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Does radiocolloid remain the gold standard in melanomas? New sentinel lymph node localization techniques

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ABSTRACT

Melanoma is one of the most aggressive types of cancer, which makes accurate staging crucial for determining appropriate treatment. In melanoma patients, lymph node status is the most significant predictor of survival. Sentinel lymph node biopsy (SLNB) is a minimally invasive technique that provides essential information for staging, prognosis, and identifying patients who require further treatment. SLNB involves using a radioactive tracer (Technetium-99) and lymphatic mapping with a vital blue dye, such as isosulfan blue, methylene blue, or patent blue. This procedure helps patients avoid unnecessary complete lymph node dissection (CLND) when pathological examination reveals no melanoma metastases. This review summarizes various techniques for sentinel lymph nodes (SLNs) mapping and explores emerging approaches, including indocyanine green (ICG), magnetic tracers, and 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT).

Keywords: sentinel lymph node biopsy, melanoma, radiotracer, indocyanine green, superparamagnetic iron oxide

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Introduction

Melanoma is a type of skin cancer that arises from malignant transformation of melanocytes located in the basal layer of the epidermis. It ranks as the fifth most common cancer in men and the sixth in women, with global prevalence increasing yearly [1].

Physicians evaluate the clinical features of skin lesions based on asymmetry, border irregularity, pigmentation changes, diameter, and evolution. Any suspicious changes, such as poor circumscription, marked cellularity, or growth confluence, warrant further diagnostic evaluation in accordance with national guidelines for managing melanoma lesions that raise suspicions.

Histopathological confirmation of malignant melanoma involves assessing the Clark Level (the depth of involvement of skin layer, without specifying thickness in millimeters), Breslow thickness (tumor depth in millimeters), and clinical staging based on tumor thickness, ulceration, and the presence of metastases in regional or distant lymph nodes, lungs, liver, or the central nervous system. Prognostic factors for stage III melanoma, as defined by the American Joint Committee on Cancer (AJCC), include the mitotic rate, primary ulceration, and tumor thickness, all of which significantly impact outcomes for patients with nodal micrometastases versus nodal macrometastases [2].

Sentinel lymph node biopsy (SLNB) is a minimally invasive technique to assess metastatic spread to regional lymph nodes. The sentinel lymph node (SLN) is the first to receive lymphatic drainage from the primary tumor [3, 4]. The term "sentinel node" was first introduced in 1960 by Gould et al. [5] in reference to parotid cancer. During the procedure, a dye is injected near the tumor and travels through lymphatic ducts to the lymph nodes. The first node to receive the dye is removed, sectioned, and typically stained with hematoxylin and eosin (H&E) [3].

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This method allows for disease risk stratification and more effective management. Sentinel lymph node biopsy is a standard of care for staging axillary lymph nodes in early-stage breast cancer [6]. The European Society for Medical Oncology (ESMO) guidelines recommend SLNB for staging stage pT1b or higher melanomas (> 0.8 mm Breslow thickness or < 0.8 mm with ulceration) according to the AJCC 8th edition [7].

Before SLNB became the standard in malignant melanoma staging, elective lymph node dissection (ELND) was commonly performed based on the belief that it provided therapeutic and staging benefits. Randomized trials initially demonstrated survival benefits of ELND for high-risk melanoma patients with intermediate tumor thickness on the trunk [8, 9]. However, further studies questioned its efficacy, particularly in patients with thin or thick melanomas [10]. Elective lymph node dissection is also associated with higher rates of complications such as chronic lymphedema and nerve injury [11].

This controversial approach, particularly for clinical stage I cutaneous melanoma patients, prompted Morton et al. [12] to develop a new procedure to identify SLNs using blue dye intraoperatively. Only patients with confirmed SLN metastases (47 of 259 SLNs, 18%) underwent selective lymphadenectomy, avoiding unnecessary lymphadenectomy, associated morbidity, and costs for about 80% of patients [12].

Cascinelli et al. [13] later presented findings that elective regional lymph node dissection did not improve survival in all melanoma patients with primary trunk melanomas thicker than 1.5mm. However, they noted improved survival in patients who underwent dissection of clinically undetectable node metastases [13]. Similarly, a study demonstrated that in patients with intermediate-thickness primary melanoma (1.2–3.5 mm), those undergoing wide excision and SLNB followed by immediate lymphadenectomy, if nodal metastases were present, had significantly higher 5-year disease-free survival and 5-year survival rate, compared to those with delayed lymphadenectomy [14]. The presence of SLN metastases remains the most critical prognostic factor for intermediate- and thick-melanoma patients [14, 15].

Sentinel lymph node biopsy is the standard for staging intermediate and thick melanomas, offering substantial prognostic information. However, randomized trials such as the second Multicenter Selective Lymphadenectomy Trial (MSLT-II) and Dermatologic Cooperative Oncology Group-Selective Lymphadenectomy Trial (DeCOG-SLT) have shown no survival benefit of immediate complete lymph node dissection (CLND) over SLNB alone [16].

Like any surgical procedure, SLNB is associated with complications such as seroma, hematoma, lymphocele, wound infection, and sensory or motor nerve damage [3]. Nevertheless, it is less invasive and carries fewer complications than CLND [11]. However, variations in the SLNB technique may influence complication rates. For instance, using radiocolloids with blue dye has improved identification rates but can cause allergic reactions and skin staining, issues not observed while using radiocolloids alone [17]. The incidence of mild to moderate lymphedema is at least 1.7%, based on 235 SLNB procedures using radiocolloids and vital blue dyes [11].

A study conducted in an Asian population reported SLNB complication rates of 22.4% compared to 47.4% for CLND in the inguinal area. However, the study did not identify whether specific SLNB techniques contributed to these rates. Lymphedema occurred in 21.1% of patients undergoing CLND after SLNB and 14.3% of those undergoing radical lymph node dissection (RLND) without prior SLNB. Notably, 84.2% of patients undergoing CLND following SLNB had indwelling drains inserted [18].

Systematic reviews of over 9,000 patients reported an average pooled complication rate of 11.3% for SLNB. The most common early postoperative complications were seroma (5.1%) and infection (2.9%). Variations in SLNB techniques, such as using radiocolloid alone versus in combination with blue dye, may influence complication rates [19].

Current standard of sentinel lymph node biopsy

The gold standard for performing SLNB in patients with cutaneous melanoma is planar lymphoscintigraphy using traditional radiocolloids and vital blue dye [20, 21]. This procedure is typically performed during the excision of the primary tumor or concurrently with radical excision of the scar following melanoma biopsy [22]. Despite the availability of several radiotracers and blue dyes for lymphoscintigraphy, no single agent has been universally established as the most accurate [23]. Moreover, access to nuclear laboratories, which are required for radiocolloid preparation, remains limited in certain medical centers.

Radiocolloids are essential for lymphoscintigraphy and are created by binding a radiotracer, such as technetium-99m (99mTc), to a colloidal carrier. An ideal radiopharmaceutical should possess the following characteristics: high radiochemical purity, non-toxicity, safety for patients and healthcare personnel, cost-effectiveness, and ease of production [17]. It must also be rapidly absorbed by lymphatics, efficiently transported to SLNs, and retained there with minimal spread to secondary nodes [24]. Though no radiocolloid fully meets these criteria, 99mTc is the most widely used due to its favorable properties. It emits high-energy gamma radiation, allowing precise localization, has a short half-life of 6.01 hours to minimize radiation exposure, and is easily produced in molybdenum-technetium generators,

which can be delivered regularly to medical centers [17]. Specialized equipment, such as gamma probes, is essential for detecting radiocolloid uptake in SLNs [25].

The radiotracer used SLNB varies globally due to differences in availability and regulatory approvals. In the United States, sulfur colloid was traditionally the primary radiotracer until the Food and Drug Administration (FDA) approved tilmanocept (Lymphoseek) in 2013 [26, 27]. Tilmanocept, which binds to 99mTc via its numerous diethylene-triamine-pentaacetic acid (DTPA) moieties, is thoroughly standardized and requires minimal preparation before injection. Moreover, it has been shown that tilmanocept bonded to 99mTc fulfills many of the characteristics of the ideal radiotracer for SLN identification [24]. In 2013, the FDA approved Lymphoseek (99mTc-tilmanocept), a receptor-based radiopharmaceutical developed specifically for lymphatic mapping and SLNB. Lymphoseek contains mannose moieties, which bind to CD206 mannose receptors on reticuloendothelial cells, concentrated in lymph nodes. The high affinity of these mannose moieties increases radiotracer uptake in first-echelon nodes, reducing transport to secondary lymph nodes. Additionally, Lymphoseek demonstrates a higher SLN localization rate and fewer adverse effects compared to standard tracers. Its small molecular size (7 nm) allows rapid uptake, retention, and site clearance. Consequently, Lymphoseek shows potential superiority over other radiocolloids [26, 27], although no study has confirmed this conclusively. Antimony sulfide colloid is commonly used in Australia and New Zealand, and 99mTc-labelled albumin nanocolloid is preferred in Europe [26].

Subsequently, vital blue dye, which is visible without imaging devices, is chosen to complement the procedure. Vital blue dyes have been used for SLNB since their introduction by Morton et al. [27]. Common dyes include patent blue V (also known as alphazurine, sulfan blue, sulfane blue, patent blue violet, and patent blue pure), isosulfan blue (also known as lymphazurin blue), and methylene blue. Isosulfan blue and patent blue V are isomers with similar mechanisms of action [27, 28]; however, isosulfan blue localizes SLN at a slightly higher rate [27]. After injection, isosulfan blue and patent blue V bind to albumin and are absorbed by the lymphatics, enabling delineation of the lymphatic drainage system. Methylene blue, an FDA-approved oxidation-reduction agent for methemoglobinemia, stains SLN after being injected into the tumor's lymphatic bed, aiding in lymphatic mapping. Methylene blue, with a smaller molecular size than isosulfan blue, demonstrates the same specificity of SLN mapping, but it is less expensive and therefore more accessible in developing countries. It also shows lower false-negative rates (FNRs) and higher identification rates compared to isosulfan blue and patent blue V [17, 28].

Preoperative lymphoscintigraphy enables lymphatic mapping, even when lymph nodes are outside standard node fields. Macrophages' phagocytosis-based clearing function facilitates tracer retention, although metastatic lymph nodes may retain less radioactivity due to impaired macrophage function. The radiotracer is injected intradermally or subdermally, approximately 0.5–1 cm from the tumor's scar or margin, depending on tumor localization. For head and neck melanoma, where lymphatic drainage is unpredictable, the radiotracer is injected in at least four aliquots around the tumor or the surgical scar. Migration of radioactivity should be observed within 10 minutes post-injection. If not, extremity exercise or gentle massage of the injection site is recommended [29].

Preoperative lymphoscintigraphy provides a precise map of lymphatic drainage from the primary tumor, which is especially important when lymph flows to multiple nodal basins. This allows the surgeon to make a small incision, enabling the procedure to be performed under local anesthesia. "In-transit" nodes, defined as lymph nodes along the lymphatic vessel from the primary melanoma to the regional basin, can also be identified and assessed histologically, which is crucial in regions with unpredictable lymphatic drainage, such as in head and neck melanomas [29].

Five minutes before the first incision, the surgeon injects vital blue dye around the tumor's primary site [20, 27, 29]. The dye colors nodes after 5 minutes, enabling visualization for up to 45 minutes [17]. Vital blue dye, in addition to a radiotracer, facilitates SLN visualization for surgeons. During surgery, a gamma probe is used to detect SLN.

The efficacy of lymphoscintigraphy with or without vital blue dye varies by source. Lymphoscintigraphy alone achieves a success rate of 95–98% [29–33], while the vital blue dye technique alone has a success rate of 80–95.2% [24, 30, 34–38]. The combination increases the success rate to nearly 100% [24, 33, 34, 39].

The primary advantage of lymphoscintigraphy with vital blue dye is its high SLN identification rate, which can reach up to 100% [28]. Lymphoscintigraphy enables mapping of lymph nodes, including those outside standard fields or along lymphatic vessels ("in transit" nodes). This is particularly vital in head and neck melanomas, where precise SLN localization reduces operation size [29] and minimizes early and late complications, making lymphoscintigraphy a minimally invasive method [22]. Importantly, the MSLT-II trial demonstrated that CLND provides no additional therapeutic benefit over SLNB [40].

As mentioned earlier, metastatic nodes retain less radiocolloid than non-metastatic nodes. Injecting vital blue dye shortly before biopsy reduces the risk of missing metastatic nodes. Additionally, blue-stained lymph

nodes are visually identifiable without a gamma probe. Combining these methods enables identification and removal of all "hot nodes" and blue-stained nodes [29].

Using radioactive tracers is considered safe when strict safety guidelines are followed. Although patients and medical personnel are exposed to ionizing radiation, the doses are minimal. Operating room staff receive less than 1 μSv per procedure, while surgeons are exposed to doses below 2 μSv [17]. The dose of radiation to the hand for the physician injecting the tracer ranges from 2.43 to 84.11 μSv. The mean radiation absorbed by surgeons' and staff members' hands ranges from 3.2–5.84 μSv and 2.65–5,47 μSv, respectively [41].

Despite minimal radiation, using radioactive materials is a drawback of lymphoscintigraphy [25]. Additionally, the method's accuracy depends on multidisciplinary collaboration among surgeons, pathologists, radiologists, and nuclear medicine specialists [17, 22, 42]. Although minimally invasive, lymphoscintigraphy can lead to complications such as lymphedema, seroma, hematoma, wound dehiscence, infection, nerve injury, thrombophlebitis, deep vein thrombosis, hemorrhage [42], allergic reactions, and anaphylaxis to blue dyes [42, 43]. Patients may experience difficulty moving the affected body part due to discomfort and edema [42].

Vital blue dyes also have limitations, including allergic reactions [17, 20, 23, 25, 27, 43, 44], bluish skin discoloration [17, 23, 27], and transient green discoloration of urine [17]. In head and neck melanomas, they may cause facial tattooing due to skin discoloration, leading to their avoidance in these cases [17, 20, 23, 27]. Additionally, injecting blue dye can result in pseudo desaturation, where oxygen saturation readings drop despite normal oxygen levels [17]. As previously mentioned, vital blue dyes are associated with anaphylactic reactions [45–47]. Isosulfan blue carries a higher risk of anaphylactic reactions and pseudo-desaturation compared to methylene blue [17, 48]. Methylene blue, which should not be used subcutaneously due to the risk of skin necrosis, can cause skin reactions and ulcerations. It is contraindicated in patients with G6PD deficiency due to acute hemolysis risk [17] and should be avoided during pregnancy due to teratogenicity and allergic reaction risks [17, 27, 48].

Radiocolloids and vital blue dyes can sometimes identify secondary echelon lymph nodes instead of first-echelon nodes [20], especially if the latter are largely occupied by metastatic cells [29]. This misidentification can lead to unnecessary extensive nodal dissection and complications. Furthermore, the procedure does not determine whether SLN is metastatic. The use of radioactive materials increases costs, and some medical centers cannot afford gamma probes [20]. Moreover, 99mTc, a decay product of Mo-99, requires biweekly replenishment and relies on limited global reactor production, reducing its accessibility and affordability [49].

Safety during pregnancy remains controversial. Limited data often list radiotracers as contraindicated, but some studies suggest negligible fetal exposure [17]. For instance, Pandit-Taskar et al. [50] demonstrated fetal exposure of only 0.014 mGy, well below the National Council on Radiation Protection and Measurements (NCRP) recommendations. Additionally, Andtbacka et al. [51] reported no adverse effects on mothers or fetuses. With dose adjustments, SLNB can be safely performed without compromising accuracy. However, breastfeeding should be avoided for a few days after SLNB [42]. Blue dyes are contraindicated during pregnancy due to teratogenicity and anaphylactic risks [17, 27, 48]. Therefore, lymphoscintigraphy alone may be a safer option during pregnancy without significant loss of efficacy [52].

Novel techniques of sentinel lymph node biopsy

In recent years, researchers have been exploring alternative methods for SLNB to address the limitations of lymphoscintigraphy. As previously mentioned, radiation exposure for both patients and healthcare workers is considered a significant drawback despite the minimal radiation dose [25]. Efforts are underway to develop a method that is safer, more cost-effective, and capable of achieving an identification rate equal to or higher than lymphoscintigraphy. Some of these methods are outlined in Tables I [25, 28, 34, 37, 53–67] and II [17, 20, 22, 23, 25, 27–29, 42–48, 51, 58, 61–63, 68–85].

Indocyanine green

Indocyanine green (ICG) is a highly water-soluble fluorescent dye detectable using near-infrared fluorescence imaging (NIRFI). It has an absorption spectrum of around 805 to 810 nm in the near-infrared range [25]. Approved by the FDA in 1958 [86], ICG was initially used for angiographic purposes. In 2009, Fujiwara et al. [25] first utilized it for detecting SLNs in skin cancers.

When injected intradermally, ICG binds almost completely to human serum albumin [25]. After the injection, it diffuses into lymphatic pathways and lymph nodes like vital dyes [71]. Detection is achieved using a near-infrared fluorescence-guided camera system [27, 72]. This device visualizes color changes and tracer migration from the injection site to the lymph node in real-time [58, 68]. Red and orange indicate the highest ICG signal, while blue and green correspond to surrounding tissue with lower ICG signals [58]. Its specificity reaches 100%, with sensitivity reported between 91% and 98% [27].

Table 1. Identification rate, sensitivity, specificity, false negative rate and concordance rate of the current standard and novel methods of sentinel lymph node biopsy (SLNB)

Method	Identification rate	Sensitivity	Specificity	FNR	Concordance rate to radiocolloid	
					For patients	For nodes
The current standard	96–100% [25, 28, 53]	66.6 –98% [34, 54]	100% [34]	0–33.3% [34, 37, 55]	–	–
ICG	60–100% [25, 55]	91–96.1% [25, 56, 57]	100% [56, 57]	7.4–16.7% [25, 55–58]	98% [59]	96% [59]
Magnetic tracers	95.3% [53]	97.2% [60]	97.7% [60]	50% [61]	100% [62]	88.2% [62]
18F-FDG PET/CT	No data available	16.7–56% [63–66]	95.8–97% [63–66]	16.7–82.4% [63, 65, 67]	84.8% [67]	80% [63]

18F-FDG PET/CT — 18F-fluorodeoxyglucose positron emission tomography/computed tomography; BMI — body mass index; FNR – false negative rate; ICG — indocyanine green

Indocyanine green is also considered a valuable complement to lymphoscintigraphy, gamma probes, and blue dyes [87]. Some studies indicate that combining ICG with 99mTc eliminates the need for vital blue dyes, so they can be safely omitted [69].

Indocyanine green demonstrates good tissue uptake and a favorable safety profile [58, 70]. Compared to patent blue and isosulfan blue, ICG carries a lower risk of anaphylactoid reactions; it occurs in 0.05% of patients versus 0.3% and 1.1% of patients in whom patent blue and isosulfan blue was used, respectively [71]. Additionally, ICG is an alternative to vital blue dye due to its superior intraoperative visibility [70]. Likely due to its higher optical sensitivity, Fadel et al. [88] reported a statistically significant higher SLN identification rate using ICG with technetium-99 (99-Tc) compared to blue dye with 99-Tc.

The main advantage of ICG is that it is a one-step technique performed entirely during surgery. Moreover, ICG is inexpensive and does not emit ionizing radiation [72]. The cost of using ICG can be as much as 2.4 times lower than blue dye [88]. Although the risk of adverse effects is minimal, ICG is contraindicated in patients allergic to iodine or shellfish components [17, 27] and patients with hepatic insufficiency [17] because it is exclusively cleared by the liver [74]. There is also uncertainty regarding body mass index (BMI) and its potential impact on identification rates [25], though the effect appears insignificant [68].

However, ICG has a significant limitation: its utility for preoperative localization is restricted. Pameijer et al. [75] reported that fewer than half of their patients exhibited visible fluorescence before skin incision. As a result, ICG alone is unsuitable for melanoma located on the trunk or in cases with potential drainage to multiple basins. It may, however, be feasible for extremity melanomas where the nodal basin is more predictable [75]. Ballardini et al. [73] indicated that ICG is equivalent to 99mTc in identifying SLN in breast cancer with predictable drainage. Consequently, ICG might be non-inferior to 99mTc for extremity tumors. Still, limited studies confirm this, and preoperative lymphoscintigraphy remains necessary [69].

Magnetic tracers

The use of magnetic tracers is based on their ferromagnetic properties [62]. Superparamagnetic iron oxide was approved by the FDA in 2022 for patients with breast cancer undergoing mastectomy. To detect SLN, a device called Sentimag is used [82]. Superparamagnetic iron oxide is coated with carboxy dextran to enhance tracer efficiency [82, 89]. The tracer is injected subcutaneously around the lesion or biopsy scar of melanoma at least 15–20 minutes before SLNB, followed by 5–20 minutes of vigorous massage to enhance tracer drainage [62, 82]. The injection can be performed up to 40–47 days before surgery, simplifying treatment scheduling [76]. After diffusing to the SLN, the tracer is detected using a magnetometer [62]. In some cases, the tracer stains the lymph nodes due to its blackish-brown color, making SLN identification easier for the surgeon [77].

Magnetic tracers do not emit radiation, which eliminates the need for nuclear medicine facilities. The surgeon can administer the tracer, making the process safer and less expensive than standard lymphoscintigraphy with staining [78, 79]. No correlation has been found between age, BMI, and the SLN detection rate during surgery [80, 81]. However, Karakatsanis et al. [80] and Thill et al. [90] observed low transcutaneous signal detection in patients with a higher BMI.

A drawback of superparamagnetic iron oxide is the brownish skin discoloration at the injection site [78]. This pigmentation can be mitigated by injecting slightly deeper [83] and typically fades over time [91].

Table 2. Advantages and disadvantages of the current standard and novel methods

Method	Advantages	Disadvantages
The current standard	High identification rate, achieving up to 100% [28]	Radiation exposure for patients and healthcare workers [25]
	Capability to identify "in-transit" nodes [29]	Dependency on multidisciplinary expertise [17, 22, 42]
	Minimally invasive method [22]	Potential complications: lymphedema, nerve injury, hemorrhage, discomfort and edema leading to mobility issues [42]
	Vital blue dye allows SLN visualization without the need for additional tools [29]	Allergic [17, 20, 23, 25, 27, 43, 44] and anaphylactic [45–47] reactions to vital blue dyes
	Minimal radiation exposure: operating room staff — below 1 μSv and surgeons performing SLNB — below 2 μSv per procedure [17]	Bluish skin discoloration [17, 23, 27] and a transient change in urine color to green [17] due to the use of vital blue dyes
	Negligible fetal exposure to radioactivity during pregnancy [17]	Risk of skin necrosis after administration of methylene blue [17]
	No adverse maternal or fetal effects of lymphoscintigraphy [51]	Risk of acute hemolysis in patients with G6PD deficiency due to administered methylene blue [17]
		Teratogenicity of methylene blue [17, 27, 48]
ICG	Color changes and tracer migration are visible in real time [58, 68]	ICG cannot be used in patients allergic to iodine components or shellfish [17, 27]
	Greater intraoperative visibility compared to vital blue dyes [69, 70]	ICG cannot be used in patients with hepatic insufficiency [17] — it is exclusively metabolized by the liver [74]
	High tissue uptake for accurate mapping [58, 70]	Potential impact of BMI on the identification rate, but insignificant [25, 68]
	Favorable safety profile [58, 70] — lower risk of anaphylactoid reactions than patent blue and isosulfan blue [71]	Limited visibility pre-incision — ICG cannot be used alone in cases with potential multiple drainage basins [75]
	One-step technique and entirely performed during the surgery [72]	
	Inexpensive [72]	
	Does not emit radiation [72]	
	Effective as a standalone method in predictable drainage scenarios [73]	
Magnetic tracers	The injection of tracer can be performed up to 40–47 days prior surgery [76]	Brownish skin discoloration at the injection site [78]
	The tracer can dye the lymph nodes [77]	Injection-related side effects: pain, vasodilation, paresthesia, skin reactions, and rare anaphylaxis [77]
	Does not emit radiation [78, 79]	Surgical instrument interference: potential signaling issues with ferromagnetic instruments [77]
	No correlation between age, BMI and SLN detection rate [80, 81]	Contraindications: hypersensitivity to iron oxide or dextran, iron overload disease, a metal implants in the axilla or chest [82]
	Suitable for centers lacking nuclear medicine facilities [62]	Lack of studies on pregnant or nursing women and pediatric patients [82]
		Device reset required before each user [83]
		No preoperative tracer drainage visualization [61]
18F-FDG PET/CT	Used to aid in melanoma staging [84]	Inferiority to SLNB [85]
	Non-invasive method [63]	

18F-FDG PET/CT — 18F-fluorodeoxyglucose positron emission tomography/computed tomography; BMI — body mass index; ICG — indocyanine green; SLN — sentinel lymph node; SLNB — sentinel lymph node biopsy

When injected intravenously, potential complications include pain, vasodilation, paresthesia, skin reactions, and anaphylaxis. During surgery, it is recommended to use plastic surgical instruments when measuring with the magnetometer to avoid interference with the ferromagnetic signaling [77]. The slightly larger diameter of the Sentimag probe (6 mm) compared to the gamma probe could be seen as a disadvantage; however, a larger incision is not required [90], and a smaller probe is available [83].

Contraindications for superparamagnetic iron oxide include hypersensitivity to iron oxide or dextran

compounds, iron overload disease, and the presence of metal implants in the axilla or chest. Additionally, no studies have been conducted on pregnant women, nursing mothers, or pediatric patients [82]. The device also requires resetting before each use to avoid erroneous readings [83].

Unlike the current gold standard, magnetic tracers do not allow for tracer drainage visualization before the surgery. However, the MAGMEN study demonstrated that SLN localization and staging could be performed using low-dose superparamagnetic iron oxide-enhanced magnetic resonance imaging (MRI) and a magnetometer. Among 15 patients with cutaneous melanoma of the extremities, the per-patient SLN identification rate was 100%. Nevertheless, due to limitations such as the small sample size and varying doses of superparamagnetic iron oxide doses, these results should be interpreted cautiously. Further research is needed to determine the optimal dose of superparamagnetic iron oxide and refine MRI protocols [61].

Magnetic tracers have been shown to be non-inferior to the current standard of SLNB in breast cancer patients [77, 79, 83, 90–92]. In the MELAMAG study, the magnetic tracer technique was compared to radioisotope alone and was found to be non-inferior. Additionally, the SLN identification rate with the magnetic technique was more favorable than with radioisotope alone. The SLN identification rate was 97.7% using the current gold standard and 95.3% using the magnetic technique. Both techniques achieved identical identification rates in the inguinal and cervical basins (95.2% and 88.5%, respectively). However, in the axillary basin, the magnetic technique had a lower identification rate, likely due to the deeper location of sentinel nodes in this area. When compared with the current standard, the magnetic technique failed to meet the predefined non-inferiority margin [53].

The IMINEM study assesses detection and concordance rates between the current gold standard and the magnetic technique for SLNB in cutaneous melanoma. The patients' and sentinel nodes' concordance rates between these techniques were 95% and 86% for head-neck and trunk melanoma and 97% and 93% for limb melanoma, respectively. For involved nodes, the concordance rates were 100% for patients and 88.2% for nodes. These findings suggest that the magnetic technique is a reliable method for SLNB in limb melanomas, particularly in centers without access to isotopic methods [62]. Similarly, the MELAMAG study reported identical SLN identification rates in the inguinal basin for both techniques [53].

Unfortunately, the non-inferiority of magnetic tracers compared to the current standard of SLNB in melanoma patients could not be conclusively demonstrated in either the IMINEM study [62] or the MELAMAG trial [53]. Both studies lacked sufficient sample sizes to confirm non-inferiority [53, 62]. Therefore, the magnetic technique is not currently indicated for SLNB in melanoma patients [53]. However, it remains a potential alternative for centers that cannot afford nuclear medicine facilities [62].

18F-FDG PET/CT

18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) is currently used to detect distant metastases in patients with melanoma, with sensitivity and specificity of 87% to 96%. This imaging method helps stage melanoma and prevent unnecessary surgeries — regional lymph node metastasis found by PET/CT increases the stage, thereby eliminating the need for lymph node dissection [84].

As a non-invasive method, 18F-FDG PET/CT has been considered a potential replacement for SLNB. Schaarschmidt et al. [63] compared the sensitivity and specificity of 18F-FDG PET/CT, 18F-fluorodeoxyglucose positron emission tomography/magnetic resonance (18F-FDG PET/MR), and 18F-FDG PET/MR with diffusion-weighted imaging (DWI) to lymphoscintigraphy for detecting SLN metastases. They reported sensitivity, specificity, positive predictive value, and negative predictive value of 17.7%, 95.6%, 50.0%, and 82.3%, respectively, for PET/CT and 23.5%, 96.9%, 66.7%, and 82.3%, respectively, for PET/MR. Although DWI was not available for all patients, the data showed an increase in false-positive SLNs when DWI was used. The authors concluded that neither 18F-FDG-PET/CT nor 18F-FDG PET/MR (even with DWI) could replace SLNB for N-staging in melanoma patients [63]. Similarly, Jiménez-Requena et al. [85] highlighted the inferiority of 18F-FDG PET to SLNB. In contrast, Dellavedova et al. [93] reported a case where 18F-FDG PET/CT identified SLN missed by preoperative ultrasonography and lymphoscintigraphy, suggesting further investigation is warranted.

SLNB in head and neck melanoma

Sentinel lymph node biopsy for melanoma in the head and neck is a challenging procedure that requires further investigation before it can become a standard management approach. In their studies, Jansen et al. [94] confirmed the utility of intraoperative lymphatic mapping and SLNB in early-stage melanoma but noted procedural difficulties. A sentinel node was successfully identified in 90% of cases, though only 53% were positive for both dye and radiotracer. Consequently, surgeons should employ both detecting techniques for lymphatic mapping in this region [94]. A systemic review of 32 studies published between

1990 and 2009 indicated an increased false-negative rate (FNR) for SLNB in head and neck melanoma compared to non-head-and-neck lesions [95].

A multicenter study examining the safety, efficacy, and prognostic value of SLNB in head and neck melanoma patients found SLNB to be a strong predictor of overall survival ($p = 0.011$) (63.1 months in the positive group and 84.1 months in the negative group) and recurrence-free survival ($p < 0.001$) (32.7 months in positive group vs. 78.4 months in the negative group). Additionally, a positive SLNB was the strongest predictor for intermediate-thickness melanomas [96].

Another study compared lymphoscintigraphy with SPECT/CT before SLNB to SLNs identified surgically using an intraoperative gamma probe. The hottest node detected on SPECT/CT and by the intraoperative gamma probe matched in 85% of cases. Data comparing SPECT/CT radioactivity count with *ex vivo* count rates of surgically removed SLNs suggest that SPECT/CT quantification identified not only the hottest nodes but also additional lymph nodes that should be addressed during surgery and follow-up [97].

Oliver et al. [98] investigated the use of artificial intelligence and machine learning algorithms to identify metastases in head and neck melanoma. Their finding suggested that these techniques could be particularly useful for patients unlikely to benefit from SLNB. Further development and implementation of machine learning algorithms may reduce SLNB-associated costs and morbidity [98].

Sentinel lymph node biopsy plays a critical role in staging and prognostication in melanoma patients, including those with head and neck melanomas. Zhang et al. [99] demonstrated that SLNB is associated with improved overall survival and highlighted sentinel node status as a significant risk factor for poor prognosis in these patients. Similarly, a positive SLNB is highly predictive of recurrence [95], which underscores its utility in identifying patients at higher risk of disease progression.

Further research has shown that a positive sentinel node is a strong predictor of reduced overall survival across all Breslow thickness categories, particularly for intermediate-thickness melanomas. Positive SLNB results also predict reduced recurrence-free survival in all melanomas, with strong pronounced prognostic value observed in intermediate-thickness cases [96].

These findings collectively affirm the importance of SLNB not only as a diagnostic tool but also as a prognostic indicator [96] in head and neck melanoma management. However, the variability in outcomes across studies suggests a need for further research to refine its predictive utility in this specific subset of patients. The increased FNRs for SLNB in head and neck melanoma, compared to non-head-and-neck lesions [95], and the anatomical complexity of the head and neck region underscore the necessity for multimodal approaches, such as radiotracers, vital blue dyes, SPECT/CT, and potentially machine learning algorithms.

Conclusions

Planar lymphoscintigraphy with traditional radiocolloid and blue dye remains the gold standard for SLNB in melanoma patients, with an identification rate of 100%, making it the most reliable option despite its limitations. However, new methods show promise. ICG, with its superior intraoperative visibility, is emerging as an alternative to vital blue dye when combined with radiocolloids. Magnetic tracers also offer a viable option for centers without access to nuclear medicine facilities. Unfortunately, 18F-FDG PET/CT cannot replace SLNB for N-staging in melanoma patients. Machine learning algorithms hold potential as non-invasive methods for identifying nodal metastases in patients at very low risk of nodal metastasis. Further research is necessary to determine the best method for SLNB in melanoma patients.

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Author contributions

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Conflict of interest

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Supplementary material

None.

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