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Original paper

Sentinel lymph node in thyroid tumors – own experience

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Aim of the study: To determine the feasibility of sentinel lymph node biopsy (SLNB) for the evaluation of the cervical lymph node status in patients with thyroid tumors.
Material and methods: Twenty-three patients with suspected thyroid cancer were enrolled in the study. 0.5–1.0 ml of 1% Patent Blue dye was injected intratumorally. After SLNB, thyroidectomy and proper lymphadenectomy were performed.
Results: Sentinel lymph node was detected in 20 (86.9%) patients. Thirty-one SLNs were found – 21 (67.7%) were located in the central neck compartment, 4 (12.9%) in the lateral neck compartment, 6 (19.4%) in the upper mediastinum. The number of SLNs ranged from 1 to 3 (mean 1.6). Sentinel lymph node was positive in 5 (25%) patients, negative in 15 (75%) in the final histopathology.
Sentinel lymph nodes were located only in the central neck compartment in 13 patients, and in both the central and lateral neck compartments in 2 patients. In one patient, SLNs were located only in the central neck compartment and upper mediastinum. Three patients had SLNs only in the upper mediastinum, while one had them only in the lateral neck compartment. In one patient a node regarded as SLN was negative, while there were metastases in removed non-sentinel lymph nodes (NSLNs).
In two patients, histopathology of SLNs showed that they were actually parathyroid glands.
Conclusions: Our results confirm that thyroid cancer SLNB is rather easy to carry out. Its performance along with intraoperative examination can help to avoid unnecessary lymphadenectomy. However, it should be kept in mind that parathyroid glands can be stained and removed by mistake during SLNB.

Key words: thyroid cancer, thyroid tumor, sentinel lymph node, sentinel lymph node biopsy, parathyroid glands.

Introduction

Thyroid carcinoma (TC) has a propensity for cervical lymphatic spread that is usually found in more than one third of patients in the standard review of surgical pathological specimens [1, 2]. However, there is controversy concerning the ideal surgical management of lymph nodes in patients with TC. A number of publications report that cervical metastases did not influence survival for papillary or follicular carcinoma, making selective lymphadenectomy seem a sufficient treatment in thyroid cancer [3–5]. Compared with total thyroidectomy alone, thyroidectomy with lymphadenectomy significantly increases the rate of postoperative complications, especially hypocalcemia [6–8].

Lymph node dissection lengthens operation time. Many metastatic lymph nodes are occult and could be destroyed during postoperative radioiodine therapy [9]. When nodal relapse is observed, it is often possible to remove engaged lymph nodes. On the other hand, two large population-based studies showed increased mortality in patients with regional lymph node metastases [10, 11]. This is an argument for an operation more extensive than selective lymphadenectomy. Moreover, relapse, which is the worst prognostic factor, is observed most frequently in the lymph nodes [12, 13]. Nodal metastases can sometimes be treated only surgically if they present no iodine uptake [14]. Perhaps the introduction of sentinel lymph node biopsy (SLNB) could resolve all these controversies. This procedure has brought about a revolution in the management of breast carcinoma and melanoma. The sentinel node status (presence or absence of metastasis) is, almost always, compatible with the status of regional lymph nodes. Therefore, intraoperative evaluation of sentinel node(s) could help to define the extent of lymphadenectomy. In the case of a negative SLNB, there is no need to perform lymphadenectomy and patients can avoid complications related to it. The limited dissection could decrease the risk of complications, especially hypoparathyroidism. In addition, SLNB can help to identify occult metastases outside the central compartment. This procedure is a logical alternative to extended elective lymphadenectomy.

The objective of this study was to determine the feasibility of SLNB for the evaluation of the cervical lymph node status in patients with thyroid carcinoma.

Material and methods

Twenty-three patients (18 women and 5 men) underwent SLNB in the Department of General Surgery and Oncology of the Medical University of Lodz from December 2009 to April 2011. They were suspected of or diagnosed with thyroid carcinoma based on fine needle aspiration biopsy (FNAB). Only patients primarily operated on were enrolled in the study. Patients after partial thyroidectomy and lymphadenectomy, operated on due to local recurrence, were excluded from the series. The operation was performed under general anesthesia. The whole thyroid gland was exposed during the operation. Tissues were prepared carefully in order not to disrupt the flow of the lymph. Subsequently, 0.5–1.0 ml of 1% Patent Blue dye (Guerbet GmbH Germany) was injected intratumorally, very slowly, under low pressure, using a 27-G needle and insulin syringe. Care was taken not to accidentally stain the surrounding structures. The volume of blue dye depended on the diameter of the tumor. 0.5 ml was injected if the diameter was 2 cm or below. 1 ml of blue dye was used for tumors larger than 2 cm. Blue stained lymph nodes were considered sentinel lymph nodes (SLNs). They were removed and sent for final histopathological examination as well as molecular examinations. Frozen section examinations were not performed. After SLNB, thyroidectomy and proper lymphadenectomy (bilateral central and lateral lymphadenectomy on the side of the tumor were performed) were performed. Other removed lymph nodes were defined as non-sentinel lymph nodes (NSLNs). In our study, the results of SLNB did not change the extent of lymphadenectomy. The location of lymph nodes was determined based on the Dralle *et al*. classification [15]. The protocol study was approved by the Ethics Committee of the Medical University of Lodz, Poland.

Statistica 10.0 software was used for analysis (StatSoft, Tulsa, OK, USA).

Table 1. Positive predictive value, negative predictive value, sensitivity and specificity for SLNB

Positive predictive value	1.0000	CI: 0.5655–1
Negative predictive value	0.4667	CI: 0.2481–0.6988
Sensitivity	0.3846	CI: 0.1771–0.6448
Specificity	1.0000	CI: 0.6457–1

Statistical analysis

Positive predictive value, negative predictive value, sensitivity and specificity for SLNB were calculated (Table 1).

Results

Final results of the histological examination of tumors

Final histopathological examination revealed 15 malignant and 8 benign tumors. Papillary thyroid carcinoma (PTC) was diagnosed in 13 patients, medullary thyroid carcinoma (MTC) in two patients, and adenoma in 8 patients (Table 2).

Table 2. Final results of the histopathological examination

Patient No.	Patient initials	Age	Gender	Histopathology	Tumor location	Size (mm)
1	P.B.	41	female	classical variant of papillary carcinoma	right lobe	30
2	B.M.	41	female	classical variant of papillary carcinoma	left lobe	20
3	E.R.	50	female	classical variant of papillary carcinoma	right lobe	7
4	K.W.	49	male	classical variant of papillary carcinoma	right lobe	9
5	W.K.	65	male	classical variant of papillary carcinoma	upper pole of the right lobe (two foci)	2 and 7
6	A.M.	68	female	classical variant of papillary carcinoma	left lobe	20
7	P.P.	47	male	classical variant of papillary carcinoma	upper pole of the right lobe	18
8	M.N.	37	female	classical variant of papillary carcinoma	upper pole of the left lobe	25
9	W.R.	73	female	classical variant of papillary carcinoma	left lobe	20
10	D.B.	47	male	medullary carcinoma	left lobe	30
11	K.K.	34	female	follicular variant of papillary thyroid carcinoma	upper pole of the right lobe	20
12	J.K.	65	male	medullary carcinoma	left lobe	9
13	M.K.	65	female	classical variant of papillary carcinoma	right lobe	25
14	J.D.	71	female	classical variant of papillary carcinoma	right lobe	20
15	M.J.	44	female	follicular variant of papillary thyroid carcinoma	border of the isthmus and right lobe	6
16	H.N.	55	female	adenoma	isthmus	15
17	T.C.	53	female	adenoma	right lobe	18
18	K.M.	54	female	adenoma	right lobe	30
19	M.B.	31	female	adenoma	border of the isthmus and right lobe	13
20	B.H.	31	female	adenoma	upper pole of the right lobe	8
21	K.Z.	67	female	adenoma	lower pole of the left lobe	35
22	S.P.	75	female	adenoma	lower pole of the left lobe	10
23	D.T.	37	female	adenoma	left lobe	20

Five, 6, 3 and 1 patients were classified with pT1a, pT1b, pT2 and pT3, respectively according to the 7th WHO Classification.

The classic type of papillary thyroid carcinoma was diagnosed in 11 patients. Two patients were considered to have the follicular variant of PTC. The mean tumor size was 1.74 cm (range: 0.2–3.5 cm) (Table 2). Sixteen tumors were larger than 1 cm, 8 were equal to or smaller than 1 cm (Table 2). One patient, W.K., had 2 foci of papillary carcinoma (Table 2). Thyroid capsule infiltration was detected in 6 out of 15 (37.5%) patients with malignant neoplasms.

Results of sentinel lymph node biopsy

Sentinel lymph nodes were detected, by using Patent Blue dye, in 20 out of 23 patients (86.9%) (Table 3). Among them, eleven had PTC, two MTC, and 7 benign lesions. Thirty-one SLNs were found – 21 (67.7%) were located in the central neck compartment (Ia and Ib), 4 (12.9%) in the lateral neck compartment, 6 (19.4%) in the upper mediastinum (Table 3). The number of SLNs ranged from 1 to 3 (mean 1.6) (Table 3). Sentinel lymph node was positive in 5 (25%) patients (P.B., A.M., M.N., D.B., K.K.), and negative in 15 (75%) patients in the final histopathological examination (Table 3).

Four patients with PTC had positive SLN, while the remaining seven had negative SLN. One of the two patients with medullary thyroid carcinoma (MTC) had SLN involved.

Sentinel lymph nodes were located only in the central neck compartment in 13 patients, and in both the central and lateral neck compartments in 2 patients. In one patient, SLNs were located only in the central neck compartment and upper mediastinum. Three patients had SLNs only in the upper mediastinum, while one patient had them only in the lateral neck compartment (Table 3). In one patient (J.K.), a node regarded as SLN was negative, while in removed NSLNs metastases were found in the final histopathological examination. In two patients, histopathology of SLNs showed that they were actually parathyroid glands. None of the patients presented permanent or temporary hypocalcemia after the operation. There was no allergy to Patent Blue dye in any patient.

Discussion

The standard treatment of thyroid carcinoma generally includes total thyroidectomy together with regional lymph

Table 3. Location of lymph nodes in the compartments

Patient No.	Patient initials	No. of metastatic/all lymph nodes in compartments									
		SLNs in Ia	All LNs in Ia	SLNs in Ib	All LNs in Ib	SLNs in II	All LNs in II	SLNs in III	All LNs in III	SLNs in IV	All LNs in IV
1	P.B.	2/2	2/2	0	0	0	0/2	0	0/2	0	0/3
2	B.M.	0	0/5	0/1	0/1	0	0/9	0	0/13	0	0/9
3	E.R.	0	0	0/1	0/4	0	0	0	0	0	0
4	K.W.	0	0/1	0	0	0/3	0/13	0	0	0	0/8
5	W.K.	0/1	0/3	0	0	0	0	0	0	0	0
6	A.M.	0	0	1/1	1	0	0	0	3/11	0	0
7	P.P.	0/2	0/3	0	0	0	0/16	0	0	0	5
8	M.N.	0	0	2/2	2/4	0	0	1/1	1/1	0	0
9	W.R.	0	0	0/1	0/3	0	0	0/1	0/12	0	0
10	D.B.	0	0	2/2	2/3	0	0	0	0/2	0	0/1
11	K.K.	1/1	1/1	0	0	0	0/1	0	0	0	0
12	J.K.	0	0	0/1	1/3	0	0	0	3/10	0	0
13	M.K.	0	0/2	0	0	0	0/3	0	0/12	0	0
14	J.D.	0	0/4	0	0	0	0	0	0	0	0
15	M.J.	0	0	0/1	0/8	0	0	0	0/16	0/2	0/8
16	H.N.	0	0	0/1	0/2	0	0	0	0	0	0
17	T.C.	0	0	0	0	0	0	0	0	0/1	0/1
18	K.M.	0/1	0/1	0	0	0	0	0	0	0	0
19	M.B.	0	0	0	0	0	0	0	0	0/2	0/2
20	B.H.	0/1	0/1	0	0	0	0	0	0	0	0
21	K.Z.	0	0	0/1	0/1	0	0	0	0	0/1	0/3
22	S.P.	0/1	0/1	0	0	0	0	0	0	0	0
23	D.T.	0	0/2	0	0	0	0	0	0	0	0

SLNs – sentinel lymph nodes, LN – lymph nodes node dissection, ^{131}I treatment, and life-long TSH-suppressive thyroid hormone replacement. However, the extent of lymph node resection remains a matter of controversy. According to some authors, selective lymphadenectomy seems a sufficient treatment in thyroid carcinoma [3–5]. Additionally, elective lymphadenectomy increases the rate of postoperative complications, especially hypocalcemia [6–8]. Lymph node dissection is also a time-consuming procedure. On the other hand, some studies present a negative prognostic impact of lymph node metastases, especially in patients older than 45 years [12, 16]. This is an argument for an operation more extensive than selective lymphadenectomy. In addition, recurrence, which is the worst prognostic factor, appears most frequently in lymph nodes in patients older than 45 years [12, 17]. Nodal metastases often present no iodine uptake and can only be treated surgically [17, 18]. Cady and Rossi created an AMES scoring system (age, metastasis, extent, size of tumor) assigning patients to groups of low and high risk. The high-risk group includes: men with PTC above 45 years of age, women above 50 years of age, distant metastasis, extracapsular invasion and tumor size larger than 5 cm [17, 19]. Nodal disease in older patients in the high-risk group with PTC is associated with a 78% mortality rate [19]. In any case, as only patients with lymph node metastases would benefit from lymph node treatment, it would be important to know the status of the lymph nodes before making a therapeutic strategy choice.

As a way to resolve these controversies, the application of sentinel lymph node biopsy has generated interest. Because of its high sensitivity, accuracy and low false-negative rate in predicting the regional lymph node status, SLNB has obtained widespread consensus and replaced routine lymphadenectomy as the standard for staging in breast cancer and melanoma. The success of SLNB in breast cancer and melanoma has set a good example for other types of solid tumors: colorectal cancer, gastric cancer, esophageal cancer, head and neck tumors, lung cancer and gynecological malignancies [20–33]. Perhaps in the case of thyroid carcinoma it will be a standard procedure. Kelemen *et al*., who used blue dye, were the first to be able to note the feasibility of the SLNB procedure in thyroid surgery [34]. In their preliminary study, the authors identified SLNs in all 12 patients with thyroid cancer; 5 SLNs were positive for metastases. In 1999 Gallowitsch *et al*. and in 2001 Sahin *et al*. used radioisotopes for the same purpose. Both reported favorable results for detecting SLNs by this technique [35, 36]. A few meta-analyses have evaluated the usefulness of SLNB in thyroid surgery [37, 38]. Many authors have investigated the feasibility and potential utility of SLN biopsy in thyroid neoplasms, both malignant and benign, reporting encouraging results, albeit based on limited case series and without following commonly accepted rules. In our study we were able to find SLNs in 83.3% of patients. This result is similar to the other studies [37, 38]. To the best of our knowledge, the detection rate is above 60% in all published studies but one [39]. The authors, who applied the radioisotope method, achieved even better results [40–43]. In three of the studies surgeons managed to find SLNs in all patients [40, 41, 43]. In the fourth study the detection rate was also excellent – 96.9% [42]. The results of those studies proved that SLNB employing radiotracer technique is feasible to perform. However, this procedure is not available in many centers. It requires special equipment and is time-consuming. Although it has been proved that using a radiocolloid is safe in SLNB for breast cancer and melanoma, some of the medical staff have concerns about safety. Doses of the radiocolloid used for SLNB for thyroid carcinoma are not higher so there is no reason not to believe that the procedure is safe [44, 45]. There are 2 studies concerning thyroid carcinoma where radioisotope and blue dye were used together. Catarci's group found SLNs in all 6 patients [46]. In another study, on a larger group of patients (n = 43), detection rates for both methods were almost the same – 93% for the blue dye and 88.4% for the radioisotope technique [47]. Our study shows that the SLNB technique is feasible, repeatable and accurate, detecting the SLN in 83.3% of patients. This sensitivity is similar to that reported by a majority of the other studies [37, 38]. We do not know why we were not able to detect SLNs in all patients. Perhaps we disrupted the lymph flow during dye injection or made another technical error. The results of SLNBs in our study have not changed the extent of operations because SLNB for thyroid cancer is not a standardized procedure. Thirty-two SLNs were found in our patients. The number of SLNs ranged from 1 to 3 (mean 1.6). Sentinel lymph nodes were engaged in 5 patients (25%), and negative in 15 patients (75%). Four PTC patients had positive SLN; the remaining seven PTC patients had negative SLN. One of the two patients with medullary thyroid carcinoma (MTC) had the SLN involved. The percentage of involved SLNs is close to that in other studies [48–50].

Sentinel lymph nodes in a majority of our patients (13) were found only in the central neck compartment. However, SLNs were observed outside the central neck compartment in 4 patients. Three patients had SLNs only in the upper mediastinum, while one patient had them only in the lateral neck compartment. Lymphadenectomy outside the central neck compartment is not routinely performed in many centers. Perhaps SLNB could help to identify cases that require it to be performed. Three patients had SLNs in two compartments – 2 in the central and lateral compartments and 1 in the central and upper mediastinum compartments.

Regrettably, in one patient a node regarded as SLN was negative, while metastases were found in removed NSLNs in the final histopathological examination. It is a disadvantage of the method. That may be due to the fact that we have been performing SLNB for a short time so we are not experienced in this technique. However, it is also possible to observe the alternative lymph flow from the thyroid. It may lead to the occurrence of skip metastases (a positive lymph node in the lateral compartment without positive lymph nodes in the central compartment) [51]. We believe that that phenomenon should be evaluated on a greater number of patients before introducing SLNB as a standard procedure.

In 3 patients, histopathology of SLNs showed that they were actually parathyroid glands. Fortunately, these patients had no permanent or temporary hypocalcemia after the operation. This complication is typical of thyroid SLNB and is regrettably the most serious complication. It was earlier reported by Rubello *et al*. and Abdalla *et al*. [52, 53].

We suppose that, in order to avoid it, the parathyroid gland should be located before blue dye injection. There is a need to look for a dye other than Patent Blue or radiotracer with lower affinity to parathyroid glands. Perhaps the introduction of nanoparticles or indocyanine green will solve this problem [54, 55].

Our results confirm that thyroid cancer SLNB is rather easy to carry out, but it should be kept in mind that parathyroid glands can be stained and removed by mistake. Its performance along with intraoperative examination can help to avoid unnecessary lymphadenectomy in the central and lateral compartments. However, central neck dissection has been proven to improve staging of the neck, use of adjuvant radioiodine treatment and ten-year disease-specific survival, in comparison to patients without central neck dissection [56]. From this perspective, SLNB can be considered a promising tool, but it needs to be tested in large prospective studies before any evidence-based conclusions can be reached.

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