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CLINICAL STUDY

The importance of sentinel lymph node diagnostic biopsy from the lateral neck compartment in the surgical treatment of papillary thyroid cancer

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ABSTRACT

OBJECTIVES: The aim of our study is to determine whether mapping the lymphatic drainage and diagnostic excision of lymph nodes from lateral neck compartment is able to detect ultrasound unknown metastases in this compartment early and thus favorably affect the prognosis of patients with papillary thyroid cancer (PTC).

BACKGROUND: Lymph node involvement in the lateral neck compartment is seen in 30–60 % of patients with PTC at the time of diagnosis and affects the prognosis of patients in terms of disease recurrence.

METHODS: From June 2012 to December 2016, 154 patients with no evidence of lateral nodal involvement on imaging studies were treated with total thyroidectomy and central comparment neck dissection. A volume of 0.2 ml of Patent Blue dye was applied in the upper half of the thyroid gland with subsequent exposure of lymphatic drainage in the lateral compartment and 2–3 sentinel lymph nodes (SLN) were removed for frozen section (Group 1). In case of metastatic involvement, a lateral comparment neck dissection was performed. The reference groups were composed of a set of patients without detected lymphatic drainage (Group 2) and a set of patients who underwent lateral compartment neck dissection for preoperatively detected metastases in the lymph nodes (Group 3). The biochemical, structural and overall persistence of the disease at the time of administration of adjuvant radioiodine ablation was evaluated.

RESULTS: The SLN identification rate was 95.45 %. In Group 1, a total of 32 patients had a positive SLN. Out of these, 24 patients had positive SLNs based on the analysis of frozen section, while in 8 patients, the positive diagnosis was confirmed through definitive histology. The comparison of data from the entire follow-up period in all three groups of patients revealed statistically significant differences in persistence of disease, namely in favor of Group 1. The percentage of reoperations for persistence and recurrence of disease was significantly lowest in Group 1 (2.04 %) compared to Groups 2 and 3 (6.94 % and 45.45 % respectively).

CONCLUSION: The method is safe and sensitive for detecting unknown lymph node metastases in the lateral neck compartment, and may facilitate a decision to perform accurate surgical treatment of patients with PTC *(Tab. 4, Fig. 2, Ref. 38)*. Text in PDF *www.elis.sk*

KEY WORDS: papillary thyroid cancer, sentinel lymph node biospy, lateral neck compartment, neck dissection, persistence.

Introduction

The current standard for surgical treatment of papillary thyroid cancer (PTC) is total thyroidectomy (TTE) and therapeutic cervical dissection in patients with lymph node metastases (LNMs) proven clinically or with imaging methods (LNM). It is currently generally accepted that metastatically affected lymph nodes need to be removed from the central neck compartment (CC), which represents the primary zone of metastatic propagation (1). Resection of nodal metastases in the lateral neck compartment (LC) is performed if nodal metastases are confirmed preoperatively or perioperatively. Unlike the central compartment, the lateral compartment, is well visualized sonographically. Therefore, even before the operation, the surgeon is usually equipped with sufficiently relevant information about the state of the lymph nodes in this area.

According to the literature, the incidence of LNM in patients with PTC at initial diagnosis is in a wide range from 20 % to 90 % (2, 3) while LNMs occur more often in the central compartment (4, 5). The frequency of occult metastases is lower in LC than in CC. Patients with LNM have a high risk of recurrence which is associated with the necessity of second surgery (6). In addition, the lateral compartment neck dissection (LCND) requires a separate (extended) incision and is associated with higher morbidity than the separate central compartment neck dissection (CCND).

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Sentinel lymph nodes (SLN) are defined as the first lymph nodes in the area of lymphatic drainage from primary tumors and reflect the status of the remaining lymph nodes. The result of the sentinel lymph node biopsy (SLNB) serves to determine the staging of the disease and whether therapeutic lymphadenectomy in the given area is needed. The advantage of sentinel node biopsy lies in its ability to detect regional metastatic lymph nodes smaller than 2–3 mm in their largest diameter, which cannot be achieved with other techniques such as high-resolution ultrasonography (7).

The aim of our study is to determine whether by mapping of lymphatic drainage and diagnostic extirpation of lymph nodes from LC, we can detect metastases in this compartment early and thus favorably affect the prognosis of patients with papillary thyroid cancer.

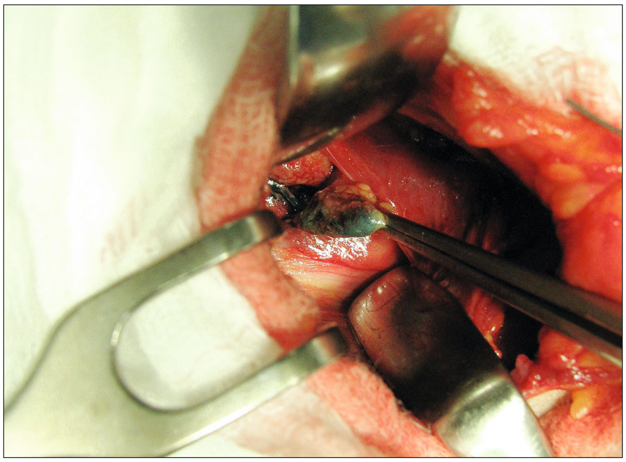

Fig. 2. Blue-stained lymph node in LC (neck sectors III + IV).

Material and methods

From the 1st of June 2012 to the 31st of December 2016 at the Department of Surgical Oncology of St. Elizabeth Cancer Institute in Bratislava, 154 patients (129 women and 25 men) from primary group (Group 1) with preoperatively and peroperatively verified PTC without proven metastases by imaging studies underwent a total thyroidectomy, prophylactic central compartment neck dissection and a sentinel lymph node biopsy of LC (TTE + CCND + SLNB). The diagnosis of PTC was based on preoperative ultrasound examination (USG), thin-needle cytology and perioperative histology. Patients with preoperatively detectable metastases in regional lymph nodes, dissemination of the disease and previous neck surgery were excluded from this group. The median age at the time of diagnosis was 47 years (in range of 19–78 years).

At the beginning of the surgical procedure, the standard Kocher incision was performed. After cutting the skin and subcutaneous tissue and forming the musculocutaneous flap and cutting the fascia (longitudinal cut along *linea alba cervicalis*), the thyroid was exposed. A volume of 0.2 ml of Patent Blue dye was applied in the upper half of the lobe of the thyroid gland on the ipsilateral side of the tumor lesion (Fig. 1), with subsequent exposure of lymphatic drainage in LC (neck sectors III + IV), and 2–3 blue-stained lymph nodes were removed for frozen section procedure (Fig. 2). If bilateral tumor was present, the procedure was carried out bilaterally. Subsequently, the patients underwent a standard TTE and prophylactic CCND. If metastases were identified in the sentinel nodes, LCND was performed.

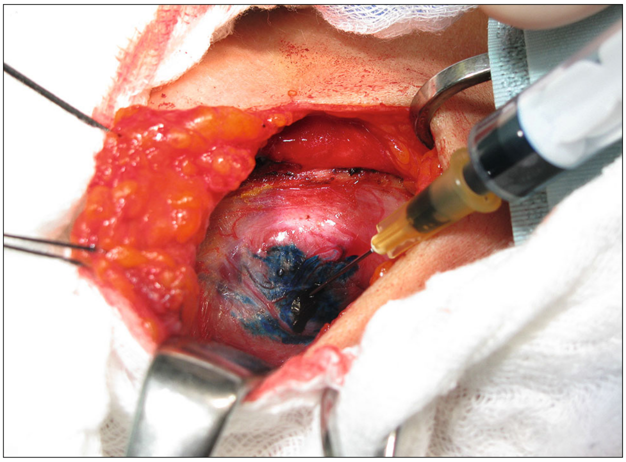

Fig. 1. Application of Patent Blue dye in the upper half of the lobe of the thyroid gland.

After the surgical procedure, the biochemical, structural and overall persistence rates of the disease were assessed at the time of administration of adjuvant treatment with radioiodine ablation (RAI) at 3, 9 and ≥ 21 months. Results were analyzed with Mann-Whitney, Fisher‘s exact, Kruskal-Wallis and Pearson‘s Chi-squared tests. Furthermore, our primary group (Group 1), was compared with a set of 72 patients from Group 2 (60 women and 12 men) with the median age at the time of diagnosis of 52 years (range 18-76 years) who underwent a total thyroidectomy and central compartment neck dissection without detected lymphatic drainage (TTE + CCND). Moreover, another comparison was made between our primary group (Group 1) and Group 3. Group 3 was defined as a set of 55 patients (36 women and 19 men) who had LCND for preoperatively detected LNM and similarly underwent a total thyroidectomy and central compartment neck dissection (TTE + CCND + LCND). The median age at the time of their diagnosis was 39 years (in range of 18–79 years). This study was approved by the Ethics Committee of St. Elizabeth Oncological Institute in Bratislava.

Results

In Group 1, sentinel lymph nodes were identified in 147 out of 154 patients. The identification rate (IR) was 95.45 %, with a specificity (Sp) of 100 % and a sensitivity (Se) of 80 %. The negative predictive value (NPV) was 86.9 % and the positive predictive value (PPV) was 100 %, with an overall accuracy of the method of 94.5 %. Overall, 118 patients (80.27 %) had T1 stage, most patients had a unifocal lesion (77.55 %), while extrathyroidal spread occurred in 17.01 %. There was autoimmune thyroiditis (AIT)

Tab. 1. Comparison of characteristics by study groups.

Characteristics		Group 1 (n = 147)	Group 2 (n = 72)	Group 3 (n = 55)
Sex	Male	125 (85.03 %)	60 (83.33 %)	36 (65.45 %)
	Female	22 (14.97 %)	12 (16.67 %)	19 (34.55 %)
Median age		47	52	39
Size of tumor	0–1 cm	48 (32.65 %)	18 (25.0 %)	15 (27.27 %)
	> 1–2cm	70 (47.62 %)	36 (50.0 %)	22 (40.0 %)
	> 2–4cm	28 (19.05 %)	15 (20.83 %)	10 (18.18 %)
	> 4cm	1 (0.68 %)	3 (4.17 %)	8 (14.55 %)
Multifocality		33 (22.45 %)	17 (23.61 %)	15 (27.27 %)
Extrathyroid spread		25 (17.01 %)	20 (27.78 %)	32 (58.18 %)
Autoimmune thyroiditis		58 (39.46 %)	28 (38.89 %)	22 (40 %)
Angioinvasion		36 (24.49 %)	22 (30.56 %)	33 (60 %)
Positive LN in CC		66 (44.90 %)	32 (44.44 %)	49 (80 %)
Number of positive LN in CC	0 LN	81 (55.10 %)	40 (55.56 %)	6 (10.91 %)
	1–4 LNs	58 (39.46 %)	25 (34.72 %)	22 (40.0 %)
	> 5 LNs	8 (5.44 %)	7 (9.72 %)	27 (49.09 %)
SLN (+) in frozen section		24 (16.33 %)	X	X
SLN (+) definitive histology		8 (5.44 %)	X	X
Total SLN (+)		32 (21.77 %)	X	X

CC – central compartment; LN – lymph nodes; SLN – sentinel lymph nodes

Tab. 2. Biochemical, structural and overall disease persistence of all three groups after administration of three doses of RAI and number of reoperations for persistence / recurrence.

	Group 1 (n = 147)	Group 2 (n = 72)	Group 3 (n = 55)
BP – RAI-1	35 (23.81 %)	24 (33.33 %)	37 (62.27 %)
SP – RAI-1	8 (5.44 %)	8 (11.11 %)	26 (47.27 %)
OP – RAI-1	39 (26.53 %)	28 (38.89 %)	38 (69.09 %)
BP – RAI-2	8 (5.44 %)	7 (9.72 %)	28 (50.91 %)
SP – RAI-2	6 (4.08 %)	8 (11.11 %)	25 (45.45 %)
OP – RAI-2	12 (8.16 %)	13 (18.06 %)	34 (61.82 %)
BP – RAI-3	6 (4.08 %)	5 (6.94 %)	19 (34.55 %)
SP – RAI-3	11 (7.48 %)	12 (16.67 %)	23 (41.82 %)
OP – RAI-3	15 (10.20 %)	14 (19.44 %)	26 (47.27 %)
Reoperations	3 (2.04 %)	5 (6.94 %)	25 (45.45 %)

BP – biochemical persistence; OP – overall persistence; SP – structural persistence; RAI – radioiodine ablation

in one-third of patients (39.46 %). Angioinvasion was detected in one-quarter of patients (24.49 %), less than a half of patients had LNM in CC (44.9 %). Characteristics of all three groups are showed in Table 1.

In 24 patients of Group 1 (16.3 %), LNMs were detected by means of frozen section biopsy. During the definitive histological examination, metastases were revealed in other 8 patients, i.e., 32 patients in total (21.7 %) in our group had LNM in LC. Lateral compartment neck dissection was performed in 16 patients in whom LNMs were detected by frozen section biopsy, while in others, it was not performed mainly because intraoperatively detected micrometastases were smaller than 2mm in diameter in the sentinel nodes. LCND was not performed in these patients because of the small size of metastases and high probability of subsequent radioiodine ablation. Therefore, in the presence of LNM in definitive histology, LCND was not performed due to the abscence of metastases during the preoperative USG examination and indication of radioiodine therapy.

Differences in patient groups were not statistically significant (by patient age, tumor size, multifocality, extrathyroidal spread, AIT, angioinvasion, presence of LNM in CC).

Three months after surgery, i.e., when the 1st dose of thyroid ablation with radioiodine (RAI-1) was administered, there were no statistically significant differences in the persistence of the disease among the groups.

Nine months after surgery, i.e., at the time of the 2nd dose of thyroid elimination with radioiodine (RAI-2) the persistence rates were as follows. In Group 1 (TTE + CCND + SLNB), biochemical persistence (BP) of the disease was detected in 5.44 % of patients, structural persistence (SP) occurred in 4.08 % of patients, while overall persistence (OP) was 8.16 %. In Group 2 (TTE + CCND), 9.72 % of patients had biochemical persistence, 11.11 % had structural persistence, and 18.06 % had overall persistence. In Group 3 (TTE + CCND + LCND) biochemical persistence of the disease was detected in 50.91 % of patients, structural persistence occurred in 45.45 % of patients, while overall persistence was 61.82 %.

Twenty-one months after surgery, i.e., at the time of the 3rd dose of radioactive iodine (RAI-3), the persistence rates were as follows. In Group 1 (TTE + CCND + SLNB), biochemical persistence of the disease was detected in 4.08 % of patients, structural persistence occurred in 7.48 % of patients, while overall persistence was 10.20 %. In Group 2 (TTE + CCND), 6.94 % of patients had biochemical persistence, 16.67 % had structural persistence, and 19.44 % had overall persistence. In Group 3 (TTE + CCND + LCND), biochemical persistence of the disease was detected in 34.55 % of patients, structural persistence occurred in 41.82 % of patients, while overall persistence was 47.27 %. When comparing the data of all three groups of patients obtained during the entire follow-up period, the percentage of reoperations for persistence and recurrence of the disease was significantly lowest in Group 1 (2.04 %) compared to Groups 2 and 3 (6.94 % and 45.45 % respectively). The data on biochemical, structural and overall disease persistence rates of all three groups after administration of three doses of RAI are presented in Table 2.

Nine months after surgery (at the time of the 2nd dose of RAI), the statistical analysis of patients from Group 2, as compared to Group 1, revealed that there was a 2.93 and 2.47 times higher risk (OR) of structural persistence ($p = 0.0457$) and overall persistence ($p = 0.0305$), respectively. Biochemical persistence in Group 2 was 1.87 times higher, but this increase in risk was not statistically significant ($p = 0.2388$). Twenty-one months after the operation (at the time of the 3rd dose of RAI), the statistical analysis of patients from Group 2 as compared to Group 1, revealed that the OR of

Tab. 3. Multivariate analysis = Group 2 vs Group 1.

TTE + CCND vs. TTE + CCND + SLNB			
	OR	CI	p
BP – RAI-2	1.8711	0.6506–5.3808	0.2388
SP – RAI-2	2.9375	0.9788–8.8156	0.0457
OP – RAI-2	2.4788	1.06783–5.7541	0.0305
BP – RAI-3	1.7537	0.5167–5.9518	0.3621
SP – RAI-3	2.4727	1.0331–5.9182	0.0373
OP – RAI-3	2.1241	0.9629–4.6854	0.0580

BP – biochemical persistence; CCND – central compartment neck dissection; CI – confidence interval; OP – overall persistence; OR – odds ratio; SLNB – sentinel lymph node biopsy; SP – structural persistence; RAI – radioiodine ablation; TTE – total thyroidectomy

Tab. 4. Multivariate analysis, Group 3 vs Group 1.

TTE + CCND + LCND vs. TTE + CCND + SLNB			
	OR	CI	p
BP – RAI-2	5.6	1.8811 – 16.6710	0.0012
SP – RAI-2	4.5	1.5100 – 13.4101	0.0052
OP – RAI-2	4.8571	1.8457 – 12.7817	0.0016
BP – RAI-3	3.6944	1.1284 – 12.0949	0.0262
SP – RAI-3	2.5669	0.9495 – 6.9412	0.0663
OP – RAI-3	2.2911	0.8995 – 5.8357	0.1124

BP – biochemical persistence; CCND – central compartment neck dissection; CI – confidence interval; LCND – lateral compartment neck dissection; OP – overall persistence; OR – odds ratio; SLNB – sentinel lymph node biopsy; SP – structural persistence; RAI – radioiodine ablation; TTE – total thyroidectomy

structural persistence was 2.47 times higher ($p = 0.0373$), while being 2.12 times higher than overall persistence ($p = 0.058$), which was close to the threshold of significance. Biochemical persistence in Group 2 was 1.75 times higher, but this increase in risk was not statistically significant ($p = 0.3621$) (Tab. 3).

Nine months after surgery (at the time of the 2nd dose of RAI), the statistical analysis of patients from Group 3 as compared to Group 1, revealed that there was a 5.6 and 4.5 times higher risk of biochemical persistence ($p = 0.0012$) and structural persistence ($p=0.0052$), respectively and 4.85 times higher risk of overall persistence ($p = 0.0016$). When comparing Group 3 to Goup 1, twenty-one months after surgery (at the time of the 3rd dose of RAI), the risk of BP was 3.69 times higher ($p = 0.0262$), SP and OP were not statistically significant (but the p value for SP was borderline) (Tab. 4).

Discussion

The presence of metastases in the lymph nodes of the lateral neck compartment is an indication for therapeutic dissection (8, 9). The extent of surgery in patients with papillary thyroid carcinoma and nodal metastases in the LC remains controversial (selective or modified radical neck dissection). Despite the high incidence of LNM in the lateral neck compartment, the prophylactic dissection of this compartment in patients with PTC is not indicated, as it does not affect the prognosis of the disease (8, 10). Lateral compartment neck dissection is known to be associated with a large neck incision, longer operative time, and the risk of additional complications such as cervical dysfunction, pain, edema, lymphorrhea and injury to the nerves and vascular structures (11).

Large retrospective studies have analyzed the prognostic impact of lymph node metastases. Some authors have demonstrated that LNMs are not associated with shortened survival and as they are therapeutically affected by radioactive iodine treatment, the authors doubted the clinical significance of occult nodal metastases (5, 12). Other studies suggest that LNMs increase the risk of local recurrence and may influence cancer-specific survival (CSS) in some patients with PTC and predict systemic disease (13). Although metastases in the lateral neck compartment in PTC are common, the prognostic significance of occult metastases in this area remains controversial (11).

In Europe and the United States, prophylactic LCND is not routinely performed, mainly because of subsequent radioiodine ablation therapy (8, 10). According to the recently published recommendations of the Japanese Association of Endocrine Surgeons, prophylactic LCND is not recommended for patients with low-risk PTC. For intermediate- or high-risk PTC, it is recommended that prophylactic LCND should be considered individually based on prognostic factors, the patient‘s overall condition, and patient´s preference (14).

Although the prognostic significance of occult lateral compartment lymph node metastases in patients with PTC remains controversial, the identification of these patients by sentinel lymph node biopsy may be helpful in avoiding secondary surgery for lateral compartment recurrence.

Sentinel lymph node biopsy has reached consensus as a staging procedure in patients with breast cancer and malignant melanoma, but the role of SLNB in thyroid cancer is unclear. After its introduction by Kelemen et al (15) in 1998, many authors described the benefit of SLNB in patients with thyroid cancer (13, 16–19). However, some authors have reported that the clinical use of SLNB in the treatment of differentiated carcinoma appears to be uncertain due to the lack of importance of lymph node dissection for the prognosis of the disease and thus the absence of a clear benefit of SLNB in papillary thyroid carcinoma (20–22).

In the past two decades, many studies have evaluated the feasibility and utility of sentinel lymph node biopsy in patients with PTC, and most of these studies focused on performing SLNB instead of prophylactic central compartment neck dissection. However, there are few studies that have investigated the performance of SLNB in the lymph nodes in the lateral compartment in patients with PTC (23). In general, SLN detection is performed using vital dye, radioisotope technique (lymphoscintigraphy), or combined technique. The vital dye method for SLN identification is the most widely used technique overall, but the use of the radioisotope technique in patients with PTC is increasing over time (24). The blue-dye method offers several advantages, including simplicity of procedure, cost effectiveness, time efficiency, and independence from specialized equipment, as well as from the need for cooperation with nuclear medicine physicians. Furthermore, it does not result in radiation exposure of personnel who are in contact with the patient (7, 23, 25). Some authors report that this method has a higher sensitivity and a lower overall false-negative rate compared to the radionuclide technique, but the overall SLN identification rate for the vital dye alone has been determined to be lower than that for the radioisotope alone (26). According to a recent review and meta-analysis, the radioisotope technique had a slightly higher SLN identification rate than the blue-dye method and combined technique in patients with PTC. However, the sensitivity, specificity, overall accuracy of the method, and negative predictive value were almost similar among the three techniques (24, 27). Both the radioisotope and vital-dye techniques have demonstrated the presence of skip metastases or LNM in the lateral lymph nodes without CC involvement. This is particularly common in tumors located in the upper pole of the thyroid gland (28, 29). According to most reported series, the SLN is localized in 80–90 % of cases using the vital-dye method (18, 30, 31) and in 95–100 % of cases with the radionuclide technique (4, 32, 33). Some authors have suggested that a combination of both procedures provides an even better result (34–36).

The vital dye method facilitates the visualization of target tissues, which may be useful in combination with the radionuclide technique in the identification of SLNs using a gamma probe (34, 37). Studies reporting on the importance of the combined technique emphasize the greater accuracy of SLN identification compared to the vital dye alone, but this procedure is expensive and requires access to a radiology laboratory equipped with special equipment (7, 11).

One of the disadvantages of SLN identification by means of the radionuclide technique alone is the very short distance between the site of application of the radioisotope and the marked draining lymph nodes. The drawback of using blue staining lies in its lower sensitivity compared to the combined method. Yet, it is worth noting that even with lower the sensitivity, the blue-staining method sufficiently sensitive to detect SLN, as was the case in our study.

Based on anatomical knowledge we decided to apply Patent Blue dye to the upper pole of the thyroid gland. The decision was made considering that the flow of lymph to the lateral neck compartment is primarily directed from the upper part of the isthmus, as well as from the medial and cranial parts of both lobes of the thyroid gland (20). Tumors located in the upper third of the thyroid lobe have a significantly higher probability of LNM occurrence compared to tumors in the middle or lower location (23). However, in comparison to the radionuclide method, the application of Patent Blue dye to the upper pole of the thyroid gland in our study partially lowered the sensitivity by not being able to detect aberrant lymphatic drainage (primarily to the IIA cervical sector). We decided not to apply the Patent Blue dye intratumorally, due to the frequent occurrence of calcifications, cystoid changes and possible damage of the thyroid capsule (false extrathyroidal spread).

The primary goal of the sentinel lymph node biopsy in the lateral neck compartment is to achieve reliable staging of the disease and thus avoid unnecessary reoperation (neck dissection) and its complications, and provide and optimal and timely selective surgical treatment. The secondary goal lies in optimal planning of adjuvant radioactive iodine therapy and potential reduction of the risk of locoregional relapse. The aim of our method was to identify patients with N1 stage of disease at N0 in the central neck compartment, in whom RAI treatment was not indicated. The result of our study shows that patients benefit from early detection of macrometastases in the lateral neck compartment, which were below the limit of identification in imaging examinations (the limit of detectable LNM according to imaging methods is up to 5 mm) (38). We are planning a prospective study of patients with PTC located in the upper pole of the thyroid gland based on the results of our work.

Conclusion

In our study, we demonstrated that early identification of clinically occult macrometastases in the lateral neck compartment has a positive effect on the further course of the disease, namely that it enabled a significant reduction in the persistence, and recurrence of the disease, and thus also in the number of further interventions.

Diagnostic sentinel lymph node biopsy from the lateral neck compartment in patients with PTC improves the further patient management (simultaneous one-step lateral neck dissection, radioactive iodine treatment in T1 stage patients without metastases in the central neck compartment). This technique is relatively easy to perform, safe, applicable and feasible for selecting patients with positive lymph nodes suitable for modified radical neck dissection.

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