin (CA), $^{99m}$Tc antimony trisulfide colloid (ATC) and $^{99m}$Tc human serum albumin (HSA) in melanoma en breast cancer studies

| | $^{99m}$Tc-SC | $^{99m}$Tc-CA | $^{99m}$Tc-ATC | $^{99m}$Tc-HSA | Reference | Tumour |
|---|---|---|---|---|---|---|
| Particle size | 100–400 nm | 5–80 nm | 3–30 nm | 2–3 nm | 26 | |
| Median transit time to SN (range) | 11 min (1–60) | 10 min (1–65) | | 5 min (1–75) | 26 | Melanoma |
| Uptake in SN after 4±2 h | 0.51±0.59%ID/g | 2.10±0.80%ID/g | | | 27 | Melanoma |
| Uptake in SN after 3 h | 0.25%ID | | 45%ID | | 45 | Breast |
| Injected dose at injection site at 3 h | 76% (range: 49–95) | | 83% (range: 74 –100) | | 45 | Breast |
| Visible nodes after 20–30 min | 2.09±1.94 | 2.17±1.33 | | 2.23±0.90 | 26 | Melanoma |
| Visible nodes after 2–4 h | 3.82±3.11 (1–14) | 2.82±1.70 (1–7) | | 2.65±2.15 (0–9) | 26 | Melanoma |
| | | 1.39±0.54 (1–3) | | | 49 | Melanoma |
| | | 1.38±0.80 (1–3) | | | 12 | Breast |
| | | 1.67±0.84 (1–4) | | | 35 | Melanoma |
| | 7.1 | | 6.5 | | 45 | Melanoma |
| Half-time washout | 13.9±12.7 h | 7.5±6.4 h | | 4.3±1.4 h | 26 | Melanoma |
| Ex-vivo counts [cps][a] | 96±92 (21–294) | 340±170 (69–716) | | | 27 | Melanoma |

[a] Gamma probe (C-trak, Care Wise Medical Products, Morgan Hill, Calif., USA)

on the surgical management of melanoma and tested the reproducibility. The SN was identified in all patients. In 11 of the 13 who underwent lymphoscintigraphy twice, sentinel node identification was reproducible. Albertini et al. [29] studied 106 patients with cutaneous melanomas. The preoperative lymphoscintigram revealed that the melanoma drained to more than one basin in 22 patients. Intraoperative localization of the SN was successful in 96% of the cases. The mean ratio of "hot spot" to background was 8.5:1 in vivo. The mean ratio ex vivo SN to non-SN activity was 135.6:1.

Smith et al. reported 11 anaphylactic or anaphylactoid reactions in 1,296 patients (0.9%) injected with dextran-stabilized preparations and only three reactions in over 3,000 patients (<0.1%) injected with gelatin-stabilized preparations [30].

### $^{99m}$Tc colloidal albumin ($^{99m}$Tc-CA)

Biodistribution of colloidal albumin depends on particle size. More than 95% of the particles of nanocolloidal albumin are smaller than 80 nm and less than 4% of the particles are 80–100 nm. Only 1% is larger than 100 nm.

Nanocolloidal albumin is licensed in Europe for lymphoscintigraphy and bone-marrow scintigraphy. It is available as a kit containing human albumin nanocolloid particles, stannous chloride, glucose, poloxamer 238, sodium phosphate and sodiumfytate. The human serum albumin is obtained from donor blood negative for hepatitis B surface antigen (HBsAg), antibodies against human immunodeficiency virus (anti-HIV 1/2) and antibodies against hepatitis C virus (anti HCV). Sodium $^{99m}$Tc pertechnetate is reduced with stannous ions and is bound at the albumin-binding sites. Exclusion of oxygen is critical to avoid the formation of stannous-technetium colloid, which will not bind to albumin. After labelling with sodium $^{99m}$Tc pertechnetate, the product is ready for use.

Microcolloidal albumin is licensed for scintigraphy of liver and spleen. The colloid has a particle size of 200–3000 nm and does not seem to be ideal for lymphoscintigraphy [31], although good results have been reported by Paganelli et al. [21].

Lymphatic capillaries filter 30–40% of the subcutaneously administered nanocolloidal $^{99m}$Tc-albumin particles. Another fraction appears in the blood and accumulates in the reticuloendothelial system of the liver, spleen and bone marrow. Minimal quantities are eliminated by the kidneys.

Table 1 summarizes the characteristics of $^{99m}$Tc-CA. After intradermal injection of 0.2–0.5 ml $^{99m}$Tc-CA, the median transit time to the SN is 10 min. At 30 min 2.17±1.33 nodes are visible, and 2.82±1.7 (range 1–7) after 2–4 h [26]. After two intracutaneous injection of 5–10 MBq $^{99m}$Tc-CA in 0.15 ml saline uptake in the SN is 2.1%ID/g lymph node [27].

After subcutaneous administration of $^{99m}$Tc-CA the absorbed dose was estimated [µGy/MBq]: whole body 4.6; testicles, 3.5; ovaries, 5.9; liver, 16; lymph nodes, 590; injection site, 12,000 [32].

Pijpers et al. [33] studied the sentinel node biopsy in 135 melanoma patients. In all patients 1–3 SNs were found, in 97% within the first 20 min. In all cases the initial focus retained the highest fraction of radioactivity for at least 18 h. They concluded that dynamic lymphoscintigraphy is essential for SN localization and that tracer kinetics allow flexible timing of surgery. Kapteijn et al. [34] studied the reproducibility of lymphoscintigraphy for lymphatic mapping in 25 patients with localized melanoma. The study was repeated with a 2- to 4-week interval. The SN was visualized within 20 min in all patients. A difference in number of SNs depicted on the first and second study was noted in three patients. In another study Kapteijn et al. [35] validated the detection of the SN detection with a gamma probe. A day after intradermal injection of 60 MBq 99mTc-CA at the primary tumour site, all SNs were detected with a gamma probe. The SN-to-background ratios were 36 (median) in vivo (range: 2–722) and 274 (median) ex vivo (range: 6–2985).

Anaphylactic or anaphylactoid reactions have been reported but are rare.

### $^{99m}$Tc antimony trisulfide colloid ($^{99m}$Tc-ATC)

The initial $^{99m}$Tc radiopharmaceutical developed for lymphoscintigraphy is $^{99m}$Tc antimony trisulfide colloid ($^{99m}$Tc-ATC). Antimony trisulfide colloid can be prepared by slowly adding a potassium antimonyltartrate solution to a hot saturated aqueous hydrogen sulfide solution. The created colloid has a particle size of 3–30 nm [9, 10]. Polyvinylpyrrolidone is added to stabilize the colloid. This polymer builds up a protective layer around the antimony trisulfide particle. To accelerate the binding of sodium pertechnetate to the colloid, hydrochloric acid is added and the preparation is heated at 100°C. Technetium is incorporated on the surface of the colloid after a redox reaction between Tc(VII) and Sb(III). Therefore the final particle size is determined by the initial size of the antimony colloid used [36]. Before injection a phosphate buffer is added for a more physiological pH.

$^{99m}$Tc-ATC was used under an investigational New Drug Application (NDA), but was never approved by the Food and Drug Administration (FDA) for routine use in the United States and is no longer available even as an investigational agent. Neither is it licensed in Europe.

Table 1 summarizes the characteristics of $^{99m}$Tc-ATC. After subcutaneous administration of $^{99m}$Tc-ATC the absorbed dose was estimated [µGy/MBq]: whole body, 5; gonads, 22; liver, 4; lymph nodes, 1000, injection site, 10,000 [37].

Uren et al. [38] studied 209 patients with melanoma of the trunk using preoperative lymphoscintigraphy with

**Table 2.** Results summary from clinical studies of breast cancer and melanoma

| Radio-pharmaceutical | Number of patients | Dose (MBq) | Route of administration | Outcome | Reference |
|---|---|---|---|---|---|
| $^{99m}$Tc-SC, 0.2 µm filter | 106 melanoma | 4 inj. 4 MBq/0.12–0.25 in ml | Intradermal | LS 0–4 h: 96%<br>1.9 SNs/pt + 1.3 non-SNs/pt<br>GPD 96% | 29 |
| $^{99m}$Tc-SC, 0.22 µm filter | 41 melanoma | 4–6 inj. 3.7 MBq/0.1 ml | Intradermal | LS 0–60 min: 100%<br>4.0±1.6 SNs/pt (range: 2–9) | 46 |
| $^{99m}$Tc-SC, 5 µm filter | 41 melanoma | 4–6 inj. 3.7 MBq/0.1 ml | Intradermal | LS 0–60 min: 100%<br>3.5±1.3 SNs/pt (range: 1–8) | |
| $^{99m}$Tc-SC, 5 µm filter | 25 melanoma | 4–6 inj. 9.25–19.5 MBq/ 0.25–0.5 ml | Intradermal | LS 0–2 h: 100%<br>GPD 100% | 88 |
| $^{99m}$Tc-SC, 5 µm filter | 16 melanoma | 4 inj. 9–18 MBq/0.25–0.5 ml | Intradermal | LS: 100% | 47 |
| $^{99m}$Tc-SC | 19 cutaneous malignancies | 4 inj. 4 MBq/0.1ml | Intradermal | LS: 95% | 48 |
| $^{99m}$Tc-HSA | | 4 inj. 4 MBq/0.1ml | Intradermal | LS: 95% | |
| $^{99m}$Tc-SC | 13 melanoma | 2 inj. 5–10 MBq/0.15 ml | Intracutaneous | LS 0–2 h: 100%<br>1.3 SNs/pt | 27 |
| $^{99m}$Tc-CA | 10 melanoma | 2 inj. 5–10 MBq/0.15 ml | Intracutaneous | LS 0–2 h: 100%<br>2.3 SNs/pt | |
| $^{99m}$Tc-CA | 41 melanoma | 1–4 inj. 10 MBq/0.15 ml | Intracutaneous | LS 20 min: 95%<br>LS 2 h: 100%<br>1.39±0.54 SNs/pt (range 1–3) | 49 |
| $^{99m}$Tc-CA | 25 melanoma | 60 MBq/0.25 ml in 2–4 inj. | Intradermal | LS 0–2 h: 100%<br>1.8±0.9 SNs/pt (range 1–4)<br>88% identical LS at repeat | 34 |
| $^{99m}$Tc-CA | 60 melanoma | 60 MBq/0.2–0.5 ml in 2–8 inj. | Intradermal | LS 0–4 h: 98%<br>1.2±0.5 | 35 |
| $^{99m}$Tc-CA | 135 melanoma | 2–4 inj. 10 MBq/0.15 ml | Intracutaneous | LS 20 min: 97%<br>LS 0–18 h: 100%<br>1.4±0.6 SNs/channel (range 1–3) | 33 |
| $^{99m}$Tc-ATC | 18 melanoma | 4.6–18 MBq | Intradermal | LS 0–4 h: 100%<br>2.1±1.1 SNs/pt (range: 1–4) | 50 |
| $^{99m}$Tc-ATC | 97 melanoma | 4–6 inj. 0.05–0.1 ml | Intradermal | LS 0–2.5 h: 98%<br>2.6±1.2 SNs /pt (range: 1–5) | 39 |
| $^{99m}$Tc-ATC | 209 melanoma | 4–14 inj. 5–7 MBq/0.1 ml | Intradermal | LS 0–2.5 h: 89%<br>2.8 SNs/pt (range: 1–7) | 38 |
| $^{99m}$Tc-SC, filter | 62 breast cancer | | | LS: 92%<br>2.2 SNs/pt + 15.5 non-SNs/pt | 18 |
| $^{99m}$Tc-CA | 37 breast cancer | 40 MBq/ 4 ml in 2–4 inj. | Peritumural | LS 0–2 h: 89%<br>LS 18 h: 92%<br>1.38±0.80 SNs/pt (range: 1–3)<br>GPD 18 h: 88% | 12 |
| $^{99m}$Tc-CA | 90 breast cancer | 50 MBq/0.2 ml | Intratumoral | LS 0–6 h: 82%<br>1.5 SNs/pt (range 1–3)<br>GPD: 87% | 17 |
| $^{99m}$Tc-CA | 30 breast cancer | 5–10 MBq/0.2 ml<br>5–10 MBq/0.5 ml | Subdermal<br>Intratumoral | LS 0–3 h: 87%<br>range: 1–4 SNs/pt | 21 |
| $^{99m}$Tc-CA, micro | 155 breast cancer | | | LS 0–3 h: 100%<br>range: 1–2 SNs/pt | |
| $^{99m}$Tc-ATC | 30 breast cancer | | | LS 0–3 h: 97%<br>range 1–5 SNs/pt | |
| $^{99m}$Tc-ATC | 34 breast cancer | 4 inj. 2.5–7 MBq/0.05–0.1 ml | Peritumoral | LS 0–4 h: 94% range 1–6 SNs/pt | 40 |

*LS*, Lymphoscintigraphy; *GPD*, gamma probe detections

$^{99m}$Tc-ATC to identify sentinel lymph node(s). They reported that lymphoscintigraphy was 94% sensitive in detecting lymph draining sites that contained metastasis. Most patients showed lymph drainage to one or two node groups (42% and 47.5%), but 22 patients (10.5%) showed drainage to three or more node groups. O'Brien et al. [39] studied 97 patients with cutaneous head and neck melanoma using preoperative lymphoscintigraphy with $^{99m}$Tc-ATC to identify sentinel lymph node(s). They reported that SNs were identified in 95 of 97 lymphoscintigrams and 85% of patients had two or more sentinel lymph nodes. They stressed the need to identify and mark all nodes receiving direct lymphatic drainage and localize them using the intra operative probe. Uren et al. [40] applied lymphoscintigraphy to locate SNs in 34 patients with breast cancer. After 4 peritumoral injections of 2.5–7 MBq $^{99m}$Tc-ATC gamma images were recorded immediately and at 2.5 h. Lymphatic drainage patterns were successfully recorded in all but three patients. Drainage to the ipsilateral axilla occurred in 85% of patients, where a single SN was seen in all cases.

Several adverse reactions requiring medical treatment have been reported following administration of $^{99m}$Tc-ATC [41, 42].

### $^{198}$Au-Gold colloid

Gold-198 has a 2.7-day half-life and emits 412 keV gamma photons and beta particles. Gold 198 colloid has a relatively uniform particle size of 5–30 nm [9]. The major limitations of this agent are (1) that it delivers a high radiation dose at the site of injection (600 mGy/MBq) and (2) the 412 keV gamma photon is not desirable for scintillation camera imaging [37, 43]. Although $^{198}$Au-colloid has allowed nodal visualization, the radiation dose and high-energy gamma photon associated with gold-198 makes this compound less suitable for lymphoscintigraphy.

## Conclusion

The distribution of administered particles heavily depends on the particle size. Factors that affect the behaviour of colloids injected interstitially include particle size and number of colloid particles injected. Molecules smaller than a few nanometres may leak into capillaries and may be dispersed into the vascular system. Particles larger than 100 nm usually become trapped in interstitial space and never enter the lymphatic system. Animal studies have suggested that the optimal lymph-node uptake of colloids should be achieved with particle sizes between 10 and 50 nm [44]. Indeed, accurate localization of SNs is demonstrated using $^{99m}$Tc-SC, $^{99m}$Tc-CA and $^{99m}$Tc-ATC [12, 18–21, 35]. The particle size of microcolloidal albumin is far beyond this optimum. However, Paganelli et al. [21] reported a 100% sensitive lymphoscintigraphy in 155 patients with microcolloidal albumin.

Early and dynamic scans are necessary in melanoma for the identification of lymphatic channels. With the smaller-sized $^{99m}$Tc-CA, dynamic scintigraphy reveals better and quicker visualization of lymphatic channels and a higher uptake in the SN than with unfiltered $^{99m}$Tc-SC, at the expense of spill to secondary nodes. If small particle size is preferred, filtering produces tracer particles of a more $^{99m}$Tc-CA-like size. Although the smallest particle $^{99m}$Tc-ATC shows quick transport, too much spill to secondary nodes seems to hamper the application in GP guided surgery. In the United States, $^{99m}$Tc-SC is the only registered tracer for lymphoscintigraphy.

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