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Comparison of Different Techniques for the Assessment of Sentinel Lymph Node Biopsy in Melanoma: A Systematic Review

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Background: The gold standard for sentinel lymph node staging in melanoma is the use of the combined technique of radioisotope plus blue dye. New techniques and alternative methods have been proposed, with the promise of achieving comparable efficacy. We then carried out a literature search.
Methods: We conducted a literature search using the "sentinel lymph node biopsy" and "melanoma" keywords, then selected the case-control studies (the quality of which was assessed using the STROBE criteria).
Results: Twelve studies of 13,017 were selected, concerning the identification rate of indocyanine green fluorescence and indocyanine green-99mtc-nanocolloid techniques. We have found a comparable identification rate between the various techniques, even if given the small population present for some techniques, the results did not reach statistical significance.
Conclusions: The use of new techniques in sentinel lymph node detection promises results comparable to the gold standard techniques, but further studies are needed to validate these methods in the context of melanoma surgery. *(Plast Reconstr Surg Glob Open 2023; 11:e5447; doi: 10.1097/GOX.0000000000005447; Published online 22 December 2023.)*

INTRODUCTION

The locoregional spread of melanoma occurs mainly through the lymphatic system. The first node to drain these cells is called the sentinel lymph node (SLN).[1,2] It is essential to identify its involvement: the occurrence of lymph node metastases is relatively frequent and depends on the thickness of the tumor. Around 60% of patients with Breslow thickness between 2 and 4 mm, especially when the tumor is ulcerated, are at risk of having locoregional metastases. The introduction of SLN biopsy (SLNB) seems to have solved the problems of elective lymphadenectomy, which in 80% of patients is not clinically useful for patient survival, burdened with sometimes disabling functional complications. Nowadays, therapeutic lymph node dissection is performed only after oncological evaluation, in the case of SLN with positive micrometastases or lymph node metastases, because its use in prophylaxis has shown no survival advantage.

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The gold standard for the detection of SLNs is a double technique that involves the injection of a nanocolloid labeled with technetium and blue dye around the tumor. It consists of an injection a few hours before the operation at the site of excision of the primary lesion, and a tracer (colloidal albumin labeled with radioactive technetium), which extends along the lymphatic pathways up to the SLN, the migration of which is recorded by a gamma camera (dynamic lymphoscintigraphy). This method is combined with the injection into the melanoma site, a few minutes before the operation of vital dye which, following the lymphatic channels, dyes the SLN.[2]

The inclusion criteria for the execution of SLNB are clinical stage pT1b, pT2, pT3, and pT4; pathologist-confirmed histological diagnosis of melanoma (American Joint Committee on Cancer); Breslow primary tumor with greater than 0.81 mm; presence of spontaneous ulceration, regardless of Breslow thickness; and presence of one or more mitosis/mm^2, even in melanomas with Breslow thickness less than 0.81 mm.

MATERIALS AND METHODS

Our review was carried out with a literature search of Medline, PubMed, Embase, and Cochrane Library to identify all original articles, describing new techniques for performing SLNB in melanoma. The search terms used were "sentinel lymph node biopsy" and "melanoma."

Disclosure statements are at the end of this article, following the correspondence information.

We also searched relevant articles including abstracts, studies, and citations by manually looking for reference lists of purchased articles. The research ran until April 18, 2023 (Fig. 1).

Studies with the following characteristics were excluded: not published in English, full text not available, letters to the editor, reports, case reports, preliminary studies, studies without the technique's identification rate reported, no involvement of human subjects, and duplicate publications.

The data were extracted from selected studies, which included information on the publication of the article, patient characteristics, the sentinel node technique, and the number of SLNs found with each technique. Quality of the cohort studies was assessed based on the recommendations of the STROBE statement,[3] and studies were included if the overall quality score was 3 of 5 or higher (Table 1).

All extracted data were tabulated and presented. RevMan 5.4 software was used for quantitative analysis.[17]

The odds ratio (OR) with a 95% confidence interval (CI) was calculated for the binary data variables. The Mantel-Haenszel method was used to combine the odds ratio for the outcome of the sentinel node success.

The fixed-effects model was used to calculate the result. The random-effects model was used to evaluate heterogeneity.[17,18]

The heterogeneity of the study results was shown on the forest plot, which displays the estimates of the different results, for a comparison between the different techniques of each study, using the χ^2 test with a value of 30% to identify the maximum heterogeneity.[19–21]

RESULTS

In total, 13,017 citations were found in the literature, of which 12 studies were selected after the exclusion of articles based on the relevance of their title and abstracts. These studies focused on the isolated use of indocyanine green (ICG) fluorescence,[4–10] a hybrid tracer of ICG with technetium-99m (Tc-99m),[11–13] and nanoparticle superparamagnetic iron oxide.[15,16] Cross-references showed that no articles were left out based on the initial research.

All studies were published between 2012 and 2021 (Table 2, Table 3, Table 4). The studies reported a total of 503 patients undergoing different SLN techniques. Seven studies have been selected for ICG; all are cohort studies, both prospective and retrospective. Five of these were compared using intraoperative ICG, blue dye, and radioisotope with different detection rates based on the position of the SLN. The other two studies describe ICG with the percentage of visualization of the lymph nodes.

For the hybrid tracer ICG and nanocolloid, six articles were found, of which only three valid studies were related. All are prospective cohorts and included a total of 140 patients who underwent the new procedure with the standard sentinel node technique (lymphoscintigraphy and blue dye). Only two studies have been found on the use of ferromagnetic particles in detecting the SLN. The two studies reported 189 patients recruited for a comparison between the magnetic technique, the gold standard technique (radioisotope and blue dye), and the radioisotope alone.

Takeaways

Question: Are the new techniques that have appeared for the identification of sentinel lymph nodes as accurate as the traditional technique?

Findings: Analyzing the works in the literature, the use of new techniques in the identification of sentinel lymph nodes in treatment seems to guarantee the same accuracy as the gold standard.

Meaning: The search for sentinel lymph nodes in melanoma can be performed with different techniques, which appear to demonstrate comparable efficacy.

INDOCYANINE GREEN

The quantity of ICG administered varies between the different studies, with the upper limit being 2 mL (Table 2). Two used ICG alone.[6,8]

The ICG was injected near the tumor in all the studies.

Regarding the quantitative analysis of the SLN, between the ICG and the blue dye, there is a significant heterogeneity with $I^2 = 63\%$ and $P = 0.008\%$ among the eight studies.[4,5,7,9–11,13] ICG was significantly better than the blue dye (OR 20.08, 95% CI, 13.45–29.99). Regarding the identification of SLNs between ICG and the radioisotope, the heterogeneity is not significant ($I^2 = 53\%$, $P = 0.05$) among the seven studies (OR 1.85, 95% CI, 1.16–2.94).[4,5,7,9–11,13]

In conclusion, the heterogeneity between the radioisotope and the blue dye is statistically valid [$I^2 = 87\%$ $P < 0.00001$ (OR = 0.10, 95% CI 0.07–0.14)].[4,5,7,9–11,13]

Regarding the cohort studies, in two, the SLN is performed only with ICG,[6–8] in the other five, the ICG is compared with the blue dye and the radioisotope.[4,5,7,9,10]

In their study of 86 patients, Namikawa et al[6] injected 0.4–1.0 mL (2.0–5.0 mg) of peritumor ICG. A near-infrared camera (photograph dynamic eye; Hamanatsu, Photonics, Hamanatsu, Japan) was used intraoperatively for the visualization of SLNs with ICG, in association with a handheld gamma probe (Neo2000; Gamma Detection System Neoprobe Corporation, Ohio) for the radioisotope, previously injected for lymphoscintigraphy.

A total of 93 lymph nodes were highlighted, of which 98.9% were identified intraoperatively; with different results based on the body district, specifically:

- Six (66.7%) of nine patients with head and neck melanoma;
- Three (15.8%) of nine patients with upper limb melanoma and with SLN in the armpit;
- Seven (46.7%) of 15 patients with upper limbs melanoma with trunk SLN;
- Eight (100%) of eight patients with trunk melanoma with SLN in the knee;
- Thirty-two (84.2%) of 38 patients with trunk melanoma with SLN in the lower limbs;
- Three (75%) of four patients with lower limb melanoma with SLN in the popliteal fossa.

Stoffels et al,[8] in a retrospective cohort study of 22 patients, injected 1 mL (200 mg) of ICG. Images

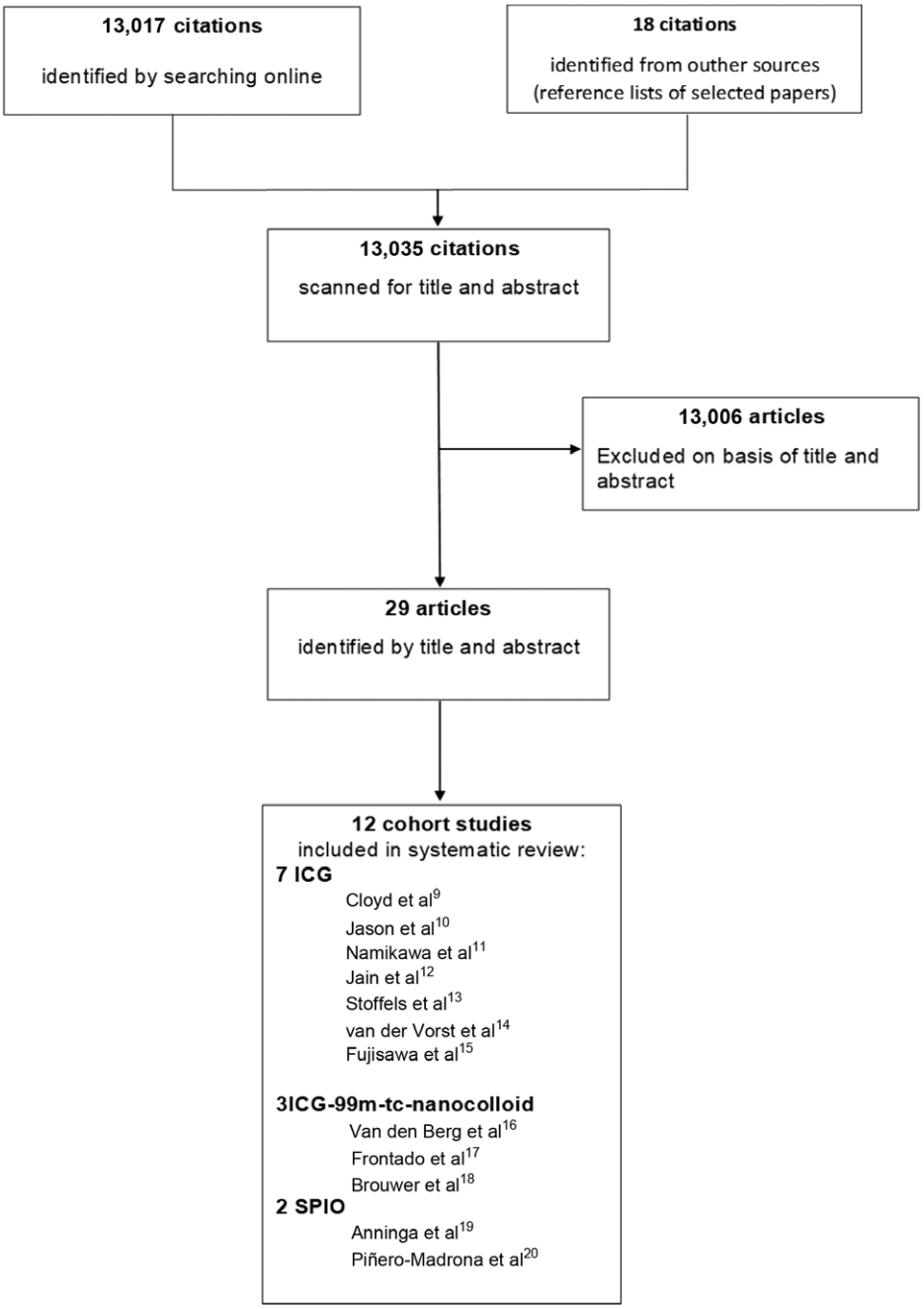

Fig. 1. Systematic search of published studies. SPIO, superparamagnetic iron oxide nanoparticles.

were taken intraoperatively with a Photodynamic Eye system (PDE; Hamamatsu, Photonics, Hamamatsu, Japan).

A total of 61 lymph nodes (100%) were highlighted:

- 9.1% in two people with head and neck melanoma with head and neck SLN;
- 59.5% in nine people with trunk melanoma with armpit drain;
- 31.8% in four patients with upper limb melanoma with inguinal SLN;
- 9.5% in seven patients with lower limb melanoma with SLN in the popliteal fossa.

In the prospective cohort study by Cloyd et al,[4] 52 people were injected with 2 mL (2.5 mg/mL) of ICG (ICGreen; Pulsion Medical Systems, Feldkircchen, Germany), 1 mL of Tc-99m sulfur colloid, and 9 mL of lymphazurin isosulfan blue (ISB) (Tyco Healthcare, Inc, Norwalk, Conn.).

An infrared camera computer system (SPY Elite; Novadaq Technologies Inc, Ontario, Canada) was used

Table 1. Agreement of the Studies with the STROBE Criteria

	Study Objectives	Clear Inclusion Criteria	Standardized Histopathology	Patient Follow-up Recorded	Withdrawals from Study Reported
Cloyd et al[4]	Yes	Yes	No	No	Yes
Jason et al[5]	Yes	Yes	Yes	No	Yes
Namikawa et al[6]	Yes	Yes	No	No	Yes
Jain et al[7]	Yes	Yes	Yes	No	Yes
Stoffels et al[8]	Yes	Yes	Yes	No	Yes
van der Vorst et al[9]	Yes	Yes	Yes	No	Yes
Fujisawa et al[10]	Yes	Yes	Yes	No	Yes
Van den Berg et al[11]	Yes	Yes	No	No	Yes
Frontado et al[12]	Yes	Yes	No	No	Yes
Brouwer et al[13,14]	Yes	Yes	Yes	No	Yes
Anninga et al[15]	Yes	Yes	Yes	Yes	Yes
Piñero-Madrona et al[16]	Yes	Yes	Yes	No	Yes

intraoperatively for imaging. The injection was made near the tumor with a primary lesion in the extremities and trunk and localization of the SLN in the armpit and the inguinal area respectively. A total of 77 lymph nodes were found: 88.5% for ICG, 96.2% for Tc-99m sulfur colloid, and 59.6% for ISB with a value of *P* less than 0.05 for ICG versus ISB.

Jason et al,[5] in a retrospective cohort study, divided a total of 90 patients into two groups: group A with 39 people, and group B with 51 people. Group A was injected with 0.5–3 mL of blue dye (ISB and methylene blue), whereas group B was injected with 0.5–1.5 mL of ICG. The imaging techniques used, respectively, were for group A, a combination of radioisotope handheld gamma probe and blue dye, and for group B, a combination of radioisotope/handheld gamma probe and real-time ICG fluorescence infrared camera (SPY Elite System). The injection into the primary site of the tumor took place in the head and neck in 28 patients, in the trunk in 27, in the lower extremities in 17, and in the upper extremities in 18. Lymph nodes were detected as follows: 79.4% with blue dye, 98% with ICG, and 97.8% with the use of the radioisotope ($P = 0.020$ for ICG versus ISB).

Jain et al[7] performed a prospective cohort study on 15 patients who were injected with 1–2 mL of methylene blue and 0.9 mL (2.25 mg) of ICG.

A SPY machine gamma probe was used intraoperatively. The primary tumors were localized in the head and neck, upper limbs, and trunk and lower limbs with respective SLNs located in the cervical, axillary, and knee areas.

They found:

- At the cervical level, nine of 41 for ICG, six of 41 for methylene blue (MB), and eight of 41 for Tc-99m;
- At the axillary level (primary tumor of upper limbs), four of 41 for ICG, zero of 41 for MB, and three of 41 for Tc-99m;
- At the axillary level (primary tumor of the trunk), 14 of 41 for ICG, five of 41 for MB, and 13 of 41 for Tc-99m;
- At the knee level (primary tumor in the lower limbs), 10 of 41 for ICG, seven of 41 for MB, and seven of 41 for Tc-99m.

Van der Vorst et al[9] performed a cohort study on 15 patients. The patients were injected with 1.6 mL of 600, 800, 1000, or 1200 μM of ICG: HSA and 1 mL of patent blue V (Guerbet, France). Near infrared fluorescence imaging was used as an intraoperative technique. A total of 30 lymph nodes were highlighted, of which 100% were detected with ICG (30/30), 100% with the radioactive tracer (30/30), and 73% (27/30) with the blue dye.

Primary tumors were found in the abdomen with localization of the SLN in the axillary area; dorsal area, with SLN in the neck; and finally, melanoma of the trunk and extremities with SLN in the knee and ventral and dorsal trunk.

Fujisawa et al[10] injected 34 patients with 0.5% ICG (Diagnogreen; Dai-ichi Pharmaceutical, Tokyo, Japan) and 0.4–0.8 mL of 2% patent blue dye. A total of 74 lymph nodes were identified. For SLNs located at the retro auricular and submandibular level, 13 were detected with ICG, eight with blue dye, and 11 with the radioisotope.

As for trunk melanomas with SLN at the axillary and knee level, 39 were found with ICG, 38 with blue dye, and 29 with the radioisotope. Ultimately, upper and lower limb tumors with SLNs in the axilla and knee were identified as follows: 22 with ICG, 15 with blue dye, and 20 with the radioisotope (Figs. 2-3).

HYBRID TRACER

Three of six articles were selected concerning the injection of a hybrid tracer formed by ICG and Tc-99m nanocolloid. Of two of these articles, it was not possible to extract the full text, so we only used the abstract. The radioactive tracer was administered in all studies.

Van den Berg et al[11] performed a prospective cohort study of 104 patients who were injected with a hybrid of ICG and Tc-99m nanocolloid. A gamma camera and a fluorescent tracer camera were used for imaging. Primary tumors were in the head, neck, trunk, and extremities. A total of 305 lymph nodes were highlighted, of which 93.8% (286/305) were detected with the radioactive tracer, 96.7% (295/305) with ICG, and 61.7% (116/305) with blue dye.

Frontado et al[12] performed a prospective cohort study of 20 patients injected with ICG/Tc-99m nanocolloid and 1 mL of blue dye. A gamma camera and a gamma probe with optical detection of the blue dye and ICG were used intraoperatively. Ninety-seven percent of

Table 2. Characteristics and Surgical Outcomes of Studies Using ICG and Nanocolloid

	Study Type	Patients (n)	ICG Composition Injected (mL)	Technique for Intraoperative Imaging	Injection Site (Primary Location)	Surgery Complication	Lymph Node Location	SLN Detection Rate (%)
Cloyd et al[4]	Cohort (prospective)	52	2 mL (2.5 mg/mL) of ICG (ICGreen; Pulsion Medical Systems) 1.0 mCi TSC 4 mL of lymphazurin ISB	Infrared camera-computer system (SPY Elite; Novadaq Technologies Inc)	Extremity Trunk	None	Axilla Inguinal	Total of 77 lymph 88.5% for ICG 96.2% for TSC 59.6% for ISB $P < 0.05$ for ICG vs ISB
Jason et al[5]	Cohort control (retrospective)	90 GP A = 39 GP B = 51	Group A 0.5–3.0 mL of blue dye (ISB or methylene blue) Group B 0.5–1.5 mL of fluorescent ICG	Group A combination of radioisotope/handheld gamma probe and blue dye methods Group B Combination of radioisotope/handheld gamma probe and real-time ICG Fluorescence infrared camera SPY *Elite* System	Head and neck 31.0 % (n = 28) Trunk 30% (n = 27) Lower extremity 19% (n = 17) Upper extremity 20% (n = 18)	Not reported	Not reported	79.4% blue dye method 98.0% using the ICG fluorescence method 97.8% using the radioisotope/handheld gamma probe method $P = 0.020$ for ICG vs ISB
Namikawa et al[6]	Cohort control (retrospective)	86	0.4–1.0 mL (=2.0–5.0 mg) of ICG (Diagnogreen) and 1.0 mL of 2% patent blue	Handheld gamma probe (Neo2000, Gamma Detection System Near-infrared camera (Photodynamic Eye)	Head and neck Upper limb Trunk Lower limb	Not reported	Neck Axilla Groin Popliteal fossa	93 node total 98.9% intraoperatory Prior skin operation 63.4% 66.7% (6/9) 15.8% (3/19) 46.7% (7/15) trunk 100% (8/8) 84.2% (32/38) lower limb 75.0% (3/4)
Jain et al[7]	Cohort control (prospective)	15	1–2 mL of methylene blue dye and 0.9 mL (2.25 mg) of ICG	SPY machine gamma probe	Head and neck Upper limb Trunk Lower limb	Not reported	Cervical Axilla Axilla Groin	100% ICG 4/4 75% MB Tech99 3/4 malignant 9/41 ICG 6/41 MB 8/41 Tech99 4/41 ICG 0/41 MB 3/41 Tech99 14/41 ICG 5/41 MB 13/41 Tech99 10/41 ICG 7/41 MB 7/41 Tech99

(*Continued*)

Table 2. ***Continued***

	Study Type	Patients (n)	ICG Composition Injected (mL)	Technique for Intraoperative Imaging	Injection Site (Primary Location)	Surgery Complication	Lymph Node Location	SLN Detection Rate (%)
Stoffels et al[8]	Cohort control (retrospective)	22	1 ml (200 μg) of the ICG	Fluorescence imaging system "Photodynamic Eye" (PDE)	Head/neck 2 (9.1%) Patient trunk 9 (40.9%) Upper limb 4 (18.2%) Lower limb 7 (31.8%)	1 (4.5 %) post-operative seroma 1 (4.5%) Postoperatively infection	Head/cervical Axilla Inguinal Popliteal	61 total (100%) 9.1% 54.5% 31.8% 45%
van der Vorst et al[9]	Cohort control	15	1.6 mL of 600, 800, 1000, or 1200 μM of ICG:HSA 1 mL total of patent blue V	Near infrared fluorescence imaging	Ventral Dorsal Trunk Extremities	None	Axilla Neck Groin Ventral trunk Dorsal trunk	30 total 30 ICG (100%) 30 radioactive (100%) 27 blue (73%)
Fujisawa et al[10]	Cohort control	34	0.5% ICG (Diagnogreen) 0.4–0.8 mL of 2% patent blue solution	Gamma probe system (Navigator GPS System; RMD Instruments Corp, Watertown, Mass.) ICG fluorescence imaging	Head/neck Trunk Upper/lower extremities	None	Retroauricular Submandibular Axilla Groin Axilla Groin	74 total ICG 13 BD 8 RI 11 ICG 39 BD 36 RI 29 ICG 22 BD 15 RI 20

BD, blue dye; RI, radioisotope; TSC, technetium-99m sulfur colloid.

Table 3. Characteristics and Surgical Outcomes of Studies Using Hybrid Tracer of ICG with TC-99m

	Study Type	Patients (n)	Hybrid Injected (mL)	Technique for Intraoperative Imaging	Surgery Complication	Location of Primary Tumor	SLNB Success Intraoperative (%)
Van den Berg et al[11]	Cohort (prospective)	104	Hybrid tracer ICG/Tc-99m nanocolloid	Gamma tracing followed by fluorescence imaging (FI) Gamma camera	Not reported	Head Neck Trunk Extremity	93.8% (286 of 305) radioactive 96.7% (295 of 305) fluorescent 61.7% (116 of 305) blue dye
Frontado et al[12]	Cohort (prospective)	20	ICG/Tc-99m nanocolloid Blue dye 1 mL	Gamma probe and optical SN-detection using blue dye and fluorescence imaging Gamma camera	Not reported	Head Neck Trunk Extremity	97% fluorescent 39.2% blue dye
Brouwer et al[13,14]	Cohort (prospective)	16	Injection of hybrid ICG/Tc-99m nano-colloid 1.0 mL of patent blue dye	Acoustic guidance provided by a G-ray detection probe (Neoprobe; Johnson & Johnson Medical) Handheld near-infrared fluorescence camera (PDE)	None	Head/neck (n = 10) Trunk (n = 6)	93% (25/27) fluorescent 37% (7/19) blue dye 89% (24/27) radioactive 93% (14/15) fluorescent 74% (11/15) blue dye 100% (15/15) radioactive

Table 4. Characteristics and Surgical Outcomes of Studies Using Magnetic Tracer

	Study Type	Patients (n)	Tracer Injected (mL)	Technique for Intraoperative Imaging	Injection Site (Primary Location)	Surgery Complication	Lymph Node Location	SLN Detection rate (%)
Anninga et al[15]	Cohort control	129 (257 nodes in 166 nodal basins)	Senna+ 0.5–2 mL	Magnetic probe (Sentimag)	Head/neck (25) Extremities (70) Trunk (71)	Persistence of dye-related discolorations (20.9% at 30 days, 16.2% after 1 y), and one case of allergic reaction	Axilla Cervical Inguinal	88% (22/25) 94.3% (66/70) 90.1% (64/71)
Piñero-Madrona et al[16]	Cohort control	60	Senna+ 0.5–2 mL	Magnetic probe (Sentimag)	Head/neck and trunk (22) Limbs (38	Not reported	Inguinal Axillary Cervical	22(100%) 37 (97.37%)

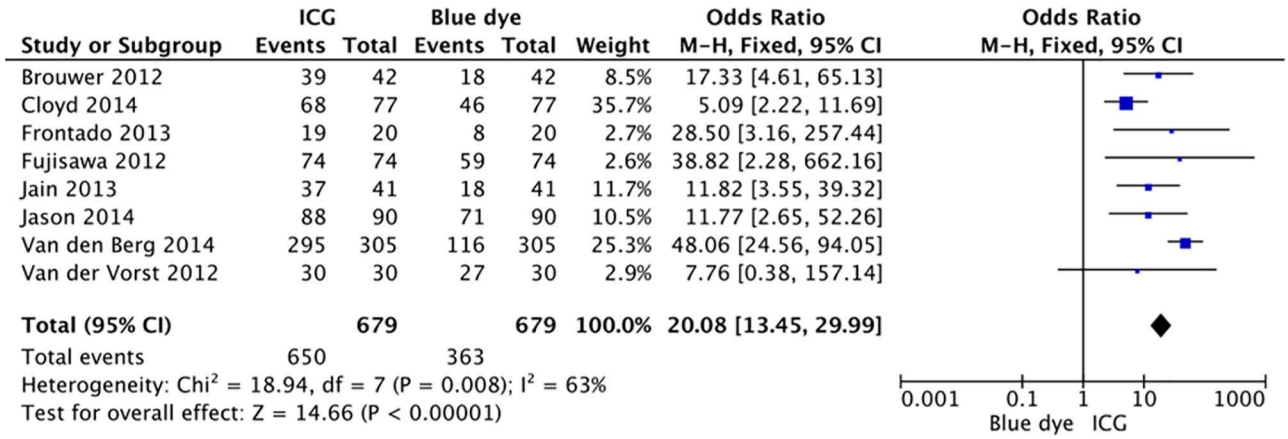

Fig. 2. Forrest plot: ICG versus blue dye.

lymph nodes were highlighted with fluorescence, and 39.2% with blue dye.

Brouwer et al[13] carried out a prospective cohort study on 16 patients, of whom 10 had primary cancer in the head and neck and six had melanoma in the trunk. The hybrid of ICG and Tc-99m nanocolloid and 1.0 mL of patent blue dye were injected peritumoral. Imaging was conducted by an acoustic guide provided by a G-ray detection

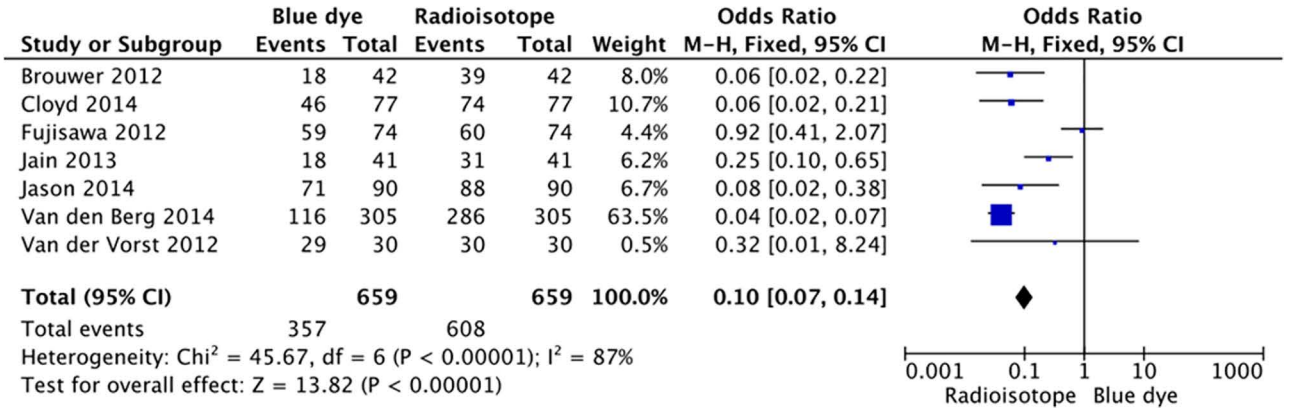

Fig. 3. Forrest plot: ICG versus radioisotope.

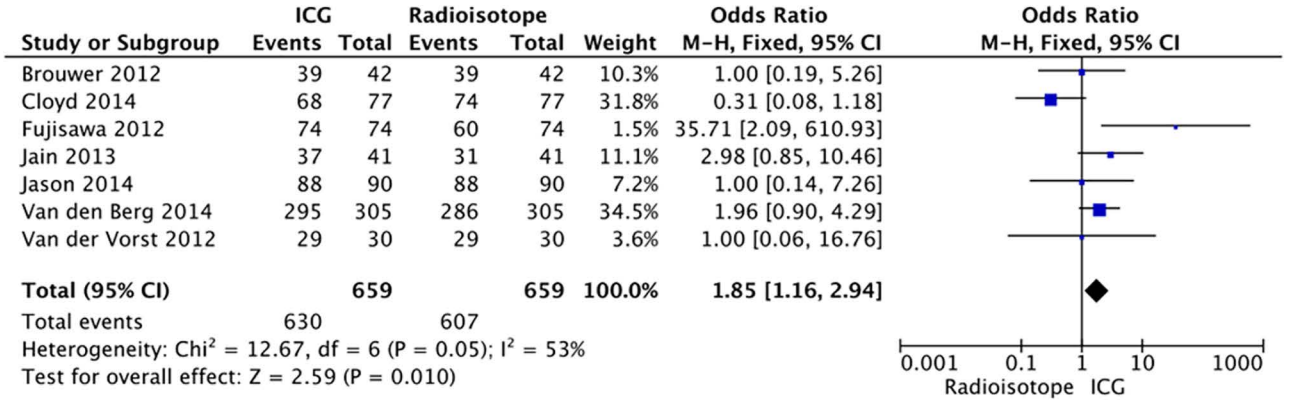

Fig. 4. Forrest plot: blue dye versus radioisotope.

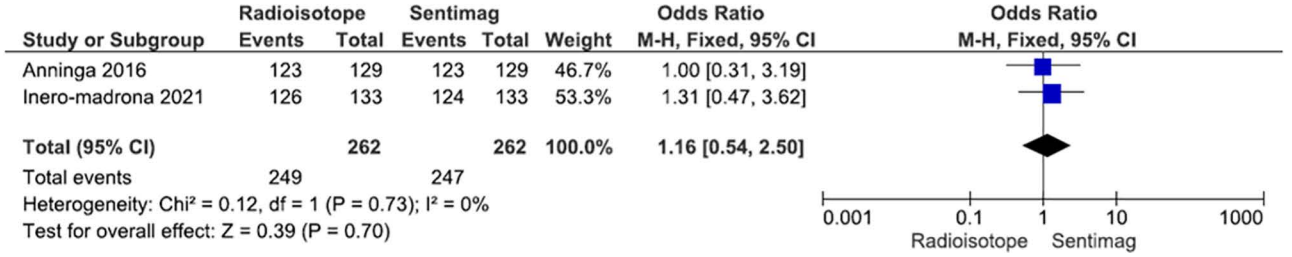

Fig. 5. Forrest plot: radioisotope versus MELAMAG trial.

probe (Neoprobe; Johnson & Johnson Medical) and by a handheld near-infrared fluorescence camera (PDE; Hamamatsu).

As regards head and neck melanomas, a total of 27 lymph nodes were highlighted, of which 93% (25/27) were detected with ICG, 37% (7/27) with the blue dye, and 89% (24/27) with the radioactive tracer. For trunk melanoma, 15 lymph nodes were found, of which 93% (14/15) were detected with ICG, 74% (11/15) with blue dye, and 100% (15/15) with the radioactive tracer.

MAGNETIC TRACER

In the 2016 MELAMAG trial,[15] 133 patients were recruited for a comparison between the magnetic technique, the gold standard technique (radioisotope and blue dye) and the radioisotope alone. Of these patients, only 129 were available for the final analysis, with the removal of 257 lymph nodes from 166 lymph node stations (86 at the axillary level, 42 at the inguinal level, 26 at the cervical level, and 12 in transit).

The primary lesions, on the other hand, were located at the level of the trunk (71), limbs (70), and head and neck area (25).

Before surgery, the patient was subjected to Tc-99m radiocolloid injection and lymphoscintigraphy.

Before the incision, a variable amount between 0.5 and 2 mL of Sienna+ was injected near the primary lesion (the amount was decided by the operator based on the size of the lesion). A magnetic probe was then used to identify the sentinel node. Its presence was then confirmed with the y probe on excision.

The combination of radiocolloid and dye obtained an identification rate of 97.7% (97.1% for melanomas located in the limbs, 97.2% for those located in the trunk, and 92% for those located in the head and neck area). The magnetic technique, on the other hand, obtained an identification rate of 95.3% (94.3% in cases with primary tumors located in the limbs, 90.1% for those located in the trunk, and 88% for those in the head/ neck district), equal to that of the radioisotope alone.

The greatest difference between the magnetic technique and the standard one was found in the lymph nodes located in the axillary area (91.9% versus 98.8%), data interpreted by the authors as a greater difficulty of the magnetic technique in detecting the deeper lymph nodes.

Follow-ups were then carried out at 30 days, 3 months, and 1 year later to evaluate any complications. Excluding the adverse effects due to surgery, the only complication related specifically to the technique detected was the persistence of dye-related discolorations (20.9% at 30 days, 16.2% after 1 year), and one case of allergic reaction during surgery following the injection of the dye (in which, however, given the temporal proximity between the injection of the radiocolloid and the magnetic medium, it was not possible to identify which of the two was the triggering medium).

The IMINEM study of 2021[16] recruited 60 patients in a comparison between the magnetic technique and the radioisotope.

Of these patients, 22 (36.7%) had head and neck melanomas and 38 (63.3%) had melanomas in the limbs.

In this study, up to 2 mL of Sienna$^+$ ferromagnetic medium was injected into the primary lesion immediately before surgery.

A total of 133 lymph nodes were removed from 66 lymph node stations (27 inguinal, 36 axillary, and three cervical); 65 in patients with primitive lesions in the trunk; and 68 in the limb. A total of 126 lymph nodes were identified with the radioisotope, whereas 125 were identified with the magnetic technique. The ferromagnetic technique achieved higher levels of identification than the radioisotope (94% versus 92%, respectively) in patients with trunk melanoma, whereas the standard technique achieved a higher identification rate in the case of sentinel node of limb melanoma (97% versus 92%), confirming an observation already made in the 2016 MELAMAG study, namely that the ferromagnetic technique is less effective in the case of lymph nodes located at axillary or inguinal levels.

The concordance rates between the two techniques were higher in cases with primary tumor localized than those located in the limbs (97% for patients and 93% for lymph nodes compared with those located in the head and trunk (95% for patients and 86% for lymph nodes).

DISCUSSION

SLNB is now the standard technique used for staging patients with melanoma. Initially, it was performed with the use of blue dye only[1]; then, the use of radiocolloid was introduced, and the combination of the two became the standard procedure.[1,22,23]

In recent years, various works have reported the use of ICG for different cancers (breast, gastric, and colorectal cancer).[24] The Society of Oncological Surgery and the American Society of Clinical Oncology have published evidence-based guidelines that recommend the sentinel node biopsy technique to be performed for patients with intermediate-thickness melanomas.[25–27]

Morton et al[2] provided definitive long-term follow-up data, with an international clinical study comparing SLNB versus observation, to increase the knowledge base for using SLNB.

Already, the MSLT-I report (Multicenter Selective Lymphadenectomy Trial) had demonstrated the feasibility and precision of the SLN with percentages of 99.4% for patients with intermediate thickness melanomas. Its results led to the confirmation that SLNB determines the pathological state of the lymph node station in 96% of cases and is the most powerful indicator for prognosis. This information is essential for determining appropriate adjuvant therapy and for subsequent new approaches.[28] Furthermore, these data demonstrate the importance of sentinel node management to avoid relapses, especially of the lymph node type. Blue dye was used in the studies.

Having established that the SLN is a crucial point, we performed a systematic review of the different techniques for visualizing the SLN; we therefore made a comparison between the most frequent tracers currently in use (ICG, blue dye, and radioisotope). There is an ongoing search for alternative methods due to the problems associated with the use of radioisotopes. Our systematic review focuses on intraoperative identification of the SLN due to the limited data available and the lack of key elements to include, such as relapse rates, follow-up, and false negatives. The paucity of global registration of false negatives against a gold standard and the absence of patient follow-up are obvious limitations of this review, which can only be reversed by acquiring appropriate data in future studies evaluating new techniques for biopsy of the SLN.

A total of 12 studies were included, all cohort studies, of which nine were prospective[4–7] and three were retrospective.[5,6,8] Clearly, not much evidence can be extracted from these studies; what is clear and what the evidence demonstrates is that the search for new technologies for the development of SLN identification is still in the initial phase.

All the included studies showed that the ICG dye did not show adverse effects, with very high SLN identification success from 88.5% to 100%.[4–10] SLN identification rate with ICG was higher in all studies with respect to blue dye, to reach a significant statistical significance ($P < 0.00001$).

In these studies, ICG was also compared with the radioisotope, with three articles finding a slight favor for ICG[7,10] and only one favoring of the radioisotope.[4]

However, statistical significance was not reached in the quantitative analysis ($P = 0.010$).

Clearly, because ICG is a well-comparable technique with radioisotope and blue dye, it has been compared in seven studies with the standard technique (blue dye and radioisotope).[4,5,7,9–11,13] In these studies, the percentages of identification of the SLN reach 100% for ICG in two of

them,[7,9] and in the remaining ones, they are in any case around this percentage, so it would be substitutable for the standard technique.

As regards the studies on the hybrid tracer of ICG and Tc-99m nanocolloid,[11–13] it was highlighted how a combination of the two could lead to both preoperative benefits, for the visualization of the SLN, and intraoperative ones, with a radiofluorescent guide, in head and neck melanomas, where there was a possibility for the blue dye to leave a stain.[13,14] Percentages from 98% to 100% are highlighted for identification of the SLN. This was not included in the meta-analysis because, in the quantitative analysis, the ICG had already been compared with the radioactive tracer, not obtaining significant results.

With reference to the use of paramagnetic means, however, it was not possible in the selected studies to statistically demonstrate the noninferiority of the magnetic technique compared with the standard, given the small sample size. Furthermore, in the studies, it was noted by the authors that, even in the case of the magnetic technique, a lymphoscintigraphy was always required before surgery for the selection of the lymph node stations to be checked, which, however, could be replaced by magnetic resonance imaging following the injection of the paramagnetic medium.

Despite this, the results obtained by the magnetic technique in detecting the SLN in various neoplasms, especially in the field of breast cancer, where it has been used for several years, should be noted. The first study of this neoplasm dates to 2014,[29] where it was demonstrated that the technique had an identification rate equal to the traditional technique (94.4% versus 95%).

The results used in the field of prostate cancer were also encouraging, with excellent diagnostic accuracy values (100% sensitivity, 97.0% specificity, 94.4% positive predictive value, 100% negative predictive value, 0.0% false negative rate, and 3.0 % additional diagnostic value) obtained in a recent study.[30]

Its noninferiority compared with the standard technique has also been demonstrated in penile cancer.[31]

Recent studies have also evaluated its use in rural environments (an undoubted advantage of the technique over the use of radiocolloids), demonstrating its oncological accuracy, cost-effectiveness, and ease of use compared with traditional techniques.[32] In this study, the identification rate was higher than the radiocolloid (91.1% versus 78.1%), with lower costs (NZ $557.70 versus NZ $1418), so much so that the authors recommended it as the main method for detecting the SLN, especially in the case of intangible injuries.

CONCLUSIONS

In this review, no significant advantage was identified with respect to the number of SLNs detected with the magnetic technique over the standard, but we have found that the detection rate of the magnetic tracer is comparable with the use of the radioisotope and blue dye.

In conclusion, there are now no reliable data that allow us to recommend the use of the radioisotope magnetic technique, but the results achieved so far, combined with greater ease of use and the convenience of not needing nuclear medicine facilities, require further studies to validate the technique.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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