Original Research Paper Medical Science

Pros and Cons of Radio-Iodine-125, Technetium-99M Nanocolloid, Indocyanine Green Fluorescence and New Techniques as Tumoral Tracers and Lymphatic Mapping in Breast Conservative Surgery

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ABSTRACT

Purpose. The main aim was to achieve a revision of the standard and new techniques developed for primary tumor localization and sentinel lymph node identification in early stages of breast cancer.

Methods. A systematic review of the literature using PubMed database to identify all original articles published in last 5 years was performed. The search terms were: sentinel lymph node biopsy, breast cancer, tracers and lymphatic mapping. Finally, most relevant articles are written in English that involved human participants were selected.

Results. The current standard for axillary lymph node staging in early breast cancer patients is a dual-technique with a radioisotope and blue dye. Radioactive seed localization with radio-Iodine-125 is more accurate in primary non-palpable breast lesions. Methylene blue (MB) alone is not recommended. Till recently, indocyanine green fluorescence (ICG) has evolved as a new promising technique combined with Technetium-99m nanocolloid (99mTc) instead of MB. Though some studies conclude that ICG was superior to 99mTc, validation studies are needed. Microbubbles, carbon and magnetic tracers are being tested.

Conclusion. Radio-Iodine-125, ICG, and new techniques are being developed with good results. Neither of the identified novel methods has demonstrated superiority to the standard dual-technique yet. Randomized controlled trials are required.

KEYWORDS: Breast neoplasms; Indocyanine green, Iodine-125 Radioisotope, Sentinel Lymph Node Biopsy; Technetium-99m Nanocolloid.

INTRODUCTION

A great diffusion of national screening programs for breast cancer, monitoring women at high-risk and improved diagnostic techniques, such as mammography and digital stereotaxic, have increased the number of women diagnosed with non-palpable malignant breast lesions, being more than 25% of the radiological suspicious breast lesions [1].

Patients with early breast cancer, no palpable lesions and clinically node-negative, are candidates to a conservative locoregional surgery. Surgical procedure includes local tumor excision and sentinel lymph node biopsy (SLNB) for a regional staging of the disease. The sentinel lymph node (SLN) is the first lymph node that receives drainage from the primary tumor [2]. SLNB is the standard of care to evaluate axillary involvement in early breast cancer [3]. Nowadays it is also accepted in neoadjuvant treatment for locally advanced breast cancer, in some cases even in the presence of metastatic nodes [4]. The result of the SLN accurately reflects the axillary lymph node status, conditioning treatment and survival [5].

The main objective of breast conservative surgery is to achieve a complete primary tumor excision with free margins, while removing the least amount of healthy breast tissue as possible. An incomplete resection is a risk factor for tumor recurrence and should be avoided whenever possible [6]. In this cases, accurate pre- and intraoperative localization of the non-palpable lesions are important, in order to perform a complete excision and therefore accurate SLN localization [1].

Different localization techniques are used for the primary tumor, mainly ultrasound- (US) or radio-guided excision, with the recent introduction of fluorescence. US-guided excision is actually less used because not all non-palpable lesions are visible. Last published articles concluded that surgical excision time, tumor margins and tumor location were improved by Radio-Iodine-125.

Nowadays, several methods for detecting SLNs are applied. The current standard SLNB method in breast cancer, involves a 2-step procedure, called as dual technique: preoperative injection of a Technetium-99m nanocolloid (^{99m}Tc), followed by intraoperative Methylene blue dye (MB) injection interstitially or peritumoral. Dual technique detection rate (DR) is 96% with a false negative rate (FNR) of 7.3% [7]. There are other options like fluorescence, paramagnetic contrast agents or radio-Iodine-125 (^{125}I / ^{125}I-seed), are currently being developed and helping enhance the technique results.

The **aim** of this brief review is to compare the current markers ^{125}I, ^{99m}Tc, MB and newly developed techniques such as Indocyanine green (ICG) fluorescence, in tumor localization and SLN identification.

METHODS

Literature research in PubMed identifying latest and more relevant articles published in last 5 years was performed. The search Medical Subject Headings (MeSH) terms applied were: *sentinel lymph node biopsy*, *breast cancer*, *tracers* and *lymphatic mapping*. Finally, 26 articles published in English that involved human participants were analyzed and included.

RESULTS AND DISCUSSION

A. First of all, some technical aspects:

How many lymph nodes removed are enough?

The number of radioactive SLNs removed to ensure accuracy and minimize morbidity is still actively discussed [8]. The optimal number of SLNs obtained is 1 or 2. The probability of detecting a second metastatic SLN in a higher nodal chain (tumor cells bypassing the first SLN) is low (11.1%). It suggests that the average detection of 2 and no more than 3 SLNs are enough, since the excision of more nodes increases slightly the sensitivity (S) of the technique and causes increased morbidity. In Lynch et al. [8] article, removal of all radioactively SLNs, except those with radiation level below 10% of the maximum detected, did not improve the accuracy of the technique. Their data support the trend of limiting the SLNB to no more than 3 excised lymph nodes.

Where to inject?

Another important aspect to discuss is the variety of injec-

tion methods used for SLN technique in different centers. The optimal location for injection is still no standardized, due to non-demonstrated superiority of one over the other. Different injection patterns: intraparenchymal in the middle of the tumor or peritumoral, subdermal and sub- or periareolar [6]. Although no certain evidence, it is recommended to perform an intratumoral injection whenever possible, or periareolar in cases of reinjection or no localization of the lesion.

The location of the injection changes the contrast-ratio either positively (the injection separates the counting of the tumor from the SLN) or negatively (increasing the background noise) [6]. The peritumoral injection into various quadrants could distort the true SLN location (by creating drainages outside the normal lymphatic area), so wrongly considered sentinel nodes are removed. Intraparenchymal injection is ideal, but the most difficult to achieve. Mateos et al. [9] obtained no differences in SLNB detection between intraparenchymal and subdermal injection. In Smith et al. [10] article, SLN location after subareolar injection was as accurate as intraparenchymal.

Studies had determined that there are many lymphatic connections between the peritumoral and the periareolar areas (91.7%) [5]. Drainage to second areas is less than 10%. SLN detection to the internal mammary lymphatic chain is around 2.7%, only detected by the intraparenchymal injection. Infraclavicular drainage is considered to be caused by obstructed lymphatic vessels due to the primary breast tumor, so it changes the normal drainage [5].

Is there a protocol?
SLNB procedures should always be performed with the same technique as usual and with doses established by a protocol. Different doses alter the procedure, making it not comparable; DR or counting levels will differ. There is a necessity/requirement to standardize the procedure.

B. Tracers (Table 1):
Radio-Iodine-125.
The placement and localization of ^{125}I-seed requires professionals from two departments: nuclear medicine and radiology [1]. The seed is inserted into the primary breast tumor with an 18-Gauche needle. In multifocal tumor or extensive lesion, more than one seed can be placed at once in the same manner. The seed is worn and slightly radioactive, but sufficiently active. ^{125}I-seed intensity should be between 0.3-1 MBq (the minimum detectable amount) and gamma-probe count (audio-sensitivity) between 10.000-50.000 gamma counting (instead of count detection threshold set to 100 for SLN detection with ^{99m}Tc). Once removed the tumor or SLN with the seed inside, residual gamma radiation emitted is minimal and confined to a peritumoral area of 2cm, with no increased risk for the patient and health-care professionals.

Due to its small size (4.5 x 0.8 mm) and not being a liquid, the seed placement is easy to perform and hardly painful [6]. ^{125}I-seed can be placed intratumorally many days or weeks before surgery, because its long half-life time of 59.4 days. Placement techniques are ultrasound, stereotaxy or magnetic resonance imaging (MRI). Although the stereotaxic procedure is more difficult and time-consuming, seed placement makes planning less complicated, allowing the work planification of the radiologist, nuclear medicine physician and surgeon [11].

After placement, it is only necessary to confirm the correct location in a post-insertion mammography control and ensure their uptake with gamma-probe during the intervention [6]. The reference of seed placement on mammography is helpful for the exact location in the tumor during and after resection [6]. The seed is usually placed in the center of the lesion, with a non-diffuse uptake that enables minimal excision of healthy breast tissue [6]. A recent study published by Alderliesten et al. [12] ensures that seed migration (detection outside their initial site of placement) was minimal, after 60 days of placing the seed in the breast tumor.

^{125}I administered intraoperatively, is safe and cost-efficient, with a 94% DR combined with MB. Combination of ^{125}I-MB can be injected intraoperatively, subareolar or in the upper outer quadrant, being quickly absorbed. ^{125}I drainage can be located 3-5 min later [13].

On non-palpable breast lesions ^{125}I-seed (as an alternative to the harpoon) can be safely excised combined with a SLNB [11]. It is also useful in SLN identification and signaling suspicious or metastatic axillary nodes in patients receiving neoadjuvant chemotherapy, before perform an axillary lymphadenectomy or SLNB [1]. ^{125}I allows better localization of the SLNs with very little radioactive footprint [13]. The ^{125}I-seed acts better as a reference than ^{99m}Tc [6]. Location and counting uptake of ^{125}I is carried out with a gamma-probe, while the MB guides by coloring the lymph node [13]. Harkrider et al. [13] published a phase II trial with 62 patients, they concluded that ^{125}I combined with MB has equivalent DR and outcomes as ^{99m}Tc, lowering radiation exposure to professionals involved in handling the patient or the surgical specimen. ^{125}I-MB is an attractive alternative to the dual procedure ^{99m}Tc-MB [13], but preliminary results did not improve the standard technique [11]. The main disadvantage of the technique was the correct placement of the ^{125}I-seed inside relatively small lymph nodes in a clinically negative axilla [11]. More studies are needed for validation of this new approach.

Methylene blue dye.
MB alone is a cost-efficient method, but has low DR (<80%) and high FNR (30%) in SLNB [7]. The procedure is technically easy to perform but requires an expert surgeon [14]. Maximum staining is obtained 10 to 15 minutes after injection, and then its strength fades out quickly. Other disadvantages are: MB is more difficult to be identified through the skin and fatty tissue, stains the skin, can cause skin necrosis after subdermal injections and allergic reactions have been reported. Thus, its use is preferred in combination, as it will be discussed. MB is considered a second option, in hospitals with no access to radiotracers [15].

Technetium-99m nanocolloid.
^{99m}Tc is applied in two techniques: (1) radio-guided occult lesion localization (ROLL-technique), based on direct injection of the breast tumor and, (2) sentinel-node and occult lesion localization (SNOLL-technique), when also included the lymphatic drainage.

There are 3 injection-protocols: long, short and ultra-short. The long protocol, commonly used in most published studies, is performed 24 hours before surgery; thus, requiring higher dose and more risk of radioactivity for healthcare professionals. The short protocol is performed 12 hours before surgery, usually the afternoon before surgery. In the ultra-short protocol the tracer is injected at least 2 hours before surgery.

As we have mentioned, the current dual standard technique for SLNB combines ^{99m}Tc, MB and detection by gamma-probe, with the highest DR (>95%) and lowest FNR (<10%). ^{99m}Tc can be administered intratumorally, by US-guidance, stereotaxic or MRI [2], or peritumoral (in a margin around the tumor of 10 mm). Peritumoral is usually applied in reinjection [1].

Although this technique is very accurate, the procedure is expensive, logistically complicated and time and resource consuming, so it is not very reliable in hospitals with high-volume of breast cancer patients [14].

A lymphoscintigraphy is performed 30 min to 1.5 - 2 hours after the ^{99m}Tc tumoral injection, due to the slow drainage. Also, a Single-photon emission computed tomography (SPECT) is usually obtained 3 hours later, to ensure the location. If there is no drainage, it can be re-injected again in 4 quadrants, peritumoral or periareolar [6]. Reinjection rate is quite high and it worsens background noise on tumor bed. Radioactive depot or background noise is a main problem for ^{99m}Tc, it is really confusing for the surgeon at the tumor site, so it often forces

to make a bigger resection with a higher incidence of affected margins and more healthy tissue removed [6]. Additionally, primary tumor drainage interferes with preoperative location and intraoperative detection of nearby lymph nodes, also known as *shine-through effect* [2].

other disadvantages of 99mTc are:
Needs a trained staff formed by a nuclear medicine physician, a radiologist and an expert surgeon. Availability requires a management protocol and strict fulfillment of legal requirements in this regard, considerations that limit its use at some hospitals, like the ^{125}I. Drainage is slower, taking 1.5-2 hours to reach the SLN, with lower avidity for the lymphatic tissue and an increased risk of leakage into the tissue. Short half-life time (only 6 hours) limiting the procedure to be performed in a maximum of 24 hours before surgery. Real-time visual guidance is not available, except by using a portable gamma camera, due to a presurgical image performed. Deep lymphatic vessels cannot be visualized [11,15].

For injections in small lesions, ^{99m}Tc requires more precision. This could be partly prevented by optical tracking systems, like stereotaxic, or guided by ^{125}I-seed. A combined technique of ^{125}I and ^{99m}Tc could be also useful in cases of weak radioactivity from the ^{125}I-seed or non-palpable breast cancer with previously ^{125}I-seed implantation. ^{125}I-seed guides the tumor excision, in non-palpable breast conserving surgery and ^{99m}Tc with/without MB identifies the SLN [6]. ^{99m}Tc is intratumorally administered at the site of a previously implanted ^{125}I-seed and detected by SPECT [6]. The average distance between the ^{125}I-seed and the center of the ^{99m}Tc injection measured by SPECT was not significantly different (P = 0.52). This technique may improve daily clinical logistics, reducing the workload of the radiology department, avoiding a second-US guided procedure [1].

Indocyanine green (ICG) Fluorescence.
Fluorescence is a new and promising tool introduced in 2005 to localize the SLN in breast cancer patients. ICG is the only fluorophore approved by the United States Food and Drug Administration (US-FDA) for clinical use [14]. ICG has previously been used in other diseases, with a major current development in the SLNB.

It is a feasible, safe and a minimally invasive method for SLNB [20]. ICG has a high avidity for lymph drainage, so it provides and accurate lymphatic mapping, identifying SLNs in unusual drainage (6% internal mammary). ICG metastases DR are 21.4% higher than other methods [16].

The dilution, dose and site of ICG injection varied between studies. It is usually injected subcutaneously or subdermally into the periareolar area and around the tumor. ICG binds to serum α1-lipoprotein and drains into the lymphatic vessels immediately after, without extravasation [16,17]. Subcutaneous lymphatic flow can be visualized with a near-infrared fluorescence optic window, like a photodynamic camera with infrared (700-900nm ICG peak emission) navigation system [18].

However, it remains unclear whether ICG should be used in combination with the MB, ^{99m}Tc or as a sole tracer agent [19,20]. Recent studies have consolidated the safety and accuracy of ICG [15]. ICG DR is greater than 93.1% [7] (99-100% [14]), S of 94.7% and FNR of 5.3% [7]. DR of ICG is significantly higher than MB [14]. Verbeek et al. [15] performed a multicenter study using ICG, ^{99m}Tc and MB for SLNB in breast cancer, with a global DR of 99% (100% ICG, 88% ^{99m}Tc and 78% MB), mean of 1.9 SLNs excised per patient and all metastatic-SLNs were detected by ICG with no adverse effects. Nodes containing metastases are more likely to be the first node removed when ICG was the tracer but no significant differences (P = 0.9) were obtained [7,19]. Sugie et al. [14] compared ICG and ^{99m}Tc for SLN in 847 node-negative breast cancer women. DR between ICG or ^{99m}Tc had no statistically differences (97.2% vs 97%, P=0.88), but global DR was improved (ICG-^{99m}Tc 99.8% vs ^{99m}Tc 97%, P<0.001) and accuracy of ICG for metastatic-SLN detection was significantly higher than with ^{99m}Tc alone (97.2 vs. 90.0 %; P<0.001). DR was independent of BMI (ALMARAC trial, p<0.001) [21]. Also, Ballardini et al. [20] concluded in their study that ICG DR and accuracy was not inferior to ^{99m}Tc so it can be used alone in breast cancer centers that currently have only access to MB [15]. According to these results they conclude that ICG is comparable to ^{99m}Tc and a combination of ICG-^{99m}Tc maximized SLN DR [14]. Until more clinical experience, ICG is an acceptable alternative to SLNB associated with ^{99m}Tc [14]. ICG avoids the need for MB and thereby minimizes potential morbidity, including skin staining and allergic/anaphylactic reactions [19].

In addition, Wishart et al. [22] performed a study comparing the DR of ICG alone (100%), ICG-MB (95%), ICG-^{99m}Tc (77.2%) and ICG-MB-^{99m}Tc (73.1%). They confirmed the high S of the ICG for SLNB. They concluded that the combined technique of ICG-MB was superior to ^{99m}Tc, which could be suppressed. Fluorescence not only avoids exposure to radiation for healthcare workers [22], but also reduces costs [17].

Since ICG introduction, an increase in number of lymph-node removal has been reported, but it has not been confirmed in recent studies [14]. It could be related to the learning curve, since in the last articles published a mean of 2.3 SLNs per patient were performed [14], without differences to other approaches.

We can summarize the advantages of ICG, such as:
ICG provides real-time and accurate lymphatic mapping with a sequential SLN dissection guided by fluorescence of lymphatic tissue [23].Less technically exigent. Prior preparation is not necessary and there is no need for a nuclear physician or radiologist [16]. Less invasive. Only an injection is needed without pre-operative imaging [20]. Less expensive than the use of radioactive tracers [16]. In selected cases, fluorescence lymphatic drainage pathway helps to perform a highly selective lymphadenectomy [5]. Fluorescence avoids radiation exposure and use of MB [22]. ICG has no allergic reactions, minimal adverse effects and no interactions with radiocolloid [7,17].

Otherwise, disadvantages of ICG are:
Widespread diffusion and high number of nodes marked [14]. It is recommended to perform the technique as quickly as possible to avoid an extensive diffusion, with the help of a trained surgeon.Infrared camera only detects subdermal nodes displayed until 1 cm deep, so it is necessary to make an incision in the skin for deeper nodes [18,19]. This is the main reason why its use combined with radiocolloid is preferred. Fluorescence navigation and lymphatic dissection at the same time is difficult to perform, since lights in the operating room must be turned off during fluorescence observation [8].To summary, ICG-fluorescence is a new and effective promising tool, easy to perform intraoperatively, highly sensitive and cost-efficient. It combines many of the advantages of MB and ^{99m}Tc [19], but some problems still remain to be solved before considering it a new standard [20]. Additional studies are warranted to clarify the clinical impact of the ICG pattern [16].

Other tracers
Contrast-enhanced ultrasound using microbubbles are phospholipid microbubbles containing sulfur hexafluoride gas injected periareolar with fast lymphatic drainage, SLN identification of 89%, 6.3% FNR, 61% S and 100% specificity. Clinical practice is limited to a few studies without superiority to the dual technique of ^{99m}Tc- MB (p<0.0001) [7]. Its use is not recommended out of clinical trials.

Supraparamagnetic iron oxide nanoparticles (**SPIO or Sienna+® magnetic tracer**) injected subcutaneously intraoperatively and detected using a handheld magnetometer (SentiMAG® probe) is another promising tool. Skin and lymph nodes are colored in dark brown and identified also visually or by MRI [24].

In published studies, the paramagnetic tracer was used jointly with the long protocol of ^{99m}Tc or MB [4,25]. The SLN DR was 64-77% in the paramagnetic compared to 90-95% in ^{99m}Tc,

mean of 1.6 SLNs excised per patient, with a higher FNR of 8-22% (compared to 4% in the standard technique) [7].

In the SentiMAG phase II multicenter trial, SLNs were identified in 95% of patients with the standard technique and in 94.4% with the magnetic technique, mean of 1.86 SLNs excised per patient. The clinical-trial concluded that magnetic tracer was not inferior to the standard approach [7]. They concluded that SPIO is a promising, effective and safe alternative in the absence of nuclear medicine [24].

Benefits are: long half-life time, no adverse effects and no radiation exposure. SPIO reduces the burden of work in nuclear medicine departments being also economically beneficial by simplifying logistics [7].

Carbon nanoparticles have a strong affinity for the lymphatic system. Synthetic nanoparticles (150 nm) of activated carbon are injected peritumoral intraoperatively, rapidly engulfed by macrophages that pass through the lymphatic vessels into the SLN and are detected 10-15minutes after [26]. It has a DR (100%) and S (96.4%) higher than MB (P = 0.001), so it can be a useful technique for SLNB in institutions without access to ^{99m}Tc [26].

Conclusion

The main limitations of the reviewed papers are the lack of a prospective analysis, the absence of the FNR and lack of an uniform protocol. Standardization of dosage is essential to optimize the performance of this technique.

The dual technique with ^{99m}Tc and MB is the standard for axillary lymph node staging in breast cancer patients with clinical and radiological negative axilla. None of the identified novel techniques have demonstrated superiority yet. ICG is being developed with very good outlook and there are many other suitable variants. But it is time to ask real and serious questions about: Which technique should be the new gold standard? Could we establish a protocol in management techniques? Or, do we have to improve and clarify some aspects before? Meanwhile, randomized controlled trials comparing the standard dual technique are required.

Conflict of Interest Statement. Begoña Díaz de la Noval has no conflict of interest.

Acknowledgments

I appreciate the assistance received by the Nuclear Medicine Unit and the support of the Breast Pathology Unit of the Ramon y Cajal Hospital.

Table legend

Table 1. Comparison of different techniques most used, a summary of advantages and disadvantages.

Acronyms: ^{125}I – radio-iodine-125; ^{99m}Tc – Technetium-99m radiocolloid; MB - methylene blue; ICG – indocyanine green fluorescence; MRI – magnetic resonance imaging; SPECT – single-photon emission computed tomography.

Table 1. Comparison of different techniques most used, summary of advantages and disadvantages.

	^{125}I	^{99m}Tc	ICG	MB
Detection rate (%)	High (94%)	High (>95% dual technique)	Very High (100%)	Low (<80%)
Accuracy	High	Medium	Very High	Medium
Placed / Injected	Intratumoral Axillary Lymph Node	Intratumoral Peritumoral	Subdermal	Subdermal Intratumoral Peritumoral
Professionals involved	Nuclear Medicina Physician, Radiologist, Surgeon.	Nuclear Medicina Physician, Radiologist, Surgeon.	Surgeon	Surgeon
Radiological techniques involved	Ultrasound, stereotaxy, MRI, Mammography	Lymphoscintigraphy, SPECT-CT	No	No
Technical Skills	High	High	Low	Medium
Preoperative injection	Yes (days or weeks)	Yes (hours)	No	No
Re-injection	Not frequent.	Yes, frequent.	No	Not frequent.
Used alone or combined	Alone or Combined (^{99m}Tc)	Combined (ICG, MB, ^{125}I)	Recommended combined (^{99m}Tc or MB).	Always combined (^{99m}Tc or ICG).
Duration of tracer (time)	Long (days)	Short (hours)	Very short (minutes)	Short (minutes)
Half-life time	59.4 days	6 hours	3-4 minutes in plasma 10-15 minutes in lymphatic tissue	5.4 hours in plasma
Tracer Diffusion	Minimum	High	Vey High	Medium
Extravasation	No	Yes	No. Only if lymph ducks broke.	No
Background noise	No	Yes	Yes	No
Drainage velocity	Fast	Slow	Too fast	Slow
Real-time visual guidance	No. It needs gamma-probe (Preoperative location)	No. It needs gamma-probe (Preoperative location)	Yes. It needs a photodynamic camera. (Intraoperative location)	Yes (Intraoperative location)
Deep-insight	Yes	Yes	No	No
Cost-efficient	Medium-cost (Seeds are reusable)	High-cost (expensive radioisotope equipment)	Low-cost	Low-cost
Legislative requirements	Very strict legislative requirements.	Strict legislative requirements.	No legal considerations.	No legal considerations.
Side effects	Rare. Minimal local radioactivity. Iodinated contract adverse reaction.	Minimal local radioactivity. Hypersensitivity reaction to intradermal injection. Hypersensitivity to albumin. Drug interactions	Rare.	Allergic/ anaphylactic reaction. Skin necrosis.

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Placed / Injected	Intratumoral Axillary Lymph Node	Intratumoral Peritumoral	Subdermal	Subdermal Intratumoral Peritumoral
Professionals involved	Nuclear Medicina Physician, Radiologist, Surgeon.	Nuclear Medicina Physician, Radiologist, Surgeon.	Surgeon	Surgeon

Radiological techniques involved	Ultra-sound, stereotaxy, MRI, Mammog-raphy	Lym-phoscin-tigraphy, SPECT-CT	No	No
Technical Skills	High	High	Low	Medium
Preoperative injection	Yes (days or weeks)	Yes (hours)	No	No
Re-injection	Not fre-quent.	Yes, fre-quent.	No	Not fre-quent.
Used alone or com-bined	Alone or Combined (^{99m}Tc)	Combined (ICG, MB, ^{125}I)	Recom-mended combined (^{99m}Tc or MB).	Always combined (^{99m}Tc or ICG).
Duration of tracer (time)	Long (days)	Short (hours)	Very short (minutes)	Short (min-utes)
Half-life time	59.4 days	6 hours	3-4 minutes in plasma 10-15 minutes in lymphatic tissue	5.4 hours in plasma
Tracer Diffusion	Minimum	High	Vey High	Medium
Extravasa-tion	No	Yes	No. Only if lymph ducks broke.	No
Background noise	No	Yes	Yes	No
Drainage velocity	Fast	Slow	Too fast	Slow
Real-time visual guid-ance	No. It needs gam-ma-probe (Preop-erative location)	No. It needs gam-ma-probe (Preop-erative location)	Yes. It needs a photo-dynamic camera. (Intraop-erative location)	Yes (Intraop-erative location)
Deep-in-sight	Yes	Yes	No	No
Cost-effi-cient	Medi-um-cost (Seeds are reusable)	High-cost (expensive radioiso-tope equip-ment)	Low-cost	Low-cost
Legislative require-ments	Very strict legislative require-ments.	Strict legislative require-ments.	No legal considera-tions.	No legal considera-tions.
Side effects	Rare. Minimal local radi-oactivity. Iodinated contract adverse reaction.	Minimal local radio-activity. Hyper-sensitivity reaction to intradermal injection. Hypersen-sitivity to albumin. Drug inter-actions	Rare.	Allergic/ anaphylactic reaction. Skin necro-sis.

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