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The importance of sentinel lymph node intraoperative frozen analysis for indication of lateral neck dissection in patients with medullary thyroid cancer

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Our research seeks to evaluate the utility of intraoperative frozen analysis of sentinel lymph nodes (SLNs) in the lateral cervical compartment (LCC) as a tool to inform decision-making regarding therapeutic neck dissection in patients with medullary thyroid carcinoma (MTC). This is particularly relevant due to the variability observed in guidelines regarding the indication for lateral neck dissection in this patient population. The study comprised 64 patients (25 males, 39 females) aged between 29 and 81 years, with a median age of 59, who underwent surgery for MTC at stage T1-3N0-1M0 between January 1, 2012, and December 31, 2020. A standardized surgical approach involving total thyroidectomy with central neck dissection was adopted. LCC dissection was reserved for patients with clinically apparent nodal metastases. In patients lacking clinical evidence of nodal involvement, SLNs were identified using patent blue dye, excised, and subjected to intraoperative frozen analysis. If metastasis was confirmed, LCC dissection was subsequently performed. Among the study participants, 14 individuals (21.9%) underwent therapeutic LCC dissection due to clinical lymph node (LN) metastases. This intervention resulted in clinical remission for 9 patients, while disease progression was observed in 5 cases, leading to 2 fatalities. In the remaining cohort of 50 patients clinically negative for nodal involvement, SLNs were successfully identified and examined in 38 cases, revealing metastases in 6 patients (15.8%). Among both subsets of patients with analyzed SLNs, irrespective of metastatic status, one patient each required repeat surgery due to disease recurrence; however, all patients eventually achieved clinical remission. Lymphatic mapping in the LCC plays a pivotal role in detecting early metastases, thereby aiding in the avoidance of unnecessary repeat neck surgeries, and ultimately improving the prognosis in patients with MTC.

Key words: medullary thyroid cancer; sentinel lymph node biopsy; lateral neck dissection

Medullary thyroid cancer (MTC), while accounting for a modest 4–5% of all thyroid cancers, often presents with metastatic disease at diagnosis, with 25–82% of patients having neck lymph node (LN) metastases and 7–23% presenting with distant metastases [1]. These metastases are significant negative prognostic indicators and substantially affect patient survival rates. In cases without neck metastases, patient remission rates stand at 100%, but these rates significantly decline to 27.4% after primary lateral cervical compartment (LCC) dissection and further to 13.5% following secondary dissections [2]. The medical community has yet to reach a consensus on when prophylactic lateral neck dissection is warranted, with recommendations varying across different guidelines [3, 4]. The agreement is only on therapeutic dissection as lateral neck dissection brings specific complications to patients – such as injuries to the accessory nerve (4.8–27%), chylous fistula (0.6–4.5%), bleeding (0.5–1%), and other rare complications (<1%) such as wound infections, seromas, and damage to neck sympathetic nerves, the phrenic nerve, and sensory nerves of the brachial plexus [5].

Given the crucial impact of metastasis detection on patient outcomes, there is a pressing need for indicators that can reliably predict the presence of metastases. These include tumor size, calcitonin levels, and the presence of a desmoid stromal reaction within the tumor, among others [6].

Sentinel lymph node biopsy (SLNB) has established itself as a gold standard in the management of other malignancies,

like breast cancer, and our previous positive experiences with SLNB in breast cancer management [7] have led us to explore its utility in MTC.

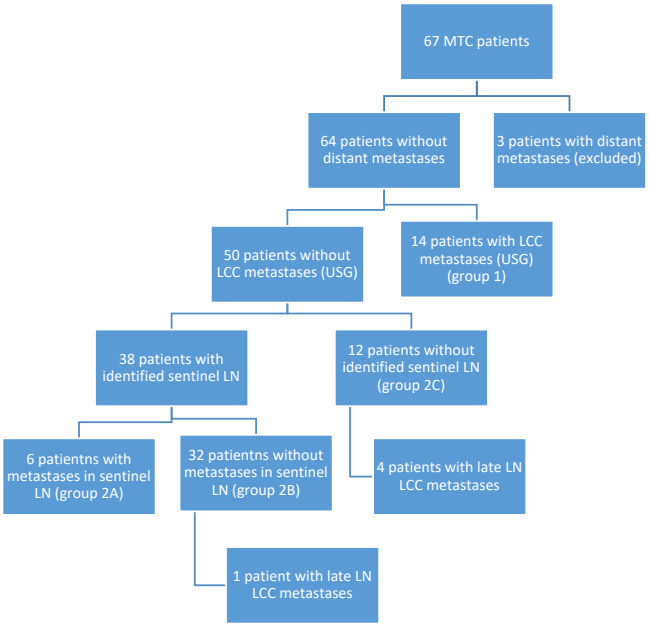
This study delves into the importance of early detection of LN metastases in the LCC for MTC patients at a clinically N0 stage. While the use of SLNB in medullary carcinoma has been documented in the literature [8, 9], its implications for patient prognosis remain under-studied, which is the gap our research aims to address.

Patients and methods

Our comprehensive single-center study spanned nine years, from January 1, 2012, to December 31, 2020, during which 1,135 patients with thyroid cancer underwent surgery at the Department of Surgical Oncology, St. Elisabeth Cancer Institute in Bratislava. Among these, 67 had MTC, and 20 of these patients required lateral neck dissection. Our stringent inclusion criteria selected MTC patients who were free of distant metastases at the time of their initial surgery and classified as T1-3N0-1M0.

The data are presented as median (interquartile range) or number (percentage). Continuous characteristics were assessed using Kruskal-Walli's test, while categorical variables were analyzed using the χ^2 test or Fisher's exact test. Assuming the order of the groups being compared, the Cochran-Armitage test for linear trend provides a more reliable estimate than Pearson's Chi-squared test. A p-value ≤0.05 was considered statistically significant.

In our study group of patients, we did not notice any adverse effects or complications associated with the administration of methylene blue or with a surgical procedure.



The study adhered to ethical standards and was approved by the ethics committee of the St. Elisabeth Cancer Institute on April 17, 2020 (N. 09/2020).

Results

After excluding 3 patients due to distant metastasis, 64 patients, comprising 25 men and 39 women with a median age of 59 years (29–81), formed our cohort (see flowchart). The median calcitonin level within this group was 685 pg/ml (3.5–57.500 pg/ml), with a follow-up period averaging 5.5 years (2–10) [2–7, 10–12].

Each patient underwent a standard total thyroidectomy and central neck dissection (see flowchart). Before the surgery, ultrasonography was used to categorize the patients into two distinct groups.

The first group (Group 1) with pre-operatively confirmed metastases in the lateral neck compartment, who then underwent therapeutic lateral neck dissection (positive control).

The second group (Group 2), did not show metastases in imaging examinations (ultrasound examination (USG), CT scan, PET scan). During surgery, this group received an injection of 0.1 ml of patent blue dye (PBD) in the upper poles of both thyroid lobes. This allowed for the identification and removal of blue-stained SLNs from LCC (sector IIA, III, and IV). The excised LNs were sent for immediate frozen sections and definitive histological examination. Group 2 included Group 2A, indicating moderate risk with intraoperatively detected metastases in these compartments via sentinel node biopsy (study group), prompting therapeutic dissection of the corresponding lateral compartment; Group 2B, representing the lowest risk with no detected metastases in the lateral and central compartments of the neck (negative control); and Group 2C with not-visualized SLNs, and also without lateral neck dissection.

Out of the cohort, 52 patients (Group 1, 2A, 2B) met the inclusion criteria for the study, and their general characteristics are summarized in Table 1. This table also includes a statistical evaluation of the risk associated with individual characteristics, which were used to stratify patients into groups based on the severity of their disease.

Clinical remission was defined as a negative or stabilizing trend in calcitonin and CEA levels without the presence of metastases on imaging exams, whereas disease progression was identified by rising calcitonin levels or the emergence of new metastases. We statistically evaluated general risk factors for both disease recurrence and progression, comparing groups of patients with preoperatively detected metastases who underwent therapeutic dissection (Group 1), and those with intraoperatively detected metastases through sentinel biopsy (Group 2A) and negative SLNs (Group 2B).

The first group consisted of 14 patients with pre-operatively confirmed metastases in the lateral neck compartment (metastasis size 14–50 mm, median 28.5 mm, Table 1), who then underwent therapeutic lateral neck dissec-

Table 1. Baseline demographic and clinical characteristics of the patients (N=52).

	Total		Negative control		SNB detection of mts		Positive control		p-value
Patients (count, %)	52	100%	32	100%	6	100%	14	100%	n.a.
Sex									
Female	30	57.7%	24	75.0%	6	100%	0	0%	<0.0001
Male	22	42.3%	8	25.0%	0	0%	14	100%	
Age	59.5	43.5–66	60.5	46.5–66	54	43–70	58	42–67	0.9123
Tumor size	20.5	10–27.5	19	10–25	20	8–25	28.5	14–50	0.0971
Calcitonin	701.6	268.5–1391	488.5	104.5–1105	1060.5	585–1313	1384	685–2959	0.0071
CEA	14.3	2.4–65.5	10.5	2.1–42	15.1	2.1–56	61.9	7.2–219	0.0990
Multifocality									
Yes	13	25.0%	3	9.4%	1	16.7%	9	64.3%	0.0004
No	39	75.0%	29	90.6%	5	83.3%	5	35.7%	
Extrathyroidal									
Yes	9	17.3%	0	0.0%	2	33.3%	7	50.0%	
Propagation									0.0001
No	43	82.7%	32	100%	4	66.7%	7	50.0%	
Angioinvasion									
Yes	17	32.7%	4	12.5%	3	50.0%	10	71.4%	0.0001
No	35	67.3%	28	87.5%	3	50.0%	4	28.6%	

Notes: continuous variables are presented as median (1st-3rd quartile) and compared with Kruskal-Walli's test; categorical variables are presented as count (n; % of group total) and compared with Chi-square test or Fisher's exact test

tion. The second group, comprising 50 patients, did not show metastases in imaging examinations. During surgery, 1–6 (median 3) of blue-stained SLNs were identified and removed from LCC in 38 patients. Our analysis revealed early metastases in 6 patients (Group 2A). Median size of the metastasis was 2 mm (0.59–3 mm). The remaining 32 patients, showing no metastases, did not undergo further dissection (Group 2B).

Within our larger group of 64 patients, 24 were found to have metastases in the lateral neck compartment, detected through various diagnostic means including preoperative ultrasonography, intraoperative SLNB histology, and reoperation. The prevalence of metastases in the LCC not detected in preoperative imaging examinations (shown by SLNB) was 18.42% (CI 7.74–34.33%). The predictive value of a positive sentinel biopsy was 100 (CI 54.07–100%), and the predictive value of a negative test was 96.88% (CI 83.78–99.92%). The mean residual risk of metastases in the LNs of LCC is 3.13% (CI 0.08–16.22%) with a negative test. The sensitivity of the sentinel lymph node method was 85.71% CI 42.13–99.64%), and its specificity was 100% (CI 88.78–100%). In the case of not-visualized SLNs, the prevalence of metastases in LCC during follow-up was about 25%.

We noted a statistically significant linear increase in the prevalence of several individual characteristics, including male gender, elevated calcitonin levels, tumor multifocality, extrathyroidal extension, angioinvasion, and metastases in the central neck compartment. This trend was evident across the groups, starting from 12.5% in patients with no preoperative or perioperative findings, rising to 33.3% in patients with early perioperative histological detection, and reaching 85.7% in patients with preoperatively detected metastases.

Regarding disease activity and progression, the Cochran-Armitage Chi-squared test for linear trend confirmed a statistically significant relationship between an unfavorable outcome and a poorer initial clinical condition, progressing from negative control through early detection of metastases to positive control (Table 2). Patients with early detection of LN metastases via SLNB (group 2A) exhibited a prognosis very similar to patients without detected LN metastases (group 2B). However, although the risk of recurrence in terms of LN metastases in the LCC was 6.2 times higher (odds ratio), no statistically significant difference was found. Conversely, patients with preoperatively identified LN metastases in the LCC demonstrated a significantly worse prognosis.

Group 2C of patients, where SLNs were not visualized, constituted 24% (12 out of 50 patients). Among them, 4 patients (25%) subsequently exhibited persistent LN metastases.

Discussion

The cornerstone of successful management for patients with MTC lies in identifying individuals with clinically apparent (N1b-stage) and USG or CT evident (N0-stage) metastases necessitating therapeutic dissection, while also exercising caution to prevent overtreatment of those not requiring LCC dissection. Consequently, many guidelines for managing and treating MTC advocate for prophylactic lateral cervical dissection [3]. However, research by Yamashita et

Table 2. Clinical outcomes of the patients (N=52).

	Recurrent metastases in LCC after surgery						
	Total		no		yes		p-value
Count, %	52	100.0%	45	86.5%	7	13.5%	n.a.
Negative control	32	61.5%	31	68.9%	1	14.3%	
Early detection of metastases	6	11.5%	5	11.1%	1	14.3%	0.0115
Positive control	14	26.9%	9	20.0%	5	71.4%	
Total	52	100.0%	45	100.0%	7	100.0%	
	Disease progression						
	Total		no		yes		p-value
Count, %	52	100.0%	43	83.0%	9	17.0%	n.a.
Negative control	32	61.5%	32	74.4%	0	0.0%	<0.0001
Early detection of metastases	6	11.5%	6	14.0%	0	0.0%	
Positive control	14	26.9%	5	11.6%	9	100.0%	
Total	52	100.0%	43	100.0%	9	100.0%	

al. [12] indicates that prophylactic LCC dissection does not decrease the risk of locoregional or overall disease recurrence, nor does it alter patient prognosis.

The presence of a desmoid stromal reaction in the primary tumor emerges as a promising prognostic marker in patients with clinically N0 disease stage [2, 6]. However, preoperative identification of this reaction necessitates the expertise of a skilled pathologist examining an adequate number of histological specimens. In the study by Scheuba et al. [6], approximately one-quarter of patients lacked a desmoid stromal reaction, leading to the avoidance of LCC dissection. Among the remaining patients with a positive desmoid stromal reaction, LCC dissection was conducted in three-quarters of cases, revealing early neck metastases in 25.8% of patients. This raises the question of whether 74.2% of patients in this group were subjected to unnecessary overtreatment.

SLNB has proven to be a reliable diagnostic tool for various malignancies such as breast cancer, malignant melanoma, and others. When employing two markers, namely patent blue and a radioactive tracer, the method demonstrates a specificity and sensitivity of approximately 96%. However, the use of a single marker reduces these figures to around 86% [7]. Drawing from the successful application of this methodology in breast cancer, we sought to explore its utility in medullary carcinoma. Kim et al. [9] in their investigation utilizing the radiopharmaceutical ^{99m}Tc, identified sentinel nodes in 87.5% of patients with MTC. Near-infrared (NIR) fluorescence imaging is a newly emerging. The use of ICG for lymphatic mapping techniques offers the ability to use NIR to visualize lymphatic anatomy and flow directly and instantly. In their work, Zang et al. [14] described similar sensitivity and specificity of using ICG and carbon nanoparticles as using 99-TC and patent blue. However, this technique requires specific machinery. The sensitivity was 83.3% (10/12) with a false negative rate of 16.7%. In our study, employing patent blue, we detected sentinel nodes in 76% of patients. While this figure is somewhat lower than that achieved with 99-Tc or ICG, the use of patent blue offers advantages in perioperative management due to its simplicity.

In our study cohort, preoperative detection of LN metastases occurred exclusively in men, and disease progression, both biochemically and morphologically, was observed solely in this group, resulting in some cases of mortality. Conversely, advanced cancer with metastases was not detected preoperatively in women. Early metastases, identified through SLN examination, were observed in six female patients, all of whom achieved a cure. Intriguingly, early metastases in sentinel nodes were absent in men, who comprised the negative prognosis group. Male gender emerged as a robust negative prognostic risk factor. While the female gender presented a lower risk profile compared to males, the status of the six women with early metastases (detected via SLNB and histological examination, despite negative imaging results) raises questions about their potential risk if LCC dissection had not been performed. Notably, LCC dissection was avoided in 38 patients, thus sparing them from unnecessary intervention.

A therapeutic challenge arises in the subgroup of patients classified as clinically N0 stage, where SLNs were not visualized (Group 2C), and among them, 25% of patients subsequently exhibited persistent LN metastases. One possible explanation could be that after the injection of PBD into the thyroid parenchyma, it enters lymphatic vessels rapidly, accumulates in the lymph nodes, and stains them blue. However, lymphatic vessels partially blocked by cancer cells can affect the staining process, and the presence of small metastases measuring up to 4–5 mm in size, which might have evaded detection during ultrasound examinations. The same situation is also described in breast cancer, in which case exenteration of the ipsilateral axilla is recommended [15]. Drawing from these observations, we also advocate for considering prophylactic (diagnostic) LCC dissection in cases where SLNs are not visualized.

Our research suggests that SLNB may offer a viable method for diagnosing early metastases in the LCC in MTC. Additionally, in patients exhibiting a positive desmoid stromal reaction, SLNB could serve as an adjunctive method for refining patient selection. We acknowledge that our findings may be influenced by the comparison of a relatively small patient cohort, and further studies are warranted to explore the utility of SLNB in MTC comprehensively.

In conclusion, early detection of metastases in patients with MTC and subsequent removal are crucial for successful patient management. SLNB performed at the clinically N0 stage shows promise as a method to identify patients with histologically N1 stage disease who require lateral neck dissection.

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