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ORIGINAL ARTICLE

Sentinel lymph node biopsy in clinically node negative patients with papillary thyroid carcinoma

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Summary

Purpose: *The incidence of histologically proven lymph node metastases (LNM) in papillary thyroid carcinoma (PTC) reaches 80%. According to different guidelines surgical management in clinically N0 (cN0) patients with PTC remains controversial. The purpose of this study was to investigate if sentinel lymph node biopsy (SLNb) using methylene blue dye is accurate in the detection of LNM in the lateral neck compartment in cN0 patients with PTC.*

Methods: *Enrolled were 153 cN0 patients with PTC. All underwent total thyroidectomy with central neck dissection and SLNb in the lateral neck compartment, using methylene blue dye as marker. Selective modified radical neck dissection was performed in cases of metastatic SLNs.*

Results: *Neck LNMs were histologically verified in 40.9% of the cases. Predictive factors for LNM were: males, younger than 45 years, tumors greater than 1cm, capsular and vascular invasion. The central neck compartment of LNM was predictive for lateral LNM in 80.5% of the cases. LNM were confirmed in 24% of SLNs in the lateral neck compartment, which were over 56% predictive of LNM to other dissected lateral LN. SLN identification rate (IR) was 91.8%. Sensitivity, specificity, positive value (PPV) and negative predictive value (NPV) were 85.7, 96.7, 88.3 and 95.9%, respectively. The overall accuracy of the method was 94.3%, with probability of 91.2% (ROC AUC, 95% CI; 84.2-98.3).*

Conclusion: *The proposed method of SLN biopsy using methylene blue dye is feasible, safe and accurate in the detection of LNM in the lateral neck compartment and may help in the decision to perform selective modified radical neck dissection in cN0 patients with PTC.*

Key words: *sentinel lymph node, papillary thyroid carcinoma*

Introduction

The first who demonstrated the potential usefulness of the sentinel lymph node biopsy (SLNb) concept in 1977 was Ramon Cabanas with his pioneering work on lymphatic drainage using lymphangiograms in 100 patients with carcinoma of the penis [1]. Many authors followed his idea and investigated the concept of SLNs in different malignant tumors. For more than 10 years SLNb has become standard of care for early breast cancer and skin melanoma patients without clinical evidence of metastases [2,3].

Papillary thyroid carcinoma (PTC) accounts for up to 80% of all thyroid malignacies. At the time of diagnosis of PTC, the incidence of lymph node metastases (LNM) ranges from 80 to 90%, based on studes in which prophylactic central and lateral neck dissection has been performed [4-7].

Although very common, in the last two decades LNM were recognized as a prognostic factor for disease recurrence and cancer specific survival, especially for older patients with large tumors and extra-thyroid extension [8-13].

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The extent of surgery of thyroid gland and cervical lymph nodes, and use of radioactive iodine therapy in papillary thyroid cancer, varies significantly and depends on which guidelines the endocrine surgeon should follow [14-18].

The subject of the current study is the surgical treatment of LNM that remain unrecognized on preoperative diagnosis, i.e. clinically node negative patients with PTC (cN0). Ultrasonography is a valuable and unavoidable tool for diagnosis of PTC and its metastases but its sensitivity is very low. Based on systemic reviews, ultrasonography detected only a small percentage of LNM while they were detected in much higher percentage postoperatively, after neck dissection [19,20].

There is general agreement that neck dissections are indicated in cases of clinically apparent LNM. The extent of operations on the lymph nodes ranges from "wait and see" principle substantiated the role of applying ablative I^{131} therapy and frequency of surgical complications (recurrent laryngeal nerve injury and hypoparathyroidism), especially for less experienced teams to prophylactic dissection of the central and lateral compartments due to the limited use of radioactive iodine therapy and significantly lower operating morbidity if dissection was done during primary operation [14-18].

The possibility that both central and lateral neck compartments can be primary metastatic sites for PTC together with the relatively low detection rate of LNM by ultrasonography has forwarded the idea of exploring the value and utility of SLNb in the lateral neck regions in patients with PTC [21].

Methods

This study was conducted at the Institute for Oncology and Radiology of Serbia from January 2004 to December 2011 on 153 consecutive patients with PTC without palpable and ultrasonically detected lymph node metastases (cN0). Patients with clinically suspicious lymph nodes (cN1) or with metastatic disease (M1) were excluded from the study. Diagnosis of PTC was made based on fine needle aspiration cytology and confirmed on frozen section analysis during operation and standard hematoxylin/eosin (HE) staining after operation.

All patients were injected intraoperatively with 0.2-0.5 ml 1% methylene blue dye peritumorably using 26 gauge needle and afterwards the capsule was coagulated to avoid dye leakage. For bilateral tumors, the same procedure was performed on the other lobe. In all patients total thyroidectomy with prophylactic central neck dissection (CND), as a standard procedure in our Institution, was done, as well as SLN checking in the lateral neck region. The lateral neck region above and below omohyoid muscle was explored, searching for blue stained lymph nodes. Blue stained lymph nodes (SLN) were removed and examined on frozen section histopathology (HP) analysis. If SLN were positive on frozen section, selective modified radical neck dissection (sMRND) was performed at the same time. If SLN were positive on definite histology, sMRND was performed as a reoperation after one week.

We performed 171 sentinel lymph node biopsies (SLNB) in the lateral neck compartments using methylene blue (153 patients and in 18 cases on both sides). During this standard procedure all parathyroid glands were preserved on their own venous–arterial pedicle, and recurrent laryngeal nerves were identified and followed to the entrance into the larynx.

Anti-thyreoglobulin antibody (Monoclonal Mouse Anti-Human Thyreoglobulin Antibody, Clone 2H11 + 6E1) was used to detect metastatic deposits of papillary thyroid carcinoma in lymph nodes with the Ultravision HRP Labeled Polymer (primary antibody and reagents were from Thermo-Labvision (Waltham, Massachusetts, USA).

Descriptive methods (frequencies, percentages, mean, standard deviation (sd), median and range) were used to summarize the data. Corresponding parametric and nonparametric tests were used for comparison of characteristics among different risk subgroups. Of the methods of analytical statistics in our work, we applied the x^2 test, Spearman's exact probability test of the null hypothesis (R), single-factor parameter (FX, FP) and nonparametric Kruskal-Wallis's test-(H) - analysis of variance, the multinomial logistic regression analysis, and

Table 1. Demographics and tumor characteristics

Characteristics	%
Gender	
Male	15
Female	85
Age (years)	
Mean (SD)	47.5 (14-76)
≤45	58.2
>45	41.8
Tumor size	
pT1a	57.2
pT1b	24.8
pT2	14.4
pT3	3.3
Histological variants	
Classic	73.2
Follicular	26.8
Capsular invasion	
Yes	26.8
No	73.2
Vascular invasion	
Yes	12.4
No	87.6
Multifocality	
Yes	34
No	66

Table 2. Characteristics of dissected and sentinel lymph nodes

Dissection	*No. of procedures*	*No. of dissected LN*	*Average no. of LN*	*Average no. of LNM*	*Max size of LNM (mm)*
Central	153	1280	7.49	4.35	7.06
SLNb	171	654	3.82	1.42	6.91
sMRND	52	661	12.71	4.20	9.07

LN: lymph nodes, LNM: lymph node metastases, sMRND: selective modified radical neck dissection

Kaplan-Meier survival curves. Sensitivity, specificity, PPV, NPV and the overall reliability of the methods were investigated by conventional methods and by means of (ROC AUC) curve. For statistical analysis we used the statistical package spss version 17.1. (IBM® SPSS® model 17.1).

Results

During the biopsy procedure stained SLNs were removed along with the surrounding non-SLNs. The average number of lymph nodes per biopsy was 3.8, from which 1.7 were stained (SLN), and 1.4 were metastatic. In total, 654 lymph nodes were removed, with the largest diameter being 6.9 mm.

All dissected SLNs were analyzed on frozen section and standard HE staining. Additional metastases in non-SLNs were found in another 1.8% of the cases. Out of a total of 171 procedures, metastases in contralateral SLNs were proven in 3.3% of the cases.

Following the positive pathohistology findings of SLNs, a total of 52 sMRND were performed and 661 lymph nodes were removed, with the average number of 12.7 per biopsy. The average number of malignant LN was 4.2, and their average size was 9 mm in the largest diameter. In summary, the average number of dissected lymph nodes of the lateral neck compartment during SLNb and sMRND was 16.6, of which 5.6 were metastatic (Table 2).

Metastases in SLNs were the only metastases in the lateral compartment in 43.9% of the cases. The presence of LNM in SLNs and in other dissected lateral lymph nodes was registered in 51.4% of the cases, while skip metastases was registered in 4.7% of the cases. Metastases in SLNs were predictive for additional lateral LNM in 56% of the cases.

Altogether, respecting the pTNM classification rules, LNM in the neck were histologically proven in 40.9% of cN0 patients with PTC. Metastases in the central compartment only (pN1a) had 16.9% of the patients, while 19.3% had LNM in both central and lateral compartments (pN1b) and an additional 4.7% of the patients had LNM only in the lateral neck compartment. The presence of LNM in the central neck compartment predicted LNM in the ipsilateral compartment in 80% of the cases. Distribution of metastatic and non-metastatic lymph nodes in the neck compartments is shown in Table 3.

Table 3. Distribution of metastatic (t) and non-metastatic (-) lymph nodes in the neck compartments

Neck compartments		*f*	%
Central	*Lateral*		
+	-	29	16.9
+	+	33	19.3
-	+	8	4.7
-	-	101	59.1
Total	171	100	

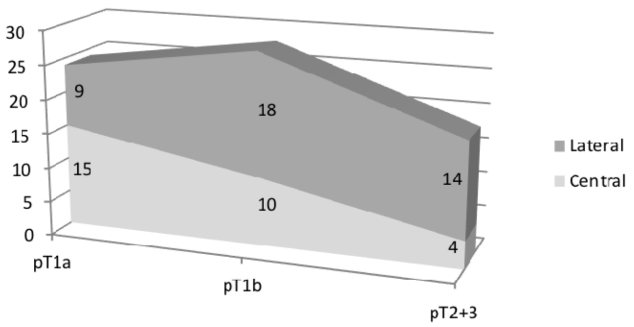

Figure 1. Distribution of LNM in neck compartments according the tumor size. x^2=7.505; df=2; p=0.023; p<0.05; r=0.311

In addition, we have analysed the distribution of LNM in the central and lateral neck compartments according to tumor size. Papillary microcarcinomas metastasize less frequently (statistically) to the lymph nodes of the neck, but when they do, they more often give metastases to the central compartment. Tumors larger than 1 cm, and especially over 2 cm metastasised significantly more often in the lateral region of the neck (p=0.023 (Figure 1).

The results obtained by multivariate logistic regression analysis showed that male gender (p=0.007), age less than 45 years (p=0.002), tumors larger than 1 cm in diameter (p=0.001) and tumor vascular invasion (p=0.024) were independent predictive factors for the existence of LNM in the neck. Multifocality, histological variants of PTC and capsular invasion did not have a predictive significance for the existence of LNM in the neck.

Table 4. Identification rate, sensitivity, specificity, PPV, NPV and overall accuracy of the sentinel lymph node biopsy technique

Diagnostic test	*Percentage (%)*
Identification rate	91.8
Sensitivity	85.7
Specificity	96.7
Positive predictive value	88.2
Negative predictive value	95.9
Overall accuracy	94.3

Area	*Std. Error*	*Asymptotic Sig.*	*Asymptotic 95% confidence interval*	
			Lower bound	*Upper bound*
0.912	0.036	0.000	0.842	0.983

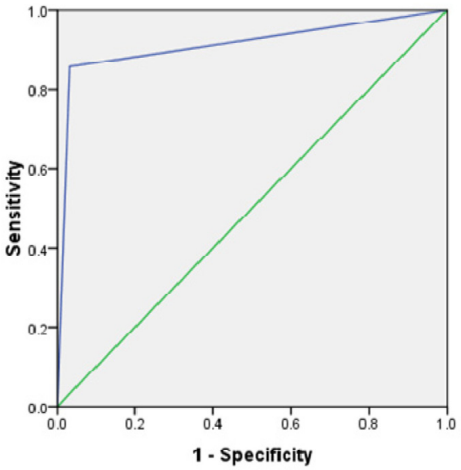

Figure 2. Accuracy of SLN biopsy method – ROC AUC. Diagonal segments are produced by ties

SLN identification rate (IR) was 91.8%. Sensitivity, specificity, PPV and NPV were 85.7, 96.7, 88.3 and 95.9%, respectively. The overall accuracy of the method was 94.3%, with probability of 91.2% (ROC AUC, 95% CI: 84.2 to 98.3) (Table 4, Figure 2). In the follow-up period (median 48 months) we did not register local or regional relapse of PTC. Lung metastases occurred in one patient (0.7%), diagnosed in the follow up by elevated serum thyroglobulin levels and confirmed on whole body scintigraphy with iodine 131.

Discussion

Despite the high prevalence of LNM, existing controversies regarding preoperative diagnosis, metastazing pathways in the neck, long-term prognostic impact and extent of lymph node surgery, motivated some authors to apply the concept of SLNb in differentiated thyroid cancer, taking into account the excellent results of SLN concept in breast cancer and skin melanoma [2,3]. In 1998 Kelemen et al were the first to perform SLNb in malignant thyroid neoplasms in 17 cases using vital dye [22].

By 2012, three meta-analyses were published investigating the SLN techniques, the use of different markers and the results of accuracy of all relevant studies.

The first meta-analysis published in 2008 by Raijmakers et al included 14 studies, of which 10 were used the vital dye, and four used radio-colloid (Tc99m). The identification rate was 83 and 96%, respectively. Sensitivity in studies with vital dye was 87.3%, and no sensitivity data were reported in the radio-colloid studies. The pitfall of this meta-analysis was the fact that not only thyroid malignancies were included in the analysis. In seven studies the percentage of thyroid malignancy was 88.6% (33-98%), while in other studies, all patients had thyroid cancer.

The second meta-analysis in 2011 by Balasubramanian and Harrison [24] presented 24 relevant original studies on the role of SLN biopsy in thyroid cancer. In 17 studies vital dye was used as a marker and in 4 radio-colloid, while in 2 studies the combination of these two markers was used. Identification rate (IR) was 83.7, 98.4 and 96%, respectively. Analysis of sensitivity, specificity and overall accuracy of the method was available in 12 studies with a vital dye, and only in one study with radio-colloid and combined method. The authors reported that 22.5% of SLNs had been identified by gamma probe in the lateral neck compartment, being the only SLNs in 14.8% of patients skipping central neck compartment. These results contribute to the controversy on the pathways of the primary lymphatic drainage in thyroid carcinoma. LNM were observed in 42.9% of the patients. The authors concluded that the SLNb method was promising in avoiding prophylactic dissection in almost 57% of patients with thyroid cancer and clinically negative lymph nodes [24].

For a long time, lateral neck compartment has been considered as secondary site of LNM, until Machens et al reported that 15% of patients had only metastases in the lateral neck region [21].

In our study, we found LNM in the lateral neck compartment in 24% of the cases. Metastases in SLNs were the only metastases in the lateral compartment in 43.9% of the cases. The presence of LNM in SLNs and in other dissected lateral lymph nodes was registered in 51.4% of the cases, while skip metastases were registered in 4.7% of the cases. Metastases in SLNs were pre-

dictive for additional lateral LNM in 56% of the cases.

The third meta-analysis published in 2012 by Kaczka and associates included 25 studies. They showed the advantage in IR of peritumoral injection of the vital dye compared to intratumoral application (92.2 and 71.8%, respectively). The IR of SLNs using methylene blue was superior to isosulfan blue and patent blue V (91.9, 86.1 and 68.3%, respectively). There were no differences in the IR between intratumoral and peritumoral applications of radio-colloid. LNM in the SLN were detected successively in 40.8, 39.9 and 52.1% of the cases, respectively [25]. In our study we reported the SLN IR of 91.8% which is higher than in studies with other dyes. In our study we have used methlylen blue dye which was proven to be safer regarding the adverse reactions patent blue V and Isosulfan blue dye [26-28].

Only few authors have searched SLNs in both neck compartments. In 2006 the results of a previous study by Dzodic and coworkers were included in all three meta-analyses. Until 2011, this concept of SLN biopsy in the lateral compartment was the only published in the relevant literature. LNM in the lateral neck compartment were histologically confirmed in 22.5% of the patients with clinically unaffected lymph nodes (cN0). SLN detection rate was 92.5%, sensitivity 77.7%, specificity 100%, PPV 100%, NPV 94%, while the overall accuracy of the method was 95% [29].

In 2011, two studies that have analyzed the results of SLNb in the lateral neck compartment were published. Ikeda presented the results of detection SLNb with Indocyanin green peritumoral application in 12 patients with PTC. The rate of detection was 100% as well as sensitivity, specificity and overall accuracy of the method. LNM in the lateral compartment were confirmed in 50% of the patients preoperatively staged as cN0 [30].

Lee et al included 94 patients with PTC, who had undergone SLN detection in the lateral compartment with intratumoral application of radiocolloid (Tc99m), preoperative lymphoscintigraphy and intraoperative hand-held gamma probe. The detection rate was 63.8%. The study included patients with PTC larger than 1 cm in diameter or evident central neck metastases. LNM in the lateral compartment were confirmed in 31.7% of cN0 patients. Approximately 93% of SLN was located in the ipsilateral compartment in the level III and IV, 4.6% in the level II and 2.3% in the third level of contraletaral neck compartment. The sensitivity and accuracy of the method were not tested in this study [31].

Lee et al. have investigated the usefulness of detection of occult metastases in SLN in the lateral neck compartment using 99mTc lymphoscintigraphy and SPECT/CT and found SLN metastases in 43.5%, concluding that SLNb is more useful for lateral than for central neck compartment in detecting metastases [32]. This is in accordance with our surgical strategy in which we always perform prophylactic central neck dissection and search SLNs in the lateral neck compartment. Our surgical team performed this method in microcarcinomas too, with high accuracy. Using SLNb 7% of patients with papillary thyroid microcarcinomas and cN0 were converted to pN1b stage [33].

In the most recent systematic review of 12 studies utilizing radio-colloid, the overall SLN IR, SLN metastatic rate, and false negative rate (FNR) were 92.1, 33.6, and 25.4%, respectively. The authors reported the presence of central lymph node metastasis in 23.0% and lateral in 10.6% and they suggested that SLN performed alone should be abandoned due to the high FNR, and converted into a technique to guide the lymphadenectomy in a specific neck compartment based on the radioactivity, regardless of the SLN status, for better lymph node staging and selection of patients for postoperative radioiodine ablation [34].

The SLN IR in our study was comparable with the IR in studies with radio-colloid as a marker, with high overall accuracy of 94.3% and probability of 91.2% (ROC AUC). We did not register locoregional relapse in a median of 48 months follow-up period.

Conclusions

Based on the results of this study we could conclude that our method of SLNb using methylene blue dye, is safe, feasible, and accurate in detecting occult lymph node metastases of PTC in the lateral neck compartment. Using methylene blue dye is cheap and does not require technical equipment.

The SLNb may prove of practical use in precise staging of cervical lymph node status, detection LNM outside the central compartment, the selection of patients who may benefit from timely selective neck dissections and thus optimizing the application of ablative radioiodine therapy.
Currently, there is no strong evidence that SLNb is associated with long-term benefit in terms of locoregional relapse and survival of patients with PTC.

Controlled randomized clinical studies with larger number of patients and longer follow-up will determine the clinical significance of occult LNM and their early detection by SLNb method in patients with PTC.

Acknowledgements

The study was reviewed by the Medical Ethics Committee of the School of Medicine in Belgrade, Republic of Serbia and performed in accordance with the ethical standards laid down in the appropriate version of the 1964 Declaration of Helsinki. Our study was approved by the Institutional Review Board of the Institute of Oncology and Radiology of Serbia and conducted with the understanding and consent of all subjects involved. The study was entirely financed by the project of the Ministry of Science of the Republic of Serbia: "Early diagnostic of lymph node metastases using sentinel lymph node biopsy in epithelial malignant tumors", 2005 (project number 111601). The study sponsors had no involvement in the study design, in the collection, analysis and interpretation of data, in the writing of the manuscript, and in the decision to submit the manuscript for publication.

Conflict of interests

The authors declare no conflict of interests.

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