European Journal of Nuclear Medicine and Molecular Imaging (2023) 50:3375–3389
https://doi.org/10.1007/s00259-023-06290-5

ORIGINAL ARTICLE

^{99m}Tc-Tilmanocept performance for sentinel node mapping in breast cancer, melanoma, and head and neck cancer: a systematic review and meta-analysis from a European expert panel

Guido Rovera[1] · Elizabeth J. de Koster[2] · Vittoria Rufini[3,4] · Mariella Zollino[3] · Luca Zagaria[3] · Francesco Giammarile[5] · Sergi Vidal-Sicart[6] · Renato Valdés Olmos[7] · Angela Collarino[3]

Received: 5 February 2023 / Accepted: 30 May 2023 / Published online: 13 June 2023

Abstract

Purpose Although multiple radiopharmaceuticals are currently available for sentinel node (SN) biopsy, ^{99m}Tc-tilmanocept is of particular interest due to its low molecular weight and specific binding capability for the mannose receptors of lymphatic reticuloendothelial cells. In the current systematic review and meta-analysis, we aimed to provide an update from a European expert panel on the performance of ^{99m}Tc-tilmanocept for SN biopsy.

Methods A systematic literature search of the PubMed/Medline and Embase databases was performed to identify studies on the use of ^{99m}Tc-tilmanocept for SN identification in oncological patients. The articles' methodological quality was assessed before inclusion. The pooled estimates of the pre-/intraoperative detection rates (DR; proportion of patients with ≥ 1 SN identified) and/or pN + sensitivity (SN + /pN + patients ratio), with 95% confidence intervals (CIs), were calculated for breast cancer, melanoma, and head and neck cancer.

Results Twenty-four articles were included in the systematic review, and twenty-one provided data for the meta-analysis. According to data availability, the ^{99m}Tc-tilmanocept-estimated pooled preoperative and intraoperative DRs were 0.94 (95%CI, 0.88–1.01) and 0.99 (0.98–1.00) for breast cancer, 0.98 (0.96–0.99) and 1.00 (0.99–1.00) for melanoma, and 0.97 (0.93–1.02) and 0.99 (0.96–1.01) for head and neck carcinoma. Finally, the pooled sensitivity for nodal metastasis in melanoma was 0.97 (95% CI, 0.92–1.03).

Conclusion ^{99m}Tc-tilmanocept is a promising radiotracer for SN mapping in patients with breast cancer, melanoma, or head and neck cancer. We strongly believe that multicenter trials are still needed to assess if ^{99m}Tc-tilmanocept is superior to other radiotracers used in clinical routine.

Keywords Sentinel node biopsy · ^{99m}Tc-tilmanocept · Breast cancer · Melanoma · Head and neck cancer

✉ Vittoria Rufini
vittoria.rufini@unicatt.it

[1] Nuclear Medicine, Department of Medical Sciences, AOU Città della Salute e della Scienza di Torino, University of Turin, Turin, Italy

[2] Department of Medical Imaging, Nuclear Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

[3] Nuclear Medicine Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

[4] Section of Nuclear Medicine, University Department of Radiological Sciences and Hematology, Università Cattolica del Sacro Cuore, Rome, Italy

[5] Nuclear Medicine and Diagnostic Imaging Section, Division of Human Health, International Atomic Energy Agency, Vienna, Austria

[6] Nuclear Medicine Department, Hospital Clinic Barcelona, Universitat de Barcelona, Institut d'investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain

[7] Interventional Molecular Imaging & Nuclear Medicine Section, Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands

Introduction

Sentinel node (SN) biopsy is a minimally invasive surgical approach to evaluate lymph node (LN) staging in clinically node-negative patients. The rationale of this technique is that, since SNs are the LNs with direct lymphatic drainage from the primary tumor and thus represent the first LNs receiving lymph-borne metastatic cells, their tumor status may predict whether the overall LNs in that lymphatic basin contain cancer or not. If the SN turns out tumor free on histopathological examination, all other LNs within the draining lymphatic basin are also assumed free of tumor, avoiding an unnecessary full lymphadenectomy and associated morbidity. Up to now, the most widely used radiopharmaceuticals for SN mapping in breast cancer, melanoma, and head and neck cancer have been ^{99m}Tc-labeled sulfur colloid in the USA and ^{99m}Tc-nanocolloidal albumin in Europe [1–4]. Compared to blue dye or fluorescent agents, the main strength of these radiopharmaceuticals is the possibility to perform preoperative lymphatic mapping, allowing a personalized surgical planning, and reducing surgical failures. The associated radiation dose of this technique is negligible at the patient level. The main drawbacks are the passive transport through the lymphatics, a relative slow clearance from the injection site resulting in a delayed migration to LNs, the pass-through to second-echelon LNs, and a possible masking of SNs that are close to the primary tumor (injection site). These limitations explain why there is a trend towards a novel radiopharmaceutical, ^{99m}Tc-tilmanocept, which contains relatively small macromolecules (molecular weight of 19,000 Da, diameter of 7 nm) that enable a rapid clearance from the injection site, resulting in a quick uptake in SNs and a more accurate detection of SNs close to the primary tumor. ^{99m}Tc-tilmanocept selectively binds to mannose receptors (CD206) expressed on the surface of LN macrophages and dendritic cells [5], thus reducing its migration to higher echelon nodes. ^{99m}Tc-tilmanocept was first used in clinical practice in breast cancer patients [6].

In the current systematic review and meta-analysis, we aimed to provide an update from a European expert panel on the performance of ^{99m}Tc-tilmanocept for SN mapping in breast cancer, melanoma, and head and neck cancer.

Materials and methods

Search strategy

A systematic literature search of the PubMed/MEDLINE and Embase databases was performed using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [7]. The search string was built using synonyms of "Sentinel Lymph Node" and "^{99m}Tc-diethylene-triamine-pentaacetic acid (DTPA)-mannosyl-dextran," including corresponding Mesh terms (Online Resource 1). The search was last updated on August 18, 2022. Search results were not limited by publication date.

Study selection

All retrieved articles were initially independently screened for eligibility by title and abstract by two authors (G.R. and A.C.). Full texts of potentially eligible studies meeting all inclusion criteria were retrieved for further evaluation. Original articles investigating the Food and Drug Administration (FDA)– and European Medicine Agency (EMA)–approved use of ^{99m}Tc-tilmanocept for SN identification in oncological patients in any tumor type were eligible for inclusion. Review articles, letters to the editor, editorials, and case reports were excluded. Articles not written in English were also excluded. A cross-reference check was performed. Any disagreements were resolved by discussion.

Quality assessment

The methodological quality of the included studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies tool version 2 (QUADAS-2) [8] to grade the risk of bias and methodological applicability on four key domains: patient selection, index test, reference standard, and flow and timing. Two authors (G.R. and E.J.d.K.) independently assessed the quality of the studies. Any disagreements were solved by consensus after re-evaluation and discussion of the respective references. The QUADAS-2 scores for all included studies were tabulated and a summary report was constructed.

Data extraction

The ^{99m}Tc-tilmanocept performance for SN mapping in breast cancer, melanoma, and head and neck cancer was evaluated by conducting separate meta-analyses per tumor type. For each study, appropriate data were extracted for both ^{99m}Tc-tilmanocept and the reference standard technique, including the number of patients, preoperative detection rate (DR), intraoperative DR, and the proportion of patients with LN metastasis at histopathology after dissection and/or follow-up (pN+) that were correctly staged by SN biopsy with ^{99m}Tc-tilmanocept (pN+ sensitivity or SN+/pN+ ratio). The preoperative and intraoperative DRs were defined as the percentage of patients in whom at least one SN was detected at lymphoscintigraphy or during surgery, respectively. In case relevant data were missing

from studies to obtain these parameters, the corresponding authors were contacted through email.

According to data availability (Tables 1, 2, and 3), the estimated performance outcomes varied among the three main tumor types. For breast cancer, the ^{99m}Tc-tilmanocept pooled per-patient preoperative DR was estimated, as well as the per-patient and per-lesion (in case of bilateral disease) intraoperative DRs. Moreover, the per-patient intraoperative ^{99m}Tc-sulfur colloid DR was also estimated by pooling studies that used ^{99m}Tc-sulfur colloid as reference standard. For melanoma and head and neck cancer patients, the pooled preoperative and intraoperative ^{99m}Tc-tilmanocept DRs were estimated, while insufficient data were available regarding reference standard techniques. Finally, the pooled proportion of pN + patients that were correctly staged by ^{99m}Tc-tilmanocept SN biopsy (SN + /pN + ratio) was estimated for melanoma, whereas no sufficient data were available for breast cancer and head and neck cancer.

Statistical analysis

Meta-analysis was performed using Stata/MP, version 14.2 (StataCorp LP, College Station, TX) [9]. The metaprop command in Stata/MP and random-effects modeling were used to estimate the pooled pre-/intraoperative DRs and/or the pooled pN + sensitivity (i.e., SN + /pN + patients ratio) with corresponding 95% confidence intervals (CIs). Pooled results are presented in forest plots. Heterogeneity between studies was assessed by visual inspection of the forest plots and estimated using the inconsistency index I^2.

Results

Literature search

The systematic literature search yielded a total of 174 articles. After removal of duplicates, screening of titles and abstracts resulted in 24 potentially eligible studies. After full-text retrieval and evaluation, no further studies were excluded. No additional studies were identified at cross-reference checking. As such, 24 articles were included (Fig. 1) [6, 10–32].

Quality assessment

The results of the QUADAS-2 assessment are shown in Supplemental Tables 1-3 (Online Resources 2–4). Studies mainly showed a low risk of bias and few concerns regarding applicability in the first two key domains (i.e., patient selection and index test). In contrast, some studies did not include ^{99m}Tc-sulfur colloid or ^{99m}Tc-nanocolloidal albumin and/or blue dye as reference standard in their design and were therefore judged as having a high risk of bias and/or applicability concerns in the last two key domains (i.e., reference standard, flow and timing) (see Supplemental Tables 1-3). Taking this risk of bias into account, these studies were included in the meta-analysis exclusively for the estimation of pooled endpoints regarding ^{99m}Tc-tilmanocept alone (pre-/intraoperative detection rates, pN + sensitivity), while their data could not be used for a pooled comparative analysis due to the absence of a reference standard. Considering all the above, the included studies were deemed of sufficient methodologic quality to be included in the systematic review and meta-analysis.

Study characteristics

The main characteristics of the included studies are summarized in Tables 1, 2, and 3. Fourteen studies had a prospective study design [6, 10–16, 18, 19, 21, 25, 31, 32], nine were retrospective [17, 20, 22–24, 26–28, 30], and one was both prospective and retrospective [29]. Most studies used both ^{99m}Tc-tilmanocept and blue dye for the SN biopsy procedure. Of the 12 studies that also compared ^{99m}Tc-tilmanocept performance with a reference standard mapping technique, ten used ^{9m}Tc-sulfur colloid [6, 10–12, 17, 21, 23, 24, 30, 32] while only two used ^{99m}Tc-nanocolloidal albumin [25, 29].

Twenty-one of 24 studies provided data on the pre-/intraoperative DR and/or the pN + sensitivity (SN + /pN + patients ratio) and were included in the meta-analysis [6, 10–18, 20–24, 26–29, 31, 32].

Breast cancer

Fourteen studies investigated the use of ^{99m}Tc-tilmanocept to identify SNs in breast cancer (Table 1) [6, 11–13, 15, 17, 19–22, 24, 26, 28, 32]. In five studies ($n = 111$ patients), the preoperative DR at a patient level varied between 76 and 100% [13, 20, 21, 24, 28]. In 11 studies ($n = 1000$ patients), the intraoperative DR [6, 11–13, 15, 17, 20–22, 28, 32] was consistently ≥ 99% with a single exception of a 94% DR reported by Leong et al. [13].

At the lesion level, the preoperative DR (two studies) [26, 28] and the intraoperative DR (five studies) [6, 15, 24, 26, 28] were higher than 93% and 97%, respectively. Eight studies (446 patients) compared ^{99m}Tc-tilmanocept SN biopsy performance with ^{99m}Tc-sulfur colloid [6, 11, 12, 17, 19, 21, 24, 32]. Both radiopharmaceuticals showed comparable intraoperative DR, close to 100% in most cases.

In more detail, Rietbergen et al. reported a preoperative and intraoperative SN DR of 100% in 13 patients ($n = 14$ tumors) [28]. At delayed images (2 h), the number of SNs was concordant with early images (15 min), but the injection site/SN ratio was 72% lower. Uptake in non-SNs was found in 7 of 15 (47%) basins, with an average SN/non-SN

Table 1 Characteristics of the included studies on breast cancer

Author	Study design	Patients (lesions)	Patients group 1 (lesions)	Patients group 2 (lesions)	Mapping method group1	Mapping method group2	SN DR of patients in group 1			SN DR of patients in group 2		
							LS (lesions)	Intraoperatively (lesions)	SN + /pN +	LS (lesions)	Intraoperatively (lesions)	SN + /pN +
Ferez-Pinzon et al. [32]	P	86	48	38	TcTM + blue dye	TcSc + blue dye	-	48/48	-	-	38/38	-
Rietbergen et al. [28]	R	13 (14)	13 (14)	-	TcTM	-	13/13 (14/14)	13/13 (14/14)	-	-	-	-
Vidal-Sicart et al. [26]	R	344 (352)	344 (352)	-	TcTM	-	(327/352)[a]	(342/352)[b]	- [c]	-	-	-
Murphy et al. [24]	R	76 (86)	47 (57)	29 (29)	TcTM ± blue dye	TcSc ± blue dye	46/47	(TcTM: 39/39); Blue: 22/30	-	29/29 (29/29)	TcSc: 28/28 (28/28); Blue 15/27	-
Unkart et al. [22]	R	617	617	-	TcTM + blue dye	-	-	TcTM: 609/617 Blue: 550/617	95/-	-	-	-
Unkart et al. [21] [19]	P	52	25	27	TcTM + blue dye	Tc Sc + blue dye	23/25	25/25	1/-	26/27	27/27	2/-
Unkart and Wallace et al. [20]	R	19	19	-	TcTM	-	13/17	19/19	3/-	-	-	-
Baker et al. [17]	R	199	84	115	TcTM + blue dye	TcSc + blue dye	-	84/84	20/-	-	115/115	20/-
Wallace et al. [15]	P	148 (326)	148	-	TcTM + blue dye	-	-	TcTM: 146/148 (320/326); Blue 131/148 (209/326)	27/-[d]	-	-	-
Leong et al. [13]	P	31	31	-	TcTM ± blue dye	-	7/9 [e]	29/31	8/9	-	-	-
Wallace et al. [12]	P	11	5	6	TcTM + blue dye	TcSc + blue dye	-	TcTM: 4/4; Blue 4/4	1/-	-	TcSc: 3/5; Blue 4/5	2/-
Wallace et al. [11]	P	10	5	5	TcTM + blue dye	TcSc + blue dye	-	TcTM:5/5; Blue 5/5	2/-	-	TcSc: 4/5; Blue 5/5	1/-
Wallace et al. [6]	P	12 (13)	6 (6)	6 (7)	TcTM + blue dye	TcSc + blue dye	-	TcTM: 6/6 (6/6); Blue: 6/6 (6/6)	1/-	-	TcSc: 5/6 (6/7); Blue: (6/7)	1/-

SN sentinel node, *LS* lymphoscintigraphy, *P* prospective, *R* retrospective, *TcTM* ^{99m}Tc-tilmanocept, *TcSc* ^{99m}Tc-sulfur colloid

[a]Higher preoperative DR in case of BMI < 25 kg/m^2 and superficial injection (intradermal/periareolar instead of peritumoral/intratumoral)

[b]12 lesions with also ^{99m}Tc-nanocolloid

[c]80 out 81 metastatic lymph nodes identified with ^{99m}Tc-tilmanocept

[d]33 metastatic lymph nodes, of which 31/33 radioactive and 25/33 blue

[e]Only 9 of 31 patients underwent lymphoscintigraphy

Table 2 Characteristics of the included studies on melanoma

Author	Study design	Patients (lesions)	Patients group 1 (lesions)	Patients group 2 (lesions)	Mapping method group 1	Mapping method group 2	SN DR of patients in group 1			SN DR of patients in group 2		
							LS	Intraoperatively (lesions)	SN+/pN+	LS	Intraoperatively (lesions)	SN+/pN+
Mwagiru et al. [31]	P	26	26	-	TcTM + blue dye	-	26/26	26/26	-	-	-	-
Eckhoff et al. [30]	R	391	133	258	TcTM ± blue dye	TcSc ± blue dye	130/133	-	8/12[a]	255/258	-	45/57 [a]
Rietbergen et al. [28]	R	15	15	-	TcTM	-	15/15	15/15	-	-	-	-
Silvestri et al. [23]	R	370	185	185	TcTM + blue dye	TcSc + blue dye	179/185	185/185	23/25	181/185	185/185	28/31
Sondak et al. [14]	P	154	154	-	TcTM + blue dye	-	-	TcTM 150/154 Blue 138/154	TcTM 34/34 Blue 30/34	-	-	-
Leong et al. [13]	P	47	47	-	TcTM ± blue dye[b]	-	45/46[c]	46/47	11/12	-	-	-
Wallace et al. [10]	P	24 (30)	18 (22)	6 (8)	TcTM + blue dye	TcSc + blue dye	-	18/18 (22/22)	-	-	6/6 (8/8)	-

SN sentinel node, *LS* lymphoscintigraphy, *P* prospective, *R* retrospective, *TcTM* ^{99m}Tc-tilmanocept, *TcSc* ^{99m}Tc-sulfur colloid

[a]Data based on a 1-year follow-up

[b]Blue used only in 34/47 patients

[c]Lymphoscintigraphy performed in 46/47 patients

Table 3 Characteristics of the included studies on head and neck cancer

Author	Study design	Patients	Tumor location	Mapping method	TcTM SN DR per patient		
					Lymphoscintigraphy	Intraoperatively	SN + /pN +
Mwagiru et al. [31]	P	9	Oral cavity	TcTM	9/9	9/9	-
Doll et al. [27]	R	13	Oral cavity	TcTM	13/13	13/13	-
Mahieu et al. [29]	P + R	P cohort: 20 R cohort: 10	Oral cavity	Prospective cohort: TcTM + ^{99m}Tc-nanocolloid [a] Retrospective cohort: TcTM	TcTM: 29/30 ^{99m}Tc-nanocolloid: 20/20	TcTM: 19/19 ^{99m}Tc-nanocolloid: 10/10	TcTM: 6/- [b] ^{99m}Tc-nanocolloid: 3/-
den Toom et al. [25]	P [c]	20	Oral cavity	TcTM + ^{99m}Tc-nanocolloid [a]	TcTM: 20/20 ^{99m}Tc-nanocolloid: 20/20	TcTM: 10/10 ^{99m}Tc-nanocolloid: 10/10	7/-
Agrawal et al. [18]	P	83	Oral cavity: 78 Cutaneous: 5	TcTM	-	81/83	38/39
Marcinow et al. [16]	P	20	Oral cavity	TcTM	19/20 [d], SPECT/CT: 20/20	20/20	12/12

SN sentinel node, *P* prospective, *R* retrospective, *TcTM* ^{99m}Tc-tilmanocept

[a]Intra-patient comparison

[b]Four SN + patients in the prospective cohort and two in the retrospective cohort; one false negative patient at follow-up (median 22.6 months, range 13–32)

[c]Same prospective cohort of Mahieu et al. [29]

[d]One patient had an acquisition error

ratio of 6.6 (range: 2.3–15.6). A multicenter study conducted by Vidal-Sicart et al. in 344 patients ($n = 352$ lesions) reported per-lesion preoperative and intraoperative SN DRs for ^{99m}Tc-tilmanocept of 92.9% and 97.2%, respectively. Moreover, 80 of 81 metastatic SNs were detected, with no axillary recurrences during follow-up (mean 19 months, range 16–25) [26]. In previous studies by Unkart and Wallace et al., the preoperative and intraoperative DRs were 76.5% and 100%, respectively [20], with a comparable mean number of removed SNs between the 1-day and the 2-day injection protocols (3.0 ± 1.9 vs 2.7 ± 1.4, respectively) [22]. Similar results were also reported by Leong et al., who also described a relative difference between the 1-day and the 2-day protocol (92.6% vs 83.3%) possibly attributed to the small sample size of the 2-day group [13].

Regarding the comparison between ^{99m}Tc-tilmanocept and ^{99m}Tc-sulfur colloid, Ferez-Pinzon et al. reported no significant differences in the number of harvested SNs (2.0 vs 1.8, respectively) and in the time to transcutaneous localization (3.3 ± 2.0 vs 3.9 ± 2.3 min) in 86 patients [32]. Similarly, Murphy et al. found no statistical difference in harvested SNs, number of identified pN + patients, or pain scores after intradermal injection [24] in a cohort of 76 patients. Previously, Unkart et al. reported the first randomized, double-blinded trial, showing a comparable preoperative DR (23/25 vs 26/27 patients) and number of harvested SNs (54 vs 61) [21], but reduced injection pain for ^{99m}Tc-tilmanocept [19]. On the contrary, in the cohort of 199 patients by Baker et al., ^{99m}Tc-tilmanocept led to fewer removed SNs per patient (mean 1.85 ± 0.78 vs 3.24 ± 1.62, $p < 0.001$), while also showing a higher sensitivity for nodal metastasis [17] and an equal intraoperative SN DR (100%). A previous study by Wallace et al., using a 2-day SN mapping protocol, found ^{99m}Tc-tilmanocept to have a significantly faster injection site clearance rate than ^{99m}Tc-sulfur colloid (mean clearance half-time: 2.18 ± 1.09 h vs 57.4 ± 92.8 h, $p < 0.001$), but an equivalent mean SN uptake and intraoperative DR (4/4 vs 3/5 patients, respectively) [12]. Similar results have been reported in two previous studies by Wallace et al. in 12 and 10 patients, respectively, using a 1-day protocol [6, 11]. Finally, Wallace et al. also compared ^{99m}Tc-tilmanocept to vital blue dye, showing the higher intraoperative DR (98.6% vs 88.5%, $p < 0.0001$) and greater metastatic nodal sensitivity (31/33 vs 25/33 LNs, $p = 0.03$) of the former [15].

Melanoma

Seven studies investigated the use of ^{99m}Tc-tilmanocept in melanoma patients (Table 2) [10, 13, 14, 23, 28, 30, 31]. The preoperative and intraoperative DRs ranged from 97

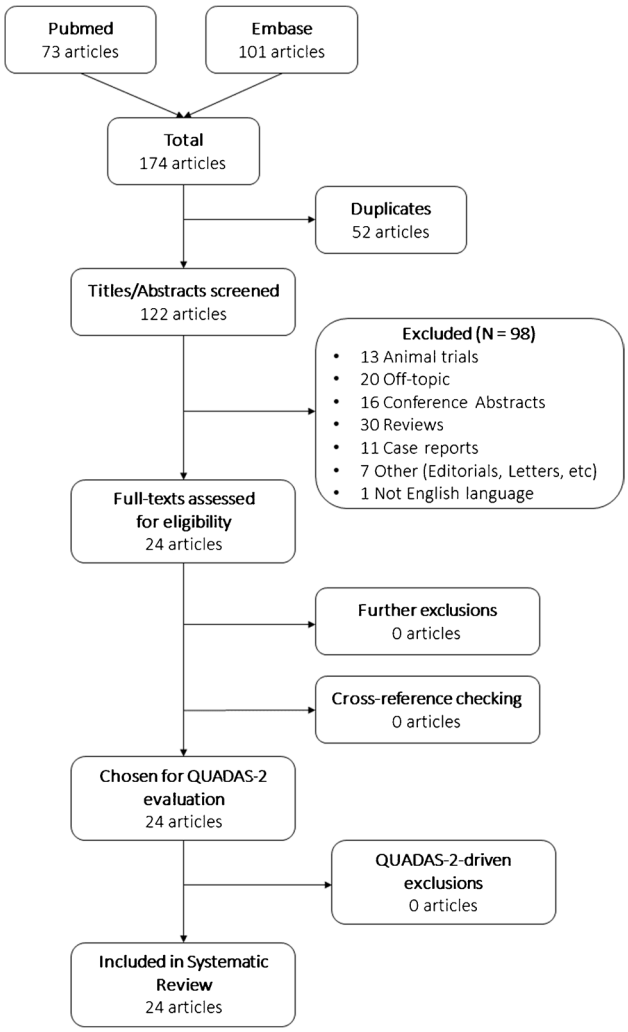

Fig. 1 Flow chart showing the search strategy

to 100%. Three studies compared ^{99m}Tc-tilmanocept with ^{99m}Tc-sulfur colloid, with preoperative and intraoperative DRs ranging between 96 and 100% for both radiotracers [10, 23, 30].

More in depth, both Rietbergen et al. and Mwagiru et al. reported a ^{99m}Tc-tilmanocept preoperative and intraoperative SN DR of 100% in 26 and 15 patients, respectively [28, 31]. Rietbergen et al. also found non-SN uptake in 11 of 20 (55%) basins, with a mean SN/non-SN ratio of 6.7 (range 3.0–15.4). Moreover, at delayed images (2 h) the injection site/SN ratio per-LN basin was 61% lower compared to early images (15 min). Comparable results were also reported by Leong et al., with a 98% preoperative and intraoperative DR, a pN + sensitivity of 91.7%, no relevant adverse events, and no significant difference between the same-day and next-day surgery protocols [13].

Regarding the comparison between ^{99m}Tc-tilmanocept and ^{99m}Tc-sulfur colloid, Eckhoff et al. ($n = 391$ patients) found significantly shorter lymphoscintigraphy mapping times for ^{99m}Tc-tilmanocept (51.8 vs 195.1 min, $p < 0.01$), but no significant differences in terms of SNs identified at lymphoscintigraphy (3.56 vs 3.28), removed SNs (3.05 vs 3.1), percentage of metastatic patients (11.3% vs 17.4%), and false negative rates (25% vs 22%) at a median follow-up of 6 months and 25 months for ^{99m}Tc-tilmanocept and ^{99m}Tc-sulfur colloid, respectively [30]. In a previous study by Silvestri et al. ($n = 370$ patients), ^{99m}Tc-tilmanocept and ^{99m}Tc-sulfur colloid showed preoperative DRs greater than 96%, intraoperative DRs of 100%, and no significant differences in sensitivity for nodal metastasis (23/25 vs 28/31 patients) and false negative cases (1.0% vs 1.6%) at a median follow-up of 5.4 months and 25.2 months, respectively [23]. However, ^{99m}Tc-tilmanocept led to lower radiation doses (503 vs 580 μCi, $p < 0.0001$), shorter mapping times (31 vs 34 min, $p = 0.008$), and fewer excised SNs (2.5 vs 2.9, $p = 0.04$) compared to ^{99m}Tc-sulfur colloids. Similarly, in a phase I clinical trial by Wallace et al. ($n = 24$ patients), ^{99m}Tc-tilmanocept exhibited a significantly faster injection site clearance rate at all dose levels (1.0, 5.0, or 10.0 nmol) (mean clearance half-time: 2.17 ± 0.96 h vs 14.7 ± 6.3 h, $p < 0.001$) and a comparable mean SN uptake (0.73% ± 0.94% vs 0.85% ± 1.19%), but a lower number of SNs visualized per basin (1.6 vs 1.9) than ^{99m}Tc-sulfur colloids [10]. Both tracers showed an intraoperative DR of 100%, with lower radiation absorbed doses for ^{99m}Tc-tilmanocept and no relevant adverse events. Finally, a study by Sondak et al. compared ^{99m}Tc-tilmanocept to blue dye showing higher intraoperative DR (97% vs 90%, $p = 0.002$), per-LN concordance (98.7% vs 63.7%, $p < 0.001$), per-patient concordance (97.8% vs 50.7%, $p < 0.001$), and number of identified metastatic SNs (45/45 vs 36/45, $p = 0.004$) [14].

Head and neck cancer

Six studies investigated the use of ^{99m}Tc-tilmanocept in patients with head and neck cancer (Table 3) [16, 18, 25, 27, 29, 31]. Besides the 97% preoperative DR reported by Mahieu et al. [29], four studies reported a DR of 100% [16, 25, 27, 29, 31]. Similarly, the intraoperative DR was 100% in five studies [16, 25, 27, 29, 31], with a slightly lower value of 98% reported by Agrawal et al. [18]. Only two studies compared ^{99m}Tc-tilmanocept to ^{99m}Tc-nanocolloid, showing a similar performance for both tracers [25, 29].

In more detail, a prospective cross-sectional study by Mwagiru et al. in oral squamous cell carcinoma (OSCC) patients ($n = 9$) reported a preoperative and intraoperative DR of 100% [31]. Equal DRs were also described by Doll et al. in floor of mouth ($n = 6$), tongue ($n = 5$), and upper alveolar crest/hard palate ($n = 2$) tumors [27], with no recurrences in SN-negative patients during follow-up (mean 20.3 months, range 10–28). Similar results were obtained

by Agrawal et al. in intraoral ($n=78$) and cutaneous ($n=5$) squamous cell carcinoma undergoing elective neck dissection [18]. ^{99m}Tc-tilmanocept showed an intraoperative DR of 97.6%, a false negative rate of 2.56%, a negative predictive value of 97.8%, and an overall accuracy of 98.8%, with no significant differences related to the injection timing (1-day vs 2-day protocol). Notably, in the subcohort of patients with floor of mouth tumors ($n=20$), ^{99m}Tc-tilmanocept DR and staging accuracy were both 100% (12/12 pN + patients identified), despite the higher risk of shine-through phenomenon and false negative results of this location. Comparable findings were reported by Marcinow et al. in 20 patients with oral cavity squamous cell carcinoma undergoing elective neck dissection [16]. All 12 pN + patients were correctly staged by ^{99m}Tc-tilmanocept, resulting in a false negative rate of 0% and a negative predictive value of 100%. Finally, the SPECT/CT images allowed to identify additional SNs in 11 of 20 (55%) cases, despite not reaching statistical significance compared to planar scintigraphy.

Regarding the comparison between ^{99m}Tc-tilmanocept and ^{99m}Tc-nanocolloid, den Toom et al. [25] described a faster injection site clearance rate for ^{99m}Tc-tilmanocept in 20 OSCC patients (remaining activity 29.9% vs 60.9%, $p<0.001$) despite a lower SN uptake (1.95% vs 3.16%, $p=0.01$), thus resulting in no significant difference in SN/injection site ratio (0.066 vs 0.054) and median number of detected SNs (3.0 vs 2.5) and higher echelon nodes (2.0 vs 2.5, respectively). The prospective cohort of den Toom et al. [25] was later combined by Mahieu et al. with a retrospective cohort ($n=10$ patients investigated only with ^{99m}Tc-tilmanocept), showing a ^{99m}Tc-tilmanocept sensitivity of 83.3% and a negative predictive value of 93.3% (average follow-up: 22.6 months), but a staging accuracy comparable to ^{99m}Tc-nanocolloid [29].

Meta-analysis

The estimated pooled per-patient preoperative and intraoperative DRs of ^{99m}Tc-tilmanocept were 0.94 (95%CI, 0.88–1.01) and 0.99 (0.98–1.00) for breast cancer (Figs. 2 and 3), 0.98 (0.96–0.99) and 1.00 (0.99–1.00) for melanoma (Figs. 4 and 5), and 0.97 (0.93–1.02) and 0.99 (0.96–1.01) for head and neck carcinoma (Figs. 6 and 7). In breast cancer, the per-lesion pooled intraoperative DR of ^{99m}Tc-tilmanocept was 0.98 (0.97–0.99) (Fig. 8), while the per-patient intraoperative DR of ^{99m}Tc-sulfur colloid was 1.00 (95% CI 0.98–1.02) (Fig. 9). Finally, the staging accuracy of ^{99m}Tc-tilmanocept SN biopsy in melanoma patients was also estimated by means of the pooled pN + sensitivity (i.e., SN + /pN + patients ratio), which was 0.97 (95% CI, 0.92–1.03) (Fig. 10).

Discussion

Although multiple radiopharmaceuticals are available for SN mapping, there is currently a particular interest in ^{99m}Tc-tilmanocept due to its favorable characteristics, including a low molecular weight and a specific binding capability for the mannose receptors (CD 206) located on the surface of lymphatic reticuloendothelial cells. Today, ^{99m}Tc-tilmanocept is approved by the FDA and EMA for the use in breast cancer, melanoma, and head and neck cancer [33, 34]. On the basis of the published evidence and

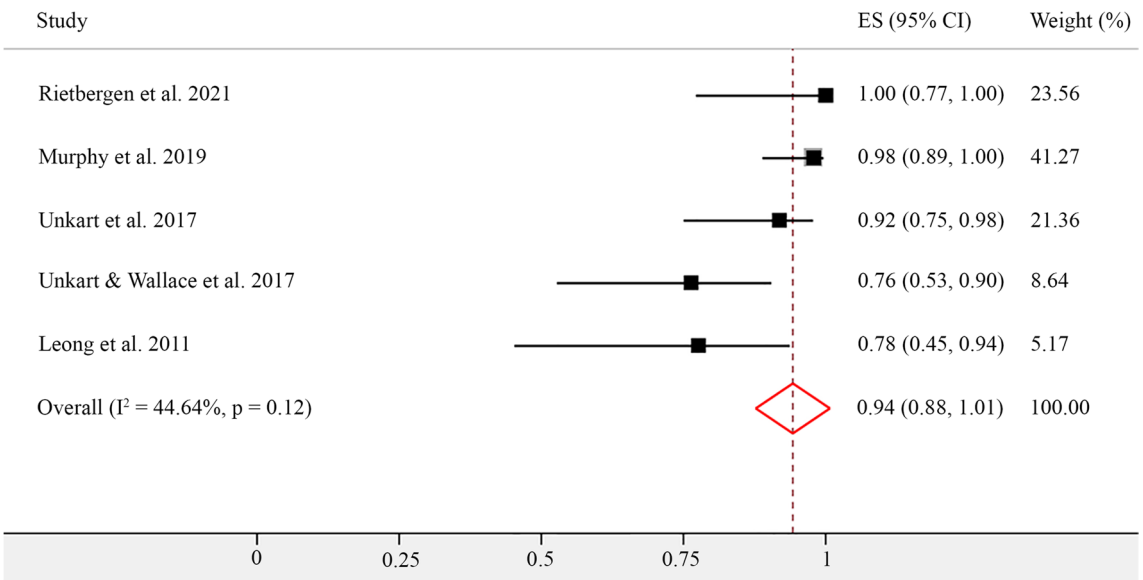

Fig. 2 Breast cancer—^{99m}Tc-tilmanocept preoperative sentinel node detection rate (per patient)

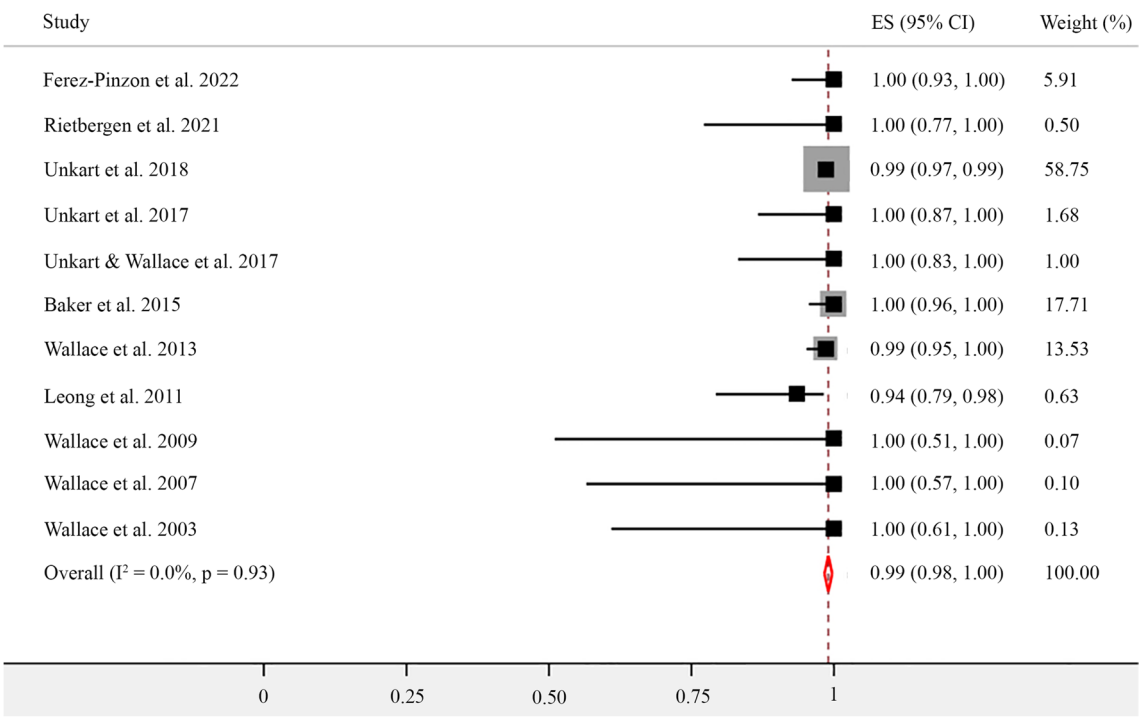

Fig. 3 Breast cancer—^{99m}Tc-tilmanocept intraoperative sentinel node detection rate (per patient)

a consensus of European experts, an updated overview on ^{99m}Tc-tilmanocept performance for SN mapping in breast cancer, melanoma, and head and neck cancer is provided.

In breast cancer and melanoma, ^{99m}Tc-tilmanocept and ^{99m}Tc-sulfur colloid have shown comparable pre- and/or intraoperative DRs [6, 10–12, 17, 19, 21, 23, 24, 30, 32]. There are, however, clinically relevant differences to consider.

First, in a study by Baker et al. on breast cancer, ^{99m}Tc-tilmanocept allowed to remove fewer SNs per patient (mean 1.85 vs 3.24) while still detecting a higher proportion of metastatic SNs among pN + patients than

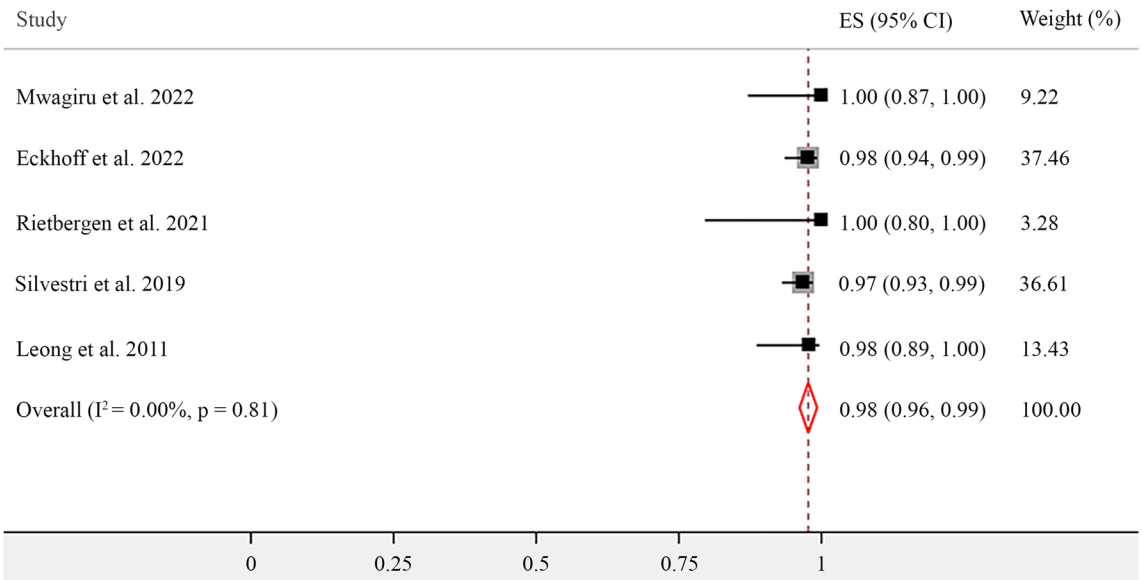

Fig. 4 Melanoma—^{99m}Tc-tilmanocept preoperative sentinel node detection rate

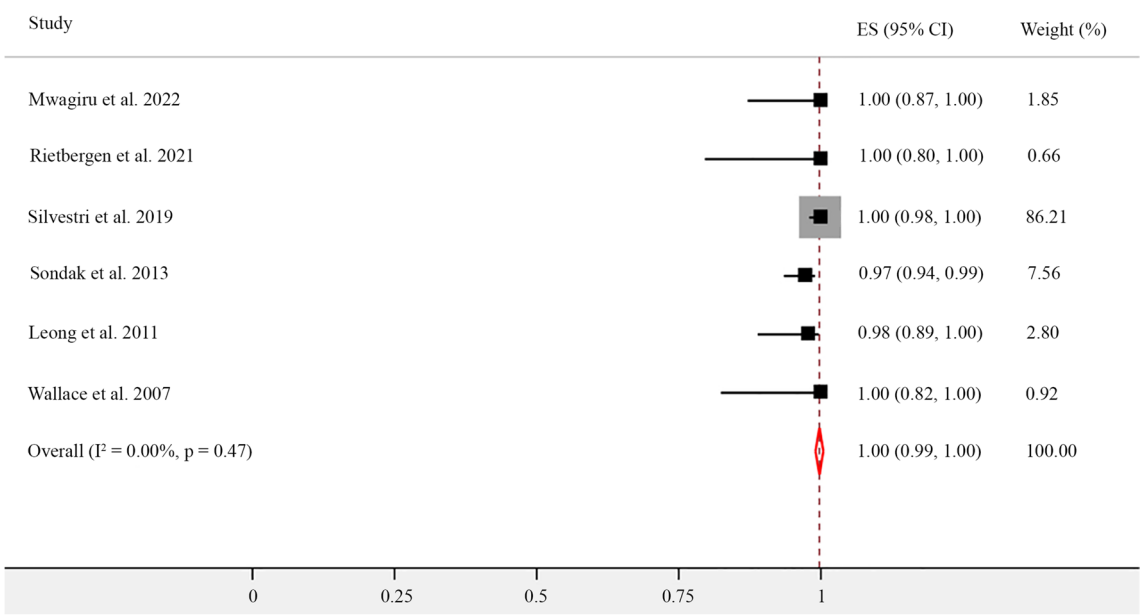

Fig. 5 Melanoma—^{99m}Tc-tilmanocept intraoperative sentinel node detection rate

^{99m}Tc-sulfur colloid [17]. This could possibly lead to a clinical benefit through the combination of improved oncological outcomes and potentially lower morbidity rates. Similar results were obtained in melanoma patients by Wallace et al. [10] and Silvestri et al. [23], who reported a lower number of SNs visualized at lymphoscintigraphy and fewer excised SNs during surgery, with comparable clinical outcomes. However, some of the later studies in breast cancer and melanoma were not able to confirm these results [21, 24, 30].

One possible reason behind the removal of fewer SNs is ^{99m}Tc-tilmanocept specificity for CD206 receptors, which allows a prolonged binding of the tracer to the first LN, thus limiting its migration to distal LNs. Furthermore, the potential benefits of removing fewer SNs include not only a decreased patient morbidity, but also a reduction in the operative time and the pathology costs of the procedure.

Multiple studies in breast cancer and melanoma also reported a faster injection site clearance rate for ^{99m}Tc-tilmanocept compared to ^{99m}Tc-sulfur colloid [6, 10–12]. The

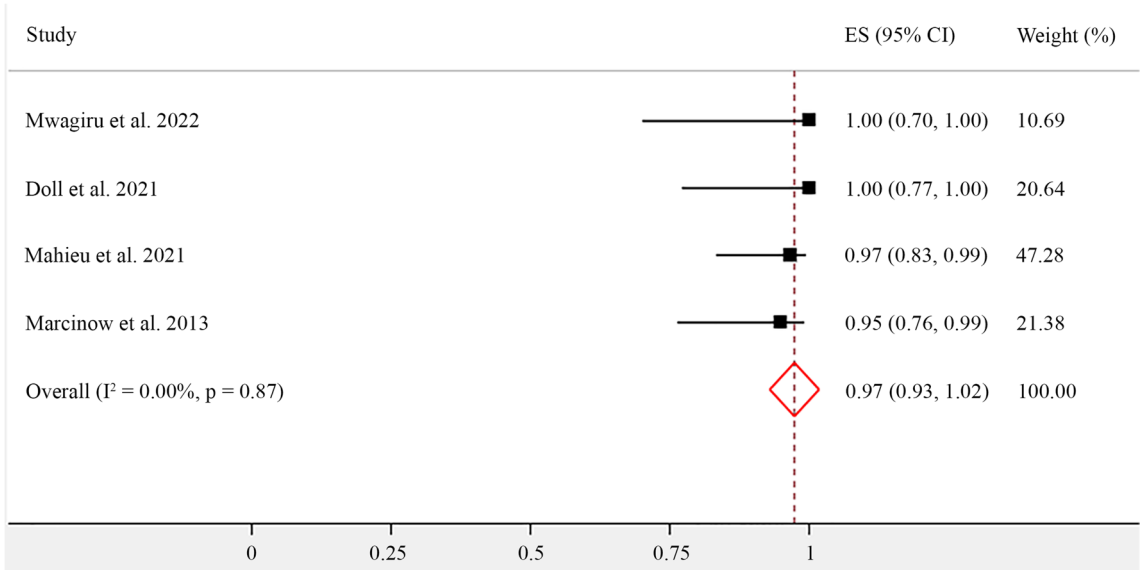

Fig. 6 Head and neck cancer—^{99m}Tc-tilmanocept preoperative sentinel node detection rate

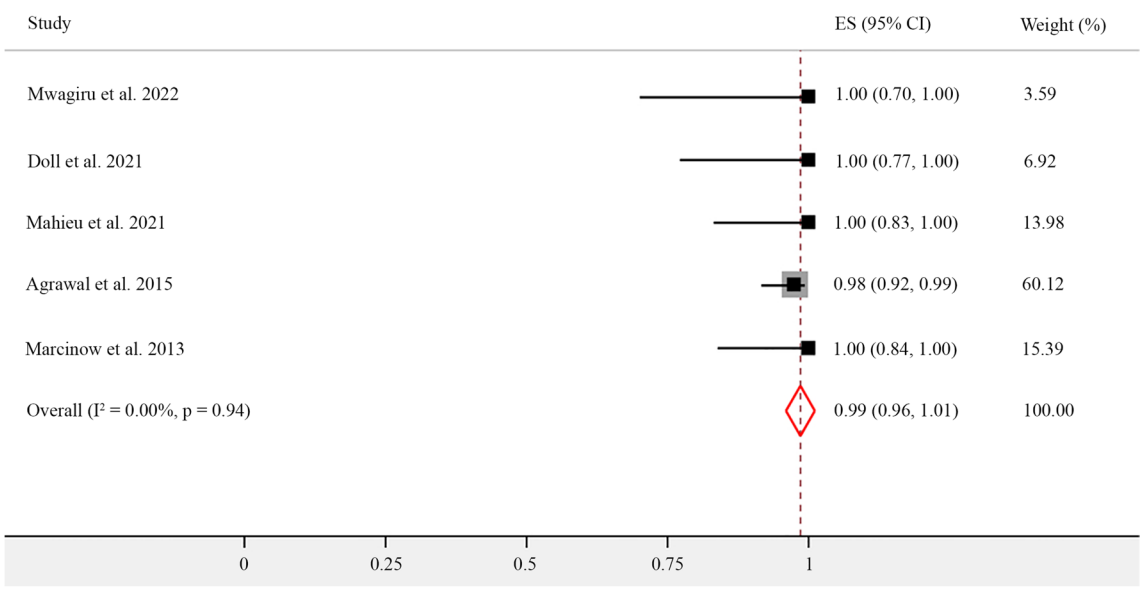

Fig. 7 Head and neck cancer—^{99m}Tc-tilmanocept intraoperative sentinel node detection rate

faster clearance of ^{99m}Tc-tilmanocept from the injection site may be explained by its smaller molecular size (diameter of 7 nm) compared to ^{99m}Tc-sulfur colloid (between 100 and 200 nm). This may benefit the preoperative SN visualization, particularly when the primary tumor (the injection site) is close to the SN(s); moreover, we strongly advise the use of ^{99m}Tc-tilmanocept in conjunction with single photon emission computed tomography/computed tomography (SPECT/CT) [35, 36].

Another potential advantage of ^{99m}Tc-tilmanocept over ^{99m}Tc-sulfur colloid could be the reduction of the injection site pain. However, currently available evidence is limited and discordant: while Murphy et al. [24] reported comparable pain scores between tracers, Unkart et al. [21] found ^{99m}Tc-sulfur colloid to be correlated with significantly more pain during the first 3 min post-injection.

A possible explanation of the reduced pain associated with ^{99m}Tc-tilmanocept injection could be the small particle size that allows for a fast clearance from the injection site and a reduced stretch on the nociceptive pain receptors in the dermis, as suggested by Unkart et al. [19]. Although a correlation between the post-injection site pain and the pH

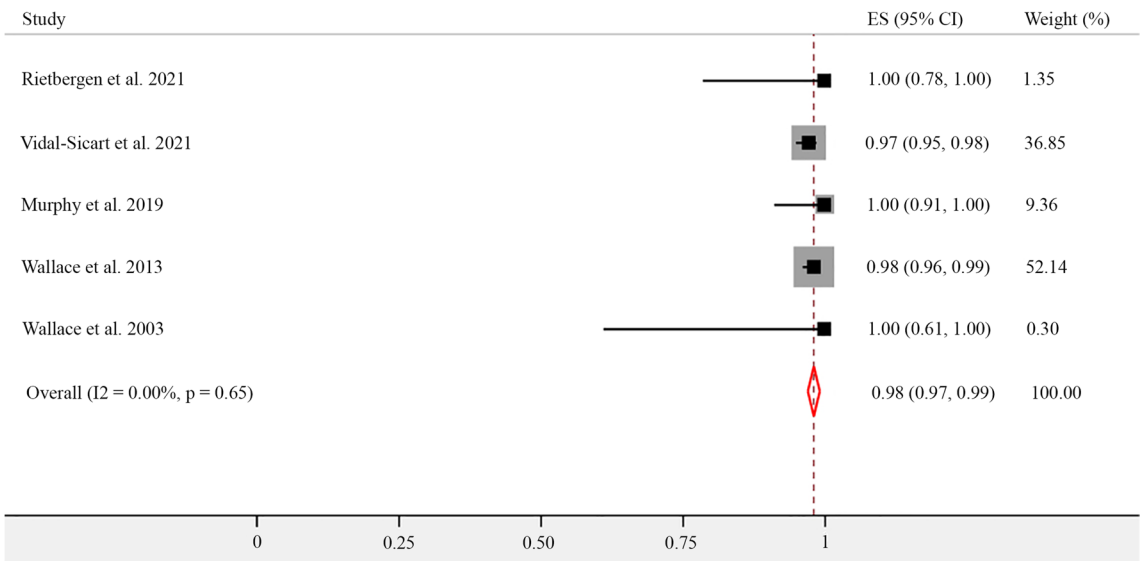

Fig. 8 Breast cancer—^{99m}Tc-tilmanocept intraoperative sentinel node detection rate (per lesion)

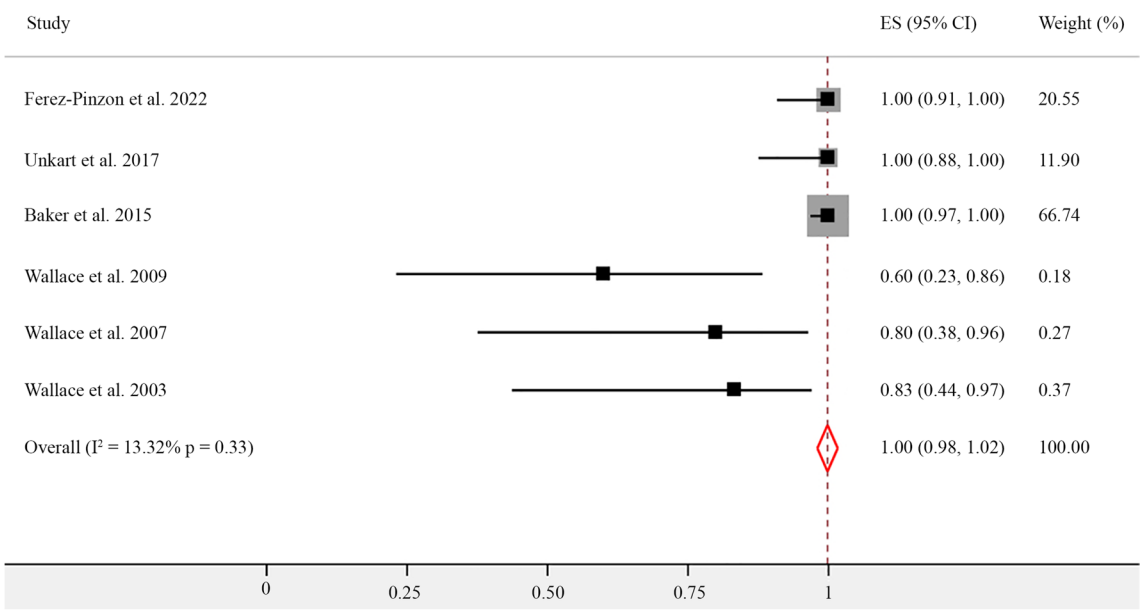

Fig. 9 Breast cancer—^{99m}Tc-sulfur colloid intraoperative sentinel node detection rate (per patient)

of the preparations could also represent a viable hypothesis, the study by Unkart et al. [19] found the pH values to be comparable between ^{99m}Tc-tilmanocept and filtered ^{99m}Tc-sulfur colloid. Moreover, a randomized double-blinded trial by Stojadinovic et al. reported that changing the pH of the ^{99m}Tc-sulfur colloid preparation by adding sodium bicarbonate did not significantly alter the post-injection pain scores [37].

Finally, the comparative performance of ^{99m}Tc-tilmanocept and ^{99m}Tc-sulfur colloid did not appear to be significantly affected by the injection-to-surgery time (1-day vs 2-day protocol) in both breast cancer [6, 11, 12] and melanoma [13]. This feature allows for greater flexibility in patient scheduling. In our opinion, the 2-day protocol is more suitable for centers with a high patient throughput as it allows surgeons to start the surgical procedures earlier in the morning.

Similarly to breast cancer and melanoma, ^{99m}Tc-tilmanocept showed a preoperative and intraoperative DR comparable to other radiocolloids (i.e., ^{99m}Tc-nanocolloidal albumin) in head and neck cancer [25, 29], as well as a significantly faster injection site clearance rate that

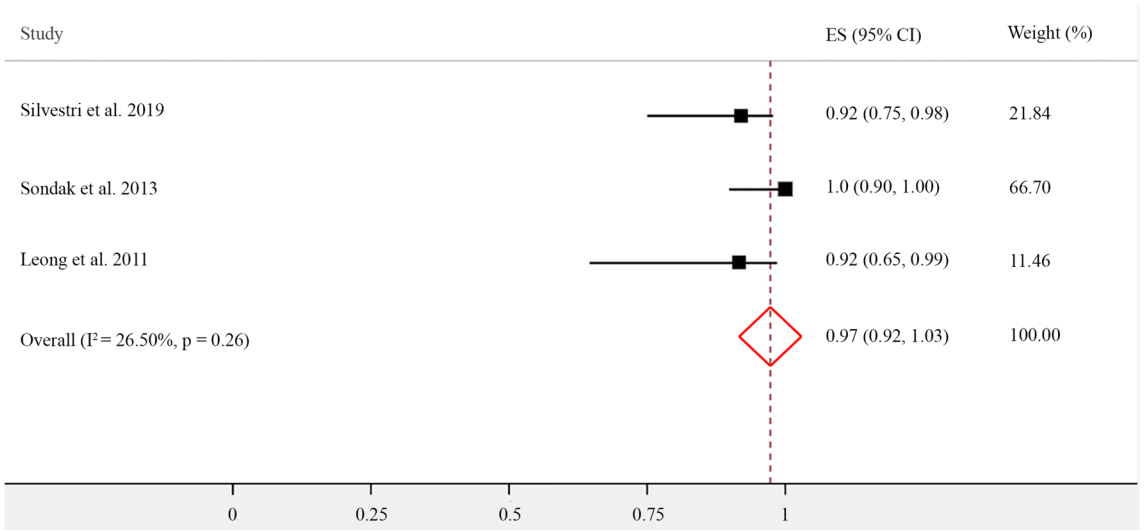

Fig. 10 Melanoma—sensitivity of ^{99m}Tc-tilmanocept sentinel node (SN) biopsy for pathology-positive (pN+) patients (SN+/ pN+patients ratio)

could be particularly useful in floor of mouth tumors [25]. However, considerations regarding the benefits of one tracer over the other are less well described for head and neck cancer. In addition, currently there are no studies that compare ^{99m}Tc-tilmanocept with a hybrid tracer such as indocyanine (ICG)-^{99m}Tc-nanocolloid. Indeed, ICG-^{99m}Tc-nanocolloid combines radioactive and fluorescent guidance in a single injection, allowing both a preoperative lymphatic mapping and a better intraoperative visualization of SNs compared to blue dye [38–40]. These favorable characteristics of ICG-^{99m}Tc-nanocolloid could be especially advantageous in localizing SNs in case of a more complex drainage pattern and/or surgical anatomy such as in head and neck cancer. Despite the promising performance of ^{99m}Tc-tilmanocept compared to other tracers, currently the cost of this new radiotracer is significantly higher than that of ^{99m}Tc-nanocolloidal albumin or ^{99m}Tc-sulfur colloid, and proper cost-effectiveness analyses are still needed.

When assessing the performance of ^{99m}Tc-tilmanocept for SN biopsy, it is also critical to consider the pathological staging accuracy in terms of sensitivity for nodal metastasis, false negative rate, and negative predictive value. In breast cancer, the reported pN + sensitivity ranged between 89 and 99% in two studies, although the estimations were based on either a limited sample size or a short follow-up [13, 26]. In melanoma, the staging accuracy was consistently higher than 90% [13, 14, 23]. In head and neck cancer, the negative predictive value ranged between 93 and 100% [16, 18, 27, 29].

The reported variation of false negative rates in head and neck cancer (range 0–16.7%) is possibly due to the use of a different reference standard (elective neck dissection vs follow-up) [16, 18, 29]. Indeed, as pointed by Mahieu et al., neck dissection specimens can still harbor undetected micro-metastases in 15% of cases, and a composite reference standard (including also long-term follow-up) can improve the estimation accuracy by identifying more false negative cases [29].

Regarding the comparison of ^{99m}Tc-tilmanocept staging performance with other tracers, no significant differences (in terms of pN + sensitivity or false negative rate) were reported between ^{99m}Tc-tilmanocept and ^{99m}Tc-sulfur colloid in two melanoma studies; however, the shorter follow-up of the ^{99m}Tc-tilmanocept cohorts could have affected the false negative rate estimation accuracy [23, 30]. ^{99m}Tc-Tilmanocept was also compared with blue dye in another study on melanoma, showing a superior staging performance of the former [14]. Finally, one study on head and neck cancer compared ^{99m}Tc-tilmanocept with ^{99m}Tc-nanocolloidal albumin, showing a comparable staging accuracy [29]. Since the evidence on the comparative pathological staging accuracy is still limited, larger prospective randomized studies are still needed to better clarify this topic.

Our study has both strengths and limitations. To our knowledge, this is the first systematic review and meta-analysis on the performance of ^{99m}Tc-tilmanocept SN biopsy in staging LN involvement in breast cancer, melanoma, and head and neck cancer. In 2012, Tokin et al. published a meta-analysis based on 148 breast cancer patients injected with ^{99m}Tc-tilmanocept to compare its efficacy to that of ^{99m}Tc-nanocolloidal albumin [41].

The main limitations of the current study include the limited number, sample sizes, limited follow-up (possibly affecting the false negative rates), and heterogeneous endpoints of the available original studies. Consequently, many studies did not have enough clinical outcome data to be pooled in meta-analysis. Moreover, some studies did not include ^{99m}Tc-sulfur colloid or ^{99m}Tc-nanocolloidal albumin and/or blue dye as reference standard in their design, hindering the possibility to perform comparative analyses and potentially causing bias.

In conclusion, ^{99m}Tc-tilmanocept is a promising radiotracer for SN mapping in breast cancer, melanoma, or head and neck cancer. However, we strongly believe that further multicentric trials are still needed to investigate whether ^{99m}Tc-tilmanocept is superior to other radiotracers used in clinical routine. Finally, we support the use of ^{99m}Tc-tilmanocept in conjunction with SPECT/CT imaging, particularly for preoperative mapping of SNs close to the primary tumor (i.e., floor of mouth tumors).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00259-023-06290-5.

Author contribution Conceptualization, methodology, writing—original draft preparation: G.R., E.J.d.K., A.C.; data curation: G.R., A.C.; formal analysis: G.R., E.J.d.K.; writing—review and editing: all authors; supervision: G.R., A.C. All authors have read and agreed to the published version of the manuscript.

Declarations

Competing interests The authors declare no competing interests.

References

1. Wilhelm AJ, Mijnhout GS, Franssen EJ. Radiopharmaceuticals in sentinel lymph-node detection - an overview. Eur J Nucl Med. 1999;26:S36-42.
2. Giammarile F, Alazraki N, Aarsvold JN, Audisio RA, Glass E, Grant SF, et al. The EANM and SNMMI practice guideline for lymphoscintigraphy and sentinel node localization in breast cancer. Eur J Nucl Med Mol Imaging. 2013;40:1932–47.
3. Bluemel C, Herrmann K, Giammarile F, Nieweg OE, Dubreuil J, Testori A, et al. EANM practice guidelines for lymphoscintigraphy and sentinel lymph node biopsy in melanoma. Eur J Nucl Med Mol Imaging. 2015;42:1750–66.
4. Giammarile F, Schilling C, Gnanasegaran G, Bal C, Oyen WJG, Rubello D, et al. The EANM practical guidelines for sentinel

lymph node localisation in oral cavity squamous cell carcinoma. Eur J Nucl Med Mol Imaging. 2019;46:623–37.
5. Vera DR, Wallace AM, Hoh CK, Mattrey RF. A synthetic macromolecule for sentinel node detection: ^{99m}Tc-DTPA-mannosyl-dextran. J Nucl Med. 2001;42:951–9.
6. Wallace AM, Hoh CK, Vera DR, Darrah DD, Schulteis G. Lymphoseek: a molecular radiopharmaceutical for sentinel node detection. Ann Surg Oncol. 2003;10:531–8.
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
8. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155:529–36.
9. StataCorp. Stata Statistical Software: release 14. College Station, TX: StataCorp LP. College Station, TX: StataCorp LP: StataCorp LP; 2015.
10. Wallace AM, Hoh CK, Ellner SJ, Darrah DD, Schulteis G, Vera DR. Lymphoseek: a molecular imaging agent for melanoma sentinel lymph node mapping. Ann Surg Oncol. 2007;14:913–21.
11. Wallace AM, Hoh CK, Darrah DD, Schulteis G, Vera DR. Sentinel lymph node mapping of breast cancer via intradermal administration of Lymphoseek. Nucl Med Biol. 2007;34:849–53.
12. Wallace AM, Hoh CK, Limmer KK, Darrah DD, Schulteis G, Vera DR. Sentinel lymph node accumulation of Lymphoseek and Tc-99m-sulfur colloid using a "2-day" protocol. Nucl Med Biol. 2009;36:687–92.
13. Leong SPL, Kim J, Ross M, Faries M, Scoggins CR, Metz WLR, et al. A phase 2 study of ^{99m}Tc-tilmanocept in the detection of sentinel lymph nodes in melanoma and breast cancer. Ann Surg Oncol. 2011;18:961–9.
14. Sondak VK, King DW, Zager JS, Schneebaum S, Kim J, Leong SPL, et al. Combined analysis of phase III trials evaluating [^{99m}Tc]tilmanocept and vital blue dye for identification of sentinel lymph nodes in clinically node-negative cutaneous melanoma. Ann Surg Oncol. 2013;20:680–8.
15. Wallace AM, Han LK, Povoski SP, Deck K, Schneebaum S, Hall NC, et al. Comparative evaluation of [^{99m}Tc]tilmanocept for sentinel lymph node mapping in breast cancer patients: results of two phase 3 trials. Ann Surg Oncol. 2013;20:2590–9.
16. Marcinow AM, Hall N, Byrum E, Teknos TN, Old MO, Agrawal A. Use of a novel receptor-targeted (CD206) radiotracer, ^{99m}Tc-tilmanocept, and SPECT/CT for sentinel lymph node detection in oral cavity squamous cell carcinoma: initial institutional report in an ongoing phase 3 study. JAMA Otolaryngol Head Neck Surg. 2013;139:895–902.
17. Baker JL, Pu M, Tokin CA, Hoh CK, Vera DR, Messer K, et al. Comparison of [^{99m}Tc]tilmanocept and filtered [^{99m}Tc]sulfur colloid for identification of SLNs in breast cancer patients. Ann Surg Oncol. 2015;22:40–5.
18. Agrawal A, Civantos FJ, Brumund KT, Chepeha DB, Hall NC, Carroll WR, et al. [^{99m}Tc]Tilmanocept accurately detects sentinel lymph nodes and predicts node pathology status in patients with oral squamous cell carcinoma of the head and neck: results of a phase III multi-institutional trial. Ann Surg Oncol. 2015;22:3708–15.
19. Unkart JT, Baker JL, Hosseini A, Hoh CK, Wallace MS, Vera DR, et al. Comparison of post-injection site pain between technetium sulfur colloid and technetium tilmanocept in breast cancer patients undergoing sentinel lymph node biopsy. Ann Surg Oncol. 2015;22(Suppl 3):S559-565.
20. Unkart JT, Wallace AM. Use of ^{99m}Tc-tilmanocept as a single agent for sentinel lymph node identification in breast cancer: a retrospective pilot study. J Nucl Med Technol. 2017;45:181–4.
21. Unkart JT, Hosseini A, Wallace AM. Tc-99m tilmanocept versus Tc-99m sulfur colloid in breast cancer sentinel lymph node identification: results from a randomized, blinded clinical trial. J Surg Oncol. 2017;116:819–23.
22. Unkart JT, Proudfoot J, Wallace AM. Outcomes of "one-day" vs "two-day" injection protocols using Tc-99m tilmanocept for sentinel lymph node biopsy in breast cancer. Breast J. 2018;24:526–30.
23. Silvestri C, Christopher A, Intenzo C, Kairys JC, Kim S, Willis A, et al. Consecutive case series of melanoma sentinel node biopsy for Lymphoseek compared to sulfur colloids. J Surg Res. 2019;233:149–53.
24. Murphy BL, Woodwick AR, Murphy KM, Chandler KJ, Johnson GB, Hunt CH, et al. ^{99m}Tc-Tilmanocept versus ^{99m}Tc-sulfur colloid in lymphoscintigraphy: sentinel lymph node identification and patient-reported pain. J Nucl Med Technol. 2019;47:300–4.
25. den Toom IJ, Mahieu R, van Rooij R, van Es RJJ, Hobbelink MGG, Krijger GC, et al. Sentinel lymph node detection in oral cancer: a within-patient comparison between [^{99m}Tc]Tc-tilmanocept and [^{99m}Tc]Tc-nanocolloid. Eur J Nucl Med Mol Imaging. 2020;
26. Vidal-Sicart S, Rioja ME, Prieto A, Goñi E, Gómez I, Albala MD, et al. Sentinel lymph node biopsy in breast cancer with ^{99m}Tc-tilmanocept: a multicenter study on real-life use of a novel tracer. J Nucl Med. 2021;62:620–7.
27. Doll C, Steffen C, Amthauer H, Thieme N, Elgeti T, Huang K, et al. Sentinel lymph node biopsy in early stages of oral squamous cell carcinoma using the receptor-targeted radiotracer 99mTc-tilmanocept. Diagnostics (Basel). 2021;11:1231.
28. Rietbergen DD, Pereira Arias-Bouda LM, van der Hage J, Valdés Olmos RA. Does ^{99m}Tc-tilmanocept, as next generation radiotracer, meet with the requirements for improved sentinel node imaging? Rev Esp Med Nucl Imagen Mol. 2021;40:275–80.
29. Mahieu R, den Toom IJ, van Rooij R, van Es RJJ, Hobbelink MGG, Krijger GC, et al. Diagnostic accuracy of [^{99m}Tc]Tc-tilmanocept compared to [^{99m}Tc]Tc-nanocolloid for sentinel lymph node identification in early-stage oral cancer. Clin Otolaryngol. 2021;46:1383–8.
30. Eckhoff A, Farrow NE, Silvestri C, Stroobant E, Intenzo C, Leddy M, et al. How much time is enough? Sentinel lymph node mapping time depends on the radiotracer agent. J Surg Oncol. 2022;125:712–8.
31. Mwagiru D, Shivashankar P, Wong E, Farlow D, Cambden B, Abdul-Razak M. Tilmanocept as a novel tracer for lymphatic mapping and sentinel lymph node biopsy in melanoma and oral cancer. ANZ J Surg. 2022;
32. Ferez-Pinzon A, Corey SL, Rochani H, Rehl EA, Burak WE Jr. A prospective double-blinded randomized controlled trial comparing the intraoperative injection of technetium Tc 99m tilmanocept with technetium Tc 99m sulfur colloid in breast cancer lymphatic mapping. Breast J Hindawi. 2022;2022:9421489.
33. Lymphoseek now FDA-approved for all solid tumors. Oncology Times. 2014;36:19.
34. EMA. Lymphoseek [Internet]. European Medicines Agency. 2018 [cited 2023 Jan 20]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/lymphoseek.
35. Vermeeren L, van der Ploeg IMC, Olmos RAV, Meinhardt W, Klop WMC, Kroon BBR, et al. SPECT/CT for preoperative sentinel node localization. J Surg Oncol. 2010;101:184–90.
36. Veenstra HJ, Vermeeren L, Olmos RAV, Nieweg OE. The additional value of lymphatic mapping with routine SPECT/CT in unselected patients with clinically localized melanoma. Ann Surg Oncol. 2012;19:1018–23.
37. Stojadinovic A, Peoples GE, Jurgens JS, Howard RS, Schuyler B, Kwon KH, et al. Standard versus pH-adjusted and lidocaine supplemented radiocolloid for patients undergoing sentinel-lymph-node mapping and biopsy for early breast cancer (PASSION-P

trial): a double-blind, randomised controlled trial. Lancet Oncol. 2009;10:849–54.
38. van den Berg NS, Brouwer OR, Klop WMC, Karakullukcu B, Zuur CL, Tan IB, et al. Concomitant radio- and fluorescence-guided sentinel lymph node biopsy in squamous cell carcinoma of the oral cavity using ICG-^{99m}Tc-nanocolloid. Eur J Nucl Med Mol Imaging. 2012;39:1128–36.
39. van den Berg NS, Simon H, Kleinjan GH, Engelen T, Bunschoten A, Welling MM, et al. First-in-human evaluation of a hybrid modality that allows combined radio- and (near-infrared) fluorescence tracing during surgery. Eur J Nucl Med Mol Imaging. 2015;42:1639–47.
40. KleinJan GH, Van Werkhoven E, van Den Berg NS, Karakullukcu MB, Zijlmans HJ, Van Der Hage JA, et al. The best of both worlds: a hybrid approach for optimal pre- and intraoperative identification of sentinel lymph nodes. Eur J Nucl Med Mol Imaging. 2018;45:1915–25.
41. Tokin CA, Cope FO, Metz WL, Blue MS, Potter BM, Abbruzzese BC, et al. The efficacy of tilmanocept in sentinel lymph mode mapping and identification in breast cancer patients: a comparative review and meta-analysis of the ^{99}mTc-labeled nanocolloid human serum albumin standard of care. Clin Exp Metastasis. 2012;29:681–6.