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Sentinel lymph node biopsy techniques in thyroid pathologies — a meta-analysis

Techniki biopsji węzła wartowniczego w patologii tarczycy — metaanaliza

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Abstract

Intoduction: To review different sentinel lymph node biopsy (SLNB) techniques in patients with thyroid neoplasm. We also compared the detection rates of the different detection methods in these patients.
Material and methods: The Medline database from 1998 until December 2010 was searched for the following terms: 'thyroid cancer', 'thyroid neoplasm', and 'sentinel lymph node'. Studies in which sentinel lymph nodes were detected by the blue dye technique and/or by a radiotracer in patients with suspected thyroid cancer were analysed.
Results: Twenty five studies were included in the meta-analysis. Based on the technique used for sentinel lymph node (SLN) detection, the included studies were divided into three groups.
Group 1 consisted of studies in which only the blue dye technique was used to detect SLNs. Group 2 was made up of studies in which the radioisotope technique was used. Studies in which both techniques were used were grouped into Group 3. There were 18 studies in which the blue dye technique was used to detect SLNs (Group 1), four studies in which only the radioisotope technique was used to detect SLNs (Group 2), and only two studies where both techniques were used (Group 3). Among 891 patients from Group 1, SLN was found in 740 (83.1%) patients. Detection rates in these studies were very different and varied from 0% to 95.5%. Among 160 patients from Group 2, SLN was detected in 158 (98.8%). In the third group of patients, in which both methods were performed, SLN was found in 48 (98%) of 49 patients. Detection rates in those studies were very high (100% and 97.8%).
Conclusions: The analysis proved that SLNB is, technically, fairly easy to perform. However, nodal metastases are of debatable prognostic value in thyroid cancer, so the clinical value of SLNB remains to be proven. It seems reasonable to perform further, prospective studies on larger groups of patients, in which both techniques would be used. They should compare the efficiency of SLNB with elective or selective central lymphadenectomy in reducing local recurrence rates. **(Pol J Endocrinol 2012; 63 (3): 222–231)**

Key words: *sentinel lymph node, thyroid cancer, radioisotope method, dye method, selective lymphadenectomy, elective lymphadenectomy*

Streszczenie

Wstęp: W pracy dokonano przeglądu technik biopsji węzła wartowniczego u pacjentów z nowotworem tarczycy. Ponadto porównano wskaźniki wykrywalności różnych metod detekcji węzła wartowniczego u tych pacjentów.
Materiał i metody: Przeanalizowano dane z bazy *Medline* z okresu od 1998 roku do grudnia 2010 roku w oparciu o następujące określenia: „rak tarczycy", „ nowotwór tarczycy", „węzeł wartowniczy". Przeanalizowano badania, w których poszukiwano węzłów wartowniczych metodą barwnikową i/lub radioizotopową u pacjentów z podejrzeniem raka tarczycy.
Wyniki: Do metaanalizy włączono 25 badań. Na podstawie zastosowanej techniki wykrywania węzła wartowniczego badania podzielono na trzy grupy. Do grupy pierwszej włączono badania, w których zastosowano jedynie metodę barwnikową. W grupie drugiej znalazły się badania, w których wykorzystano jedynie metodę radioizotopową, natomiast do grupy trzeciej włączono badania, w których zastosowano obie metody. W 18 badaniach węzły wartownicze wykrywano technikami barwnikowymi (grupa 1), w czterech — tylko metodami radioizotopowymi (grupa 2). Jedynie w dwóch pracach zastosowano obie techniki (grupa 3). Wśród 891 pacjentów z grupy 1. węzeł wartowniczy znaleziono u 704 (83,1%). Wykrywalność węzła wartowniczego w analizowanych badaniach była bardzo zróżnicowana i wahała się od 0% do 95,5%. Wśród 160 pacjentów z 2. grupy węzeł wartowniczy znaleziono u 158 (98,8%). W 3. grupie chorych, w której zastosowano obie metody, węzeł wartowniczy znaleziono u 48 (98%) z 49 pacjentów. Wykrywalność w obu badaniach była bardzo wysoka (100% i 97,8%).
Wnioski: Analiza udowodniła, że biopsja węzła wartowniczego w raku tarczycy jest technicznie dość łatwa do wykonania. Jednakże znaczenie rokownicze przerzutów raka tarczycy do węzłów chłonnych jest przedmiotem kontrowersji, co wymusza udowodnienie klinicznego znaczenia biopsji węzła wartowniczego. Wydaje się racjonalne przeprowadzenie dalszych, prospektywnych badań z udziałem większych grup pacjentów, w których będą stosowane obie techniki. W badaniach tych trzeba porównać efektywność biopsji węzła wartowniczego z elektywną i selektywną limfadenektomią w zmniejszeniu liczby wznów miejscowych. **(Endokrynol Pol 2012; 63 (3): 222–231)**

Słowa kluczowe: *węzeł wartowniczy, rak tarczycy, metoda radioizotopowa, metoda barwnikowa, selektywna limfadenektomia, elektywna limfadenektomia*

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Introduction

Surgery is the treatment of choice for differentiated thyroid carcinoma. Most surgeons perform total thyreoidectomy and lymphadenectomy. However, the extent of lymph node resection remains a matter of controversy. In differentiated thyroid carcinoma, either selective lymphadenectomy or, more aggressive, modified radical neck dissection can be performed. During selective lymphadenectomy, clinically or intraoperatively suspected lymph nodes are removed. This approach decreases the risk of recurrent laryngeal nerve injury and the occurrence of hypocalcaemia.

A number of publications have reported that the removal of lymph node metastases does not affect survival, making selective lymphadenectomy appear to be sufficient treatment in thyroid carcinoma [1–3]. According to some authors, many metastatic lymph nodes are occult and could be destroyed during postoperative radioiodine therapy [4]. In cases of locoregional relapse, it is often possible to remove them [5, 6]. Other surgeons propose more aggressive treatment. Many patients with differentiated thyroid carcinoma have involved lymph nodes: in the ipsilateral cervicocentral compartment (42–86%), in the ipsilateral cervicolateral compartment (32–68%), in the contralateral cervicolateral compartment (12–24%), and in the mediastinal compartment (3–20%) [7]. Most publications have shown a negative prognostic impact of lymph node metastases [7–9]. This argues for a more extensive operation than selective lymphadenectomy. In addition, recurrence, which is the worst prognostic factor, appears most often in the lymph nodes [8, 10, 11]. Nodal metastases often present no iodine uptake and can only be treated surgically [4–6]. There is also a possibility of the formation of further metastases from lymph node metastases [12].

Elective lymphadenectomy increases the rate of postoperative complications, especially hypocalcaemia [13–15]. Lymph node dissection is also a time-consuming procedure. As a result of these controversies, the use of the sentinel lymph node biopsy technique, as a means to detect occult lymph node metastases in thyroid carcinoma, has begun to attract interest [16, 17].

The sentinel lymph node is the first lymph node that receives lymph flow from the primary tumour. The identification of this node was introduced by Morton et al. in 1992 [18]. They used isosulfan blue dye, intraoperatively, to map the pathway of lymph flow from a primary cutaneous melanoma to one or more sentinel lymph nodes in the regional lymphatic basin. The theory of sentinel lymph node biopsy has become a revolutionary concept in the management of breast carcinoma and melanoma. This procedure is being adopted in the management of other solid malignancies such as: colorectal cancer [19, 20], gastric cancer [21, 22], oesophageal cancer [23–25], head and neck tumours [26–28], lung cancer [29–32], endometrial, cervical and vulvar cancers [33, 34].

In 1998, Kelemen et al. pioneered the vital blue dye technique of sentinel lymph node biopsy, in a study composed of 17 thyroid patients [35]. Lymphatic mapping was successful in 15 patients. Gallowitsch et al. and Rettenbacher et al. were the first to describe the use of a radiotracer to intraoperatively count involved lymph nodes using a handheld gamma probe [36, 37]. We believe that thyroid carcinoma patients may benefit from sentinel lymph node biopsy. In cases when the sentinel lymph node is not affected, performing a limited lymphatic dissection could decrease the risk of laryngeal recurrent nerve injury and hypoparathyroidism. In addition, sentinel lymph node biopsy can help to identify occult metastases outside the central compartment. This procedure is a logical alternative to extended elective lymphadenectomy. Since Kelemens' first report, a number of other studies have demonstrated that sentinel lymph node biopsy is indeed an appropriate procedure for obtaining information about lymph node metastases in patients undergoing thyroidectomy. The purpose of this meta-analysis was to review different sentinel lymph node biopsy techniques in thyroid cancer patients. The subject of this paper is not entirely new, as two meta-analyses, published recently, have focused on the same topic [16, 17]. However, we additionally compared the effect of different detection methods on the sentinel detection rate in these patients.

Material and methods

The Medline database was searched from 1998 until December 2010 for the following terms: 'thyroid cancer', 'thyroid neoplasm', and 'sentinel lymph node' as the medical subject headlines (MeSH). The manuscript includes all necessary items for meta-analysis according to the PRISMA statement [38]. Data from review papers, comments, letters, conference abstracts, case reports etc. were not included in our analysis. We analysed the studies in which sentinel lymph nodes were detected in patients with suspected thyroid cancer by the blue dye technique and/or by a radiotracer. The studies included in the analysis also had to meet certain criteria.

The resected specimens had to be evaluated histopathologically and there had to be sufficient data to reassess sensitivity (number of true positive and false negatives) or the sentinel node detection rate had to be given. In all but one study, thyroidectomy and lymph node resection were performed by the classical technique [39]. Only in the Ja Seong Bae et al. study were endoscopic thyroidectomies and sentinel lymph node biopsies carried out [39].

Table I. *Characteristics of patients in whom the dye technique was used to detect SLNs*
Tabela I. *Charakterystyka pacjentów, u których zastosowano metodę barwnikową w celu wykrycia węzłów wartowniczych*

No.	Study and year	n	Female/male ratio	Age (yrs) range (mean)	Tumour size [cm] range (mean)	Final histopathological examination	% malignant
1.	Kelemen et al. 1998 [35]	17	14/3	22–69 (48)	0.8–4 (2)	11 — papillary ca 1 — follicular ca 5 — benign lesions	70.6
2.	Dixon et al 2000 [40]	40	35/5	25–74 (42)	1–3.5 (–)	14 — papillary ca 1 — thyroid lymphoma 25 — benign lesions	37.5
3.	Arch-Ferrer et al. 2001 [41]	22	22/2	23–51 (37)	1.5–3.5 (–)	22 — papillary ca	100
4.	Pelizzo et al. 2001 [42]	29	21/8	21–86 (44)	0.5–4 (1.77)	29 — papillary ca	100
5.	Fukui et al. 2001 [43]	22	19/3	35–76 (52.8)	5.9–21.1 (–)	22 — papillary ca	100
6.	Tsugawa et al. 2002 [44]	38	30/8	24–72 (–)	0.5–2.8 (–)	38 — papillary ca	100
7.	Takami et al. 2003 [45]	68	60/8	22–69 (42)	0.6–3.9 (1.9)	68 — papillary ca	100
8.	Chow et al. 2004 [46]	15	12/3	26–71 (54)	–	15 — papillary ca	100
9.	Peparini et al. 2006 [47]	8	4/4	31–58 (45.1)	0.8–2.5 (1.4)	8 — papillary ca	100
10.	Rubello et al. 2006 [45]	153	122/31	(44.9)	0.3–4.7 (1.8)	153 — papillary ca	100
11.	Dzodic et al. 2006 [49]	40	30/10	23–57 (42)	(1.5)	34 — papillary ca 5 — Hürthle cell ca 1 — follicular ca	100
12.	Abdalla et al. 2006 [50]	30	25/5	18–54 (31)	–	30 — benign lesions	0
13.	Roh et al. 2008 [51]	50	40/10	23–75 (47.7)	0.5–1.7 (1.1)	50 — papillary ca	100
14.	Wang et al. 2008 [52]	25	13/12	20–79 (45)	–	25 — papillary ca	100
15.	Bae et al. 2009 [39]	11	11/0	22–46 (37.3)	0.6–26 (1.2)	11 — papillary ca	100
16.	Takeyama et al. 2009 [53]	37	18/19	24–70 (42)	> 4 cm	8 — papillary ca 4 — follicular ca 25 — benign lesions	32.4
17.	Anand et al. 2009 [54]	75	82/16	19–78 (48.3)	–	70 — papillary ca 2 — follicular ca 3 — Hürthle cell ca	76.5
18.	Cunningham et al. 2010 [55]	211	165/46	19–86 (51)	0.1–6 (1.8)	211 — papillary ca	100

Twenty five studies were included in the analysis.

There was a considerable variance in the histopathological procedure among the studies. Tables I, II, and III show only the final results of histopathological examinations, because different frozen section techniques were used, making it difficult to compare the results.

The studies were divided into three groups based on the technique used for sentinel lymph node detection.

Group 1 was made up of studies in which only the blue dye technique was used to detect SLNs [35, 39–55]. This group was further subdivided into two subgroups depending on the site of the blue dye injection: intratumoural (Group 1A) or peritumoural (Group 1B). Group 2 consisted of studies in which only the radioisotope technique was used to detect SLNs [56–59], while studies in which both techniques of SLN detection were used were grouped into Group 3 [60, 61].

Results

The blue dye technique was used to detect SLNs in 18 studies, making up Group 1 (Table I) [35, 39–55]. In these studies, sentinel lymph node biopsy was performed on 891 patients.

In 789 (88.6%) of them, papillary thyroid carcinoma was diagnosed. Eight (0.9%) patients were diagnosed with follicular carcinomas, eight (0.9%) with Hürthle cell carcinomas, one (0.1%) with thyroid lymphoma, and 85 (9.5%) had benign lesions.

Table II. *Characteristics of patients of the studies in which the radioisotope technique was used to detect SLNs*
Tabela II. *Charakterystyka pacjentów, u których zastosowano metodę radioizotopową w celu wykrycia węzłów wartowniczych*

No.	Study and year	n	Female/male ratio	Age (yrs) range (mean)	Tumour size [cm] range (mean)	Final histopathological examination	% malignant
1.	Stoeckli et al. 2003 [56]	6	4/2	20–74 (50)	–	1 — papillary ca 3 — follicular ca 2 — benign lesions	66.6
2.	Pelizzo et al. 2007 [57]	25	17/8	22–64 Mean 48	0.5–3	24 — papillary ca 1 — mixed medullary-papillary ca	100
3.	Carcoforo et al. 2007 [58]	64	57/7	50.3 ± 13.5	0.87 ± 0.65	59 — papillary ca 5 — benign lesions	92.2
4.	Boschin et al. 2008 [59]	65	48/17	20–69 (43.2)	0.5–4.3 (1.7)	65 — papillary ca	100

Table III. *Characteristics of patients of the studies in which both techniques were used to detect SLNs*
Tabela III. *Charakterystyka pacjentów, u których zastosowano obie metody w celu wykrycia węzłów wartowniczych*

No.	Study and year	n	Female/male ratio	Age (yrs) range (mean)	Tumour size [cm] range (mean)	Final histopathological examination	% malignant
1.	Catarci et al. 2001 [60]	6	4/2	38–73 (48.7)	1.8–4.8	6 — papillary ca	100
2.	Lee et al. 2009 [61]	43	76/21	23–81 (46)	0.3–1.8	43 — papillary ca	100

There were only four studies in which only the radioisotope technique was used to detect SLNs. These were included in the analysis as Group 2 (Table II) [56–59]. The group consisted of 160 patients. Among them, 149 (93.1%) patients were diagnosed with papillary thyroid carcinoma. Three (1.9%) had follicular carcinoma, one (0.6%) had mixed medullary-papillary carcinoma, and eight (5%) had benign lesions.

To the best of our knowledge, there have been only two studies in which both techniques have been used, and these were included in our analysis as Group 3 (Table III) [60, 61]. This group consisted of 49 patients. All of them were diagnosed with papillary thyroid carcinoma.

SLN detection results

Studies in which only the blue dye technique was used were analysed in Group 1 (Table IV). SLN was found in 740 (83.1%) of the 891 patients in this group. Detection rates in these studies varied greatly, from 0% [47] to 95.5% [43] (Table V). In all but the Peparini et al. study, SLN detection rates were high. In seven studies [41, 43, 45, 49, 51, 54, 55], they ranged above 90% (Table V), while in the other ten studies [35, 39, 40, 42, 44, 46, 48, 50, 52, 53] they were between 60% and 90% (Table V). SLN was identified in 680 (84.4%) of the 806 patients who had a thyroid malignancy. When analysing only these patients, we noted that detection rates were also rather high. In all but one study [47] they were above 65% (Table V) [40]. In nine studies, the blue dye was injected intratumourally [35, 40–43, 46, 48, 50, 55] — Group 1A (Table IV). In six studies, the dye was injected peritumourally [45, 49, 51–54] — Group 1B (Table IV). In the study performed by Peparini et al., five patients were enrolled into Group 1A, and three into Group 1B [47]. Results obtained by Tsugawa et al. and Bae et al. were excluded from this part of analysis because the site of the blue dye administration was not exactly determined [39, 44]. So, 544 patients (484 malignant patients) were included into Group 1A.

SLN was found in 431 (79.2%) of them. In 298 (273 malignant) patients, the blue dye was injected peritumourally — Group 1B. SLN was detected in 270 (90.6%), and 249 (92.2%) patients had malignancy. Out of the 488 malignant patients in whom SLNs were detected, metastatic SLNs were found in 199 (40.8%).

Three different kinds of dyes were used to find SLN(s): Isosulfan blue dye [35, 40, 41, 45, 50, 53, 55], Patent blue dye [42, 44, 46–48], and Methylene blue [39, 43, 49, 51, 52, 54].

Isosulfan blue dye was injected in 425 patients, out of which SLN(s) were found in 366 (86.1%) patients. SLN(s) were detected in 166 (68.3%) of the 243 patients using Patent blue dye, while Methylene blue was used in 223 patients, in whom SLN(s) were found in 205 (91.9%) of them.

Group 2 was made up of studies in which the radioisotope technique was used to detect SLNs.

Among 160 patients in this group, SLN was detected in 158 (98.8%) of them (Table VI). In all but one study, the detection rates of SLN were 100% (Table VII). The

Table IV. *Methodology and results of studies in which only the blue dye technique was used*
Tabela IV. *Metodologia i wyniki badań, w których zastosowano jedynie metodę barwnikową*

No.	Study and year	Detection technique	Tracer volume and dose	Injectionsite	No of pts	No. of malignant pts	No. of pts with detected SLNs	No. of malignant pts with detected SLNs	No. of malignant pts with detected and metastatic SLNs
1.	Kelemen et al. 1998 [35]	1% Isosulfan blue dye	0.1–0.8 mL, average 0.5 mL	Intratumoural	17	12	15	12	5
2.	Dixon et al 2000 [40]	1% Isosulfan blue dye dye	0.1–0.8 mL, average 0.7 mL	Intratumoural	40	15	26	11	7
3.	Arch-Ferrer et al. 2001 [41]	1% Isosulfan blue dye	0.5 mL	Intratumoural	22	22	20	20	12
4.	Pelizzo et al. 2001 [42]	0.5% Patent Blue V	0.5 mL	Intratumoural	29	29	22	22	4
5.	Fukui et al. 2001 [43]	2% Methylene blue	0.1 mL 4 quadrant	Intratumoural	22	22	21	21	7
6.	Tsugawa et al. 2001 [44]	1% Patent blue dye	0.2–0.5 mL	Directly in the thyroid mass	38	38	27	27	16
7.	Takami et al. 2003 [45]	Isosulfan blue dye	0.3 mL	Peritumoural	68	68	63	63	35
8.	Chow et al. 2004 [46]	2.5% Patent Blue V	0.5–1 mL	Intratumoural	15	15	10	10	7
9.	Peparini et al. 2006 [47]	2.5% Patent blue V	0.1–1.2 mL mean 0.5	5 — intratumoural 3 — peritumoural	8	8	0	0	0
10.	Rubello et al. 2006 [48]	0.5% Patent blue V	0.25 mL for 1 cm diameter	Intratumoural	153	153	107	107	36
11.	Dzodic et al. 2006 [49]	1% Methylene blue dye	0.2 mL	Peritumoural	40	40	37	37	9
12.	Abdalla et al. 2006 [50]	1% Isosulfan blue dye	0.5–1 mL	Intratumoural	30	0	18	0	0
13.	Roh et al. 2008 [51]	2% Methylene blue	0.2 mL	Peritumoural	50	50	46	46	18
14.	Wang et al. 2008 [52]	2% Methylene blue	0.5 mL	Peritumoural	25	25	22	22	19
15.	Bae et al. 2009 [50]	2% Methylene blue	0.5 mL	Intratumoural and surrounding parenchyma	11	11	9	9	5
16.	Takeyama et al. 2009 [53]	1% Isosulfan blue dye	0.1 mL 4 quadrant	Peritumoural	37	12	32	11	4
17.	Anand et al. 2009 [54]	1% Methylene blue	0.2–0.3 mL	Peritumoural	75*	75	70	70	15
18.	Cunningham et al. 2010 [55]	1% Isosulfan blue dye	0.5–2 mL	Intratumoural	211	211	192	192	71

*Sentinel lymph node biopsy in patients with benign lesions was not analysed

Carcoforo group failed to detect SLN in two patients with benign diseases, making the detection rate slightly lower, yet still very high — 96.9% [58]. The site of radioisotope injection (intratumoural or peritumoural) did not influence the detection rate in patients with malignancy from Group 2 (Table VII).

In 153 thyroid carcinoma patients in whom SLNs were found, 61 (39.9%) had involved SLNs.

Group 3 comprised studies in which both techniques of SLN detection were used. In this group, SLNs were detected in 48 (98%) of the 49 patients. The detection rates were very high (100% and 97.8%) (Table VIII). In the Catarci et al. study, the radioisotope technique was able to detect more SLNs than the blue dye technique (83.3% v 50%) [60], while in the Lee et al. study, the blue dye technique was slightly more efficient (93% v 88.4%)

Table V. *Detection rates in patients using only the blue dye method*
Tabela V. *Wskaźniki wykrywania u pacjentów, u których zastosowano jedynie metodę barwnikową*

No.	Study and year	Detection rate — all patients %	Detection rate — malignant patients only %
1.	Kelemen et al. 1998 [35]	88.2	100
2.	Dixon et al 2000 [40]	65	73.3
3.	Arch-Ferrer et al. 2001 [41]	90.9	90.1
4.	Pelizzo et al. 2001 [42]	75.9	75.9
5.	Fukui et al. 2001 [43]	95.5	95.5
6.	Tsugawa et al. 2001 [44]	71.1	71.1
7.	Takami et al. 2003 [45]	92.6	92.6
8.	Chow et al. 2004 [46]	66.6	66.6
9.	Peparini et al. 2006 [47]	0	0
10.	Rubello et al. 2006 [48]	69.9	69.9
11.	Dzodic et al. 2006 [49]	92.5	92.5
12.	Abdalla et al. 2006 [50]	60	–
13.	Roh et al. 2008 [51]	92	92
14.	Wang et al. 2008 [52]	88	88
15.	Bae et al. 2009 [39]	81.8	81.9
16.	Takeyama et al. 2009 [53]	86.5	91.7
17.	Anand et al. 2009 [54]	93.3	93.3
18.	Cunningham et al. 2010 [55]	91	91
	All studies	83.1	84.4

[61]. Twenty five (52.1%) of the 48 patients with thyroid carcinoma in whom SLNs were detected had metastases in the nodes. All patients from both studies had a malignancy.

Discussion

The SLN is the first lymph node in the regional lymphatic basin that receives lymph flow from a tumour. There are several, general, reasons for sentinel lymph node biopsy such as: minimising the morbidity of lymph node assessment, altering the surgical procedure performed, and improving the accuracy of the nodal assessment. SLNB can be considered as a minimally invasive surgical alternative to elective lymphadenectomy. The functional identification of this node was made practical by Morton et al. for the first time in 1992 for melanoma [18].

Using blue dye, Kelemen et al. were the first to be able to note the feasibility of the SLN procedure in thyroid surgery [35]. In this pilot study, the authors indentified SLNs in all 12 patients with thyroid cancer; five SLNs were positive for metastases.

In 1999, Gallowitsch et al. and, in 2001, Sahin et al. used radioisotope for the same purpose [36, 62]. Both of them reported favourable results for detecting SLNs by this technique. The primary treatment for thyroid carcinoma is surgery, yet it remains controversial as to whether prophylactic lymph node dissection improves the prognosis of thyroid carcinoma patients [63, 64]. Lymph nodes from the central compartment are usually the first to be involved. However, routine lymph node dissection of the central compartment can cause complications such as recurrent laryngeal injury and transient or even permanent hypoparathyroidism. Also, according to a Swedish multicentre audit comprising 3,660 thyroid operated patients, postoperative infection occurred in 1.6% and was associated with lymph node operation [14]. Dissection is unnecessary in negative lymph node patients.

Table VI. *Methodology and results of studies in which only the radioisotope technique was used*
Tabela VI. *Metodologia i wyniki badań, w których zastosowano jedynie metodę radioizotopową*

No.	Study and year	Detection technique	Tracer volume and dose	Injection site	No. of pts	No. of malignant pts	No. of pts with detected SLNs	No. of malignant pts with detected SLNs	No. of malignant pts with detected and metastatic SLNs
1.	Stoeckli et al. 2003 [56]	^{99m}Tc Sulfurcolloid	0.2 mL 20 MBq	Intratumoural	6	4	6	4	1
2.	Pelizzo et al. 2007 [57]	^{99m}Tc Nanocolloid	0.1–0.2 mL 4–9 MBq, mean 6	Intratumoural	25	25	25	25	12
3.	Carcoforo et al. 2007 [58]	^{99m}Tc Nanocolloid	0.3 mL 12–154 MBq, mean 120	Peritumoural (ultrasound guided)	64	59	62	59	14
4.	Boschin et al. 2008 [59]	^{99m}Tc Nanocolloid	0.1–0.3 mL 4–7 MBq, mean 5.5	Intratumoural	65	65	65	65	34

Table VII. *Detection rates in patients using only the radioisotope method*
Tabela VII. *Wskaźniki wykrywania u pacjentów, u których zastosowano jedynie metodę radioizotopową*

No.	Study and year	Detection rate — all patients %	Detection rate — malignant patients only %
1.	Stoeckli et al. 2003 [56]	100	100
2.	Pelizzo et al. 2007 [57]	100	100
3.	Carcoforo et al. 2007 [58]	96,9	100
4.	Boschin et al. 2008 [59]	100	100

Table VIII. *Detection rates in patients where both methods of SLN detection were used*
Tabela VIII. *Wskaźniki wykrywania u pacjentów, u których zastosowano obie metody detekcji*

No.	Study and year	Detection rate — all patients %
1.	Catarci et al. 2001 [60]	
	Radioisotope	83.3
	Blue dye	50
	Both	100
2.	Lee et al. 2009 [61]	
	Radioisotope	88.4
	Blue dye	93
	Both	97.8

All patients from both studies had a malignancy

The SLN procedure may allow the avoidance of elective lymphadenectomy and reduce complication rates of recurrent laryngeal nerve damage and hypoparathyreoidismus. Other benefits from SLNB in thyroid carcinoma may lie in finding SLNs, perhaps with occult metastases, outside of the central neck compartment, although the number of patients who would benefit from this approach may be rather small, because, in most patients, SLNs are located in the central neck compartment. A totally new application of SLNB has been presented by Takeyama et al. [53]. It is difficult to histologically differentiate between benign and malignant follicular tumours. The study shows that SLNB is helpful in obtaining the correct diagnosis of follicular carcinoma, since metastasis to the lymph node is sufficient evidence to diagnose cancer. SLN detection can be performed using the vital dye technique, the radioisotope technique, or a combined procedure. In our analysis, we included 18 studies in which the blue dye technique was applied. 680 patients were enrolled in these studies. The radioisotope technique was used only in four studies, with a total of 160 patients. Only two studies in which both methods were applied were included: 49 patients were enrolled in them.

SLN was found in 83.1% of patients using the blue dye technique. This percentage is rather high and similar to that of other solid tumours. In all but one study, it was higher than 65% [47]. Peparini et al. performed SLNB only in eight patients. This was the smallest group included in our analysis. SLNB is a relatively difficult procedure to master and it has a steep learning curve. Perhaps Peparini's study should have been performed on a larger number of patients before the results were presented.

When focusing on the site of injection, intratumoural or peritumoural, it has been pointed out that in colon cancer, breast cancer and melanoma, the injection is administered either peritumourally or on the boundaries of the biopsy.

In this analysis for thyroid carcinoma, SLN detection using intratumoural injection was found to be less specific than peritumoural injection. The rates of sentinel node detection were 71.8% for intratumoural injection and 90.6% for peritumoural injection.

Surgeons used Isosulfan blue dye, Patent blue and Methylene blue dyes, to find SLNs. Of these three, Methylene blue showed the best detection rate (91.9%) compared to Isosulfan blue dye (86.1%) and Patent blue dye (68.3%). In the experimental study of LiX et al., Methylene blue dye was better than the other two dyes [65]. The lymph nodes were deeply stained by 2% Methylene blue. Also, the time it took to dye the lymph nodes was the shortest, while the effect lasted the longest. It is a pity that these dyes were only tested on rabbits. We suggest that similar research should be performed on humans.

The amount of injected dye ranged from 0.1 mL to 2 mL. Surgeons have not reached consensus as to how much dye should be used.

The phenomenon of skip metastases (negative central and positive lateral or mediastinal compartment lymph nodes) is observed in thyroid carcinoma. Depending on the lymph node levels being compared, the frequency of skip metastasis (of which the pattern of spread is unpredictable) varied between 11.1% and 37.5% in node-positive papillary thyroid cancer [66, 67]. These facts suggested performing elective rather than selective lymphadenectomy in the

Table IX. *Methodology and results of studies in which both methods were used*
Tabela IX. *Metodologia i wyniki badań, w których zastosowano obie metody*

No.	Study and year	Detection technique	Tracer volume and dose	Injection site	No. of pts	No. of malignant pts	No. of pts with detected SLNs	No. of malignant pts with detected SLNs	No. of malignant pts with detected and metastatic SLNs
1.	Catarci et al. 2001 [60]	^{99m}Tc	0.1 mL	Intratumoural	6	6	5	5	4
		Nanocolloid	11–37 MBq	Intratumoural		6	3	3	
		2.5% Patent Blue V	0.1 mL for 1 cm diameter both			6	6	6	
2.	Lee et al. 2009 [61]*	^{99m}Tc- tin colloid 2%	0.1–0.2 mL	Intratumoural	43	43	38	38	21
		Methylene blue both	0.1–0.5 mL	Peritumoural			40	40	
							42	42	

*Only cases in whom both methods were used are included in the analysis

lateral compartment. Perhaps the introduction of SLNB in thyroid carcinoma and intraoperative techniques of SLN assessment will improve the choice for patients for selective lateral lymphadenectomy. The Chow et al. study showed the effectiveness of SLNB in detecting the involved SLN, despite an unusual draining pattern [46]. SLNs were found only in the lateral compartment in one out of ten patients. In the others, the SLNs were detected in both the central and lateral compartments. Also Takami et al. had three patients in whom a SLN was only detected in the lateral compartment [45]. According to this, it seems rational that for mapping purposes, neck exploration should not be restricted to the lymph nodes of the central compartment.

Using blue dyes during SLNB seems to be safe. Barthelmes et al. analysed adverse reactions to patent blue V in 7,917 breast cancer patients who participated in the NEW START training programme and the ALMANAC trial [68]. Only a total of 0.9% of patients experienced adverse reactions. Also, allergic reactions after isosulfan blue dye use are uncommon [69]. Thirty nine (1.6%) of 2,392 patients were described as having an allergic reaction during the mapping procedure by isosulfan blue dye [69].

It is now impossible to evaluate the safety of blue dye in such a large number of thyroid cancer patients but there is no reason to think that dye injection is more dangerous than in breast cancer patients.

Additionally, blue dyes need no special equipment, are relatively cheap, and can be used even in ordinary hospitals.

Gallowitsch et al. and Rettenbacher et al. were the first to describe a technique using a radiotracer during intraoperative SLN counting with a handheld gamma probe [3, 37]. Some authors do not perform it to find SLNs in thyroid carcinoma [70]. According to them, a 'shine-through' phenomenon is observed during the detection of thyroid cancer SLNs. In breast carcinoma and melanoma, the localisation of the primary tumour and SLN results in high radiation counts throughout the entire lymphatic basin, enabling the precise localisation of the SLN(s). Data from the studies in our analysis does not confirm this theory. Among the 160 patients in whom only the radioisotope technique was used for detection, SLN was found in all but two patients (Table VI). The results of all involved studies are similar. This procedure has a much higher SLN detection rate than the blue dye SLN detection rate (80.6%). Our results are similar to those previously obtained by Raijmakers et al. [16]. The method of radioisotope injection (intratumoural or peritumoural) does not influence the detection rate in patients with malignancy.

Evidence from the studies using the radiotracer technique confirms that SLNB is a feasible and easily performed procedure, although using radiocolloid for SLN mapping is both more costly and time-consuming, as well as not readily available in many centres. Perhaps for these reasons, the radionuclide injection technique has not been evaluated in as many studies as the blue dye injection technique.

In many malignant solid tumours, especially in breast carcinoma and melanoma, radionuclides and blue dye are used together to increase the possibility of identifying SLN(s). In our analysis, we looked at two such studies which concerned thyroid carcinoma (Table IX) [57, 58]. Catarci et al. found SLNs using 2.5% Patent Blue V in three out of six patients, making the detection rate not very high [60]. Yet when they added the radionuclide, it allowed them to find SLNs in all the patients. It is possible that when both the methods are combined, the use of a gamma-probe leads to less careful research of blue-stained lymph nodes. Catarci et al. underlined the necessity of using both methods: the detection rate when using blue dye was 50%, while with radioisotope it was 83%, yet when both methods were used, it was 100% (Table VIII). However, Catarci's group investigated a small number of patients (only six). In another study performed on a larger group of patients (n = 43), the detection rates for both of the methods were almost the same: 93% for the blue dye, and 88.4% for the radioisotope technique (Table VIII) [61]. The radioisotope was injected preoperatively in all the studies in which it was used (combined with blue dye or not). This eliminates disrupting the lymphatics during the initial dissection. The radioisotope technique, like the blue dye technique, allows the identification of SLNs outside the central compartment.

Conclusions

After analysing 24 studies, we conclude that SLN biopsy for thyroid carcinoma seems to be technically feasible in most patients.

SLNB applied to patients with thyroid carcinoma revealed several advantages. The most important are avoiding unnecessary lymphadenectomy and, related to this, the possibilities of recurrent laryngeal nerve injury and hypoparathyreoidismus. However, this benefit is questioned because non-invasive imaging with high-resolution ultrasonography can produce similar results [17]. SLNB can help to find SLNs outside the central compartment, making it easier to identify metastatic lymph nodes that are not resected by central lymph node dissection alone, and provide a more logical approach to lateral neck dissection.

Additionally, it improves clinical staging in thyroid carcinoma patients and allows a better selection of patients who require ^{131}I treatment after surgery. With the use of immunohistochemistry or RT-PCR, it is now possible to reveal micrometastases, which, in the past, would have remained undetected, thus making it possible to make a more accurate evaluation regarding the nodal status. Performing additional examinations (immunohistochemistry, RT-PCR) to evaluate all resected lymph nodes seems to be expensive and time-consuming. It is easier to do that only on SLNs.

The analysis proved the SLNB is, technically, fairly easy to perform. However, nodal metastases are of debatable prognostic value in thyroid cancer, so the clinical value of SLNB needs to be proven [71]. It seems reasonable to perform further, well designed studies on larger groups of patients. In our analysis, only five of the 18 studies in which only the blue dye technique was used comprised 50 or more patients. Only blue dye was used in these studies.

Probably, like in breast cancer and melanoma, using both techniques together is superior to blue dye only. It might allow a quicker identification of sentinel lymph nodes with greater accuracy. However, there have been only two studies in which both techniques were used. They comprised only 49 patients, too few to draw such a conclusion for thyroid cancer. The next prospective studies should compare the efficiency of SLNB with elective or selective central lymphadenectomy in reducing local recurrence rates. In these studies, SLNB must be performed using both techniques.

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