ORIGINAL RESEARCH

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The Effect of Central Lymph Node Dissection Before Thyroidectomy on Incidental Parathyroidectomy in Patients with Thyroid Cancer

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Abstract

Objective
It is the fact that the incidence of thyroid cancer has been increasing recently. Thyroid cancer often tends to metastasize to the cervical lymph nodes and as a result, central region lymph node dissection increases the risk of incidental parathyroidectomy. In this study, the effect of two different surgical techniques on incidental parathyroidectomy (IP) has been investigated.

Material and Method
A total of 115 patients who underwent bilateral total thyroidectomy (BTT) and cervical neck dissection (CND) for thyroid cancer at the Department of General Surgery Clinics have been included in the study. Patients were divided into two groups according to the surgical technique used. The first group consisted of patients who underwent CND after thyroidectomy. The second group consisted of patients who underwent lateral neck dissection (LND) before CND or then underwent CND after ligation and transection of the middle thyroid vein and, if necessary, the superior thyroid artery.

Results
Incidental parathyroidectomy (IP) has been identified in the pathology specimen in 47.4% (54) of the patients. While IP was performed on 1 gland in 29.8% (34) of the patients in group 1, on 2 glands in 14% (16), and on 3 glands in 3.5% (4) of the patients, no IP was detected in group 2 ($p < 0.001$). It was observed that hypoparathyroidism did not develop in patients in the second group. However, 12.3% (14) of the patients who underwent BTT followed by CND developed transient hypoparathyroidism and 3.5% (4) of them developed permanent hypoparathyroidism. When the collected data is analyzed, it has been concluded that the tumor size and the diameter of the largest metastatic lymph node are significantly larger in men than in women ($p < 0.001$ and $p < 0.001$, respectively).

Conclusion
IP is commonly encountered in thyroid surgery. It is concluded that performing CND and LND before thyroidectomy might reduce IP.

Keywords: Thyroid carcinoma, lymph node metastasis, central compartment lymph node dissection, postoperative hypoparathyroidism, incidental parathyroidectomy

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Introduction

It is a known fact that well-differentiated thyroid cancers include papillary, follicular, and Hurthle cell carcinomas. Also, other thyroid cancers include medullary thyroid cancer (MTC) and anaplastic thyroid cancer (1, 2). Over the past decade, the incidence of papillary thyroid cancer (PTC), which accounts for 80-85% of thyroid malignancies worldwide, has steadily increased (3, 4). The prognosis of PTC is generally more favorable when it is compared to other thyroid malignancies (4, 5). In PTC, the incidence of cervical lymph node metastasis (CLNM) can reach 20-50% (6, 7). In PTC patients, CLNM is the primary risk factor for high recurrence rates (8, 9). The presence of CLNM is a positive predictive factor independent of tumor size (10, 11). Other factors influencing CLNM include gender (male), age (<45 years), bilaterality, extrathyroidal extension, multifocality, tumor size >1 cm, and the presence of capsular or lymph vascular invasion in the tumor (10-13).

MTC is a neuroendocrine neoplasm that originates from the parafollicular C-cells of the thyroid. It frequently metastasizes to cervical lymph nodes (14). Serum calcitonin levels are directly proportional to tumor size and the number of metastatic lymph nodes (15). Therefore, the decision to perform lymph node dissection is based on the assessment of serum calcitonin levels (16).

Some studies have reported that the female gender is an independent risk factor for hypoparathyroidism (17, 18), while other studies have failed to obtain similar results (19, 20). During central neck dissection (CND), temporary or permanent hypoparathyroidism is thought to occur due to traumatic or ischaemic damage (21, 22). This condition may also result from an incidental parathyroidectomy performed accidentally during lymph node dissection (23). In addition, whether CND is performed unilaterally or bilaterally may have different effects on transient and permanent hypoparathyroidism (24). However, some studies do not report a significant relationship between postoperative hypoparathyroidism and CND (25, 26). The short vertical length of the thyroid gland and the presence of small nodules increase the risk of incidental parathyroidectomy (27). Surgeon experience and higher volumes of thyroid surgery performed in surgical centers lead to a reduction in incidental parathyroidectomy (28). For these reasons, in this study, the effects of thyroid capsule invasion (CI), lymph vascular invasion (LVI), and multicentricity on LNM and the largest metastatic lymph node in patients undergoing bilateral total thyroidectomy (BTT) along with CND and/or lateral neck lymph node dissection (LND) for thyroid cancer have been investigated. Besides, the impact of two different surgical techniques on incidental parathyroidectomy (IP) has been evaluated.

Material and Method

The study has been conducted following the approval by the Clinical Research Ethics Committee on 21 June 2023 under decision number 3746. Firstly, 128 patients who underwent bilateral total thyroidectomy (BTT) and cervical neck dissection (CND) for thyroid cancer at the General Surgery Clinic between 1st March 2019 and 1st March 2023 have been included in the study. All patients enrolled in the trial were aged 18 years or older. The research has been conducted under the World Medical Association (WMA) Declaration of Helsinki Ethical Principles for Medical Research on Human Volunteers and related guidelines/regulations. Patients were informed about the study in advance. An informed consent was obtained from all patients who enrolled in the study. Ten patients were found to have undergone thyroid surgery for thyroid cancer at another medical center, and for this reason, they were excluded from the study. Of the remaining patients, a total of 115 patients had the necessary surgical and

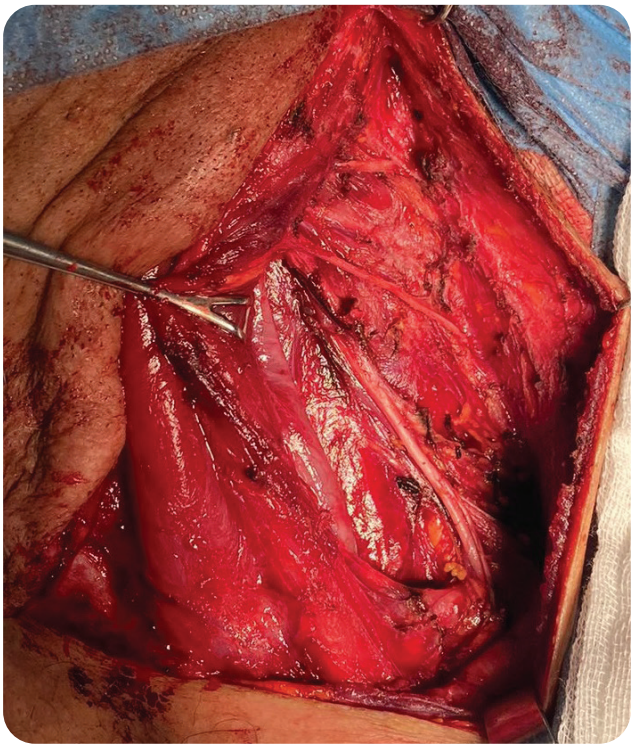

Figure 1
Operative view of the patient who first underwent left LND, before proceeding to left CND.

pathological reports and other data required for this study. Patients were divided into 2 groups according to the surgical technique used. The first group consisted of patients who underwent CND after thyroidectomy. The second group consisted of patients who underwent lateral neck dissection (LND) before CND and or then underwent CND after ligation and transection of the middle thyroid vein and, if necessary, the superior thyroid artery (Figure 1-2).

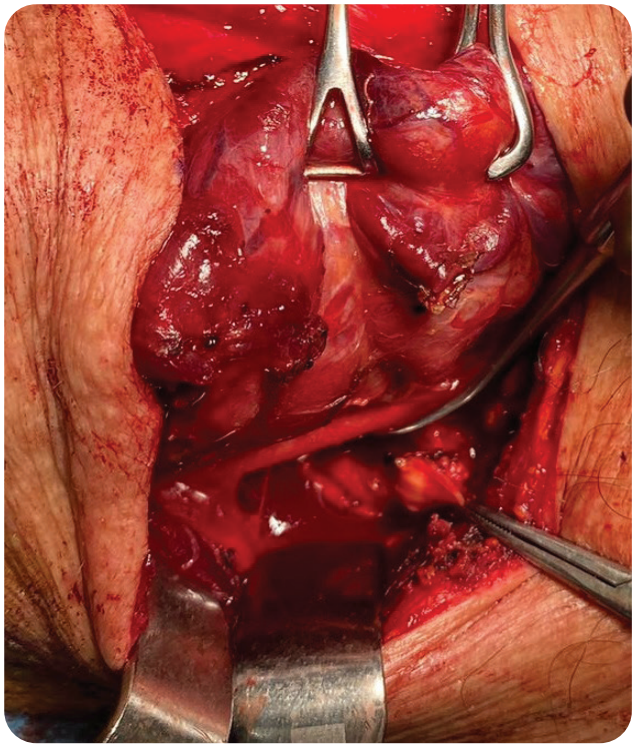

Figure 2
Image of the same patient's thyroid lobe taken before right CND after the lobe has been displaced upwards and towards the midline.

Patient records have been reviewed by evaluating data related to various factors such as age, sex, tumor histopathology, tumor size, type, differentiation, thyroid capsule invasion (CI), lymph vascular invasion (LVI), extrathyroidal extension, number of metastatic lymph nodes, the diameter of the largest metastatic lymph node, and the presence of incidental parathyroidectomy (IP). In the follow-up assessments whether a second operation was performed because of lymph node metastasis or residual tissue has also been checked. Patients with normalized serum PTH levels at 1-year postoperative follow-up were considered to have transient hypoparathyroidism and patients without normalized serum PTH levels were considered to have permanent hypoparathyroidism.

Statistical Analysis
The Shapiro-Wilk test is used to determine whether the data show a normal distribution between the groups subjected to different surgical techniques. For the analysis of categorical variables, the Pearson Chi-Square test is used to assess the significance of differences between groups, whereas, for non-categorical data, the Mann-Whitney U test is used to assess the significance of differences between groups. To evaluate the relationship between the presence of CI, LVI, and tumor size, a ROC curve was constructed, and the cut-off value was determined.

Results

Of the patients included in the study, 35.7% (41) are male and 64.3% (74) are female. The median age of the patients in group 1 is 47 years (minimum: 18, IQR: 28, maximum: 80), and the median age of the patients in group 2 is 35 years (minimum: 29, IQR: 52, maximum: 81). In terms of the presence of CLNM and the gender of the patient, it has been observed that there is no significant relation (p=0.446). Similarly, between the presence of CLNM and the age of the patient less than 45 years, there has also been no significant relation (p=0.774). There has been no significant difference between the operation times in terms of both surgical techniques (time spent for LND was excluded) (p = 0.129). The mean operative time is 158.75±30.69 minutes. Of the patients, 1.7% (2) had poorly differentiated thyroid carcinoma, 1.7% (2) had Hürthle cell carcinoma, 1.7% (2) had NIFTP, 10.4% (12) had medullary carcinoma, and 83.5% (97) had PTC. In the pathology of PTC cases, 4.1% (4) were microcarcinomas, 64.9% (63) were classic, 8.2% (8) were follicular, 8.2% (8) were mixed, 2.1% (2) were hobnail, 4.1% (4) were oncocytic, 4.1% (4) were tall cell, and 4.1% (4) were Warthin tumor-like variants (Table 1). The mean tumor size of thyroid cancer was 2.17±1.8 cm (minimum: 0.1, median: 1.5, maximum: 9 cm). The median tumour size in men was 2 cm (minimum: 0.1, IQR: 3.1 cm, and maximum: 9 cm), and 1.4 cm in women (minimum: 0.6, IQR: 0.8 cm, and maximum: 6.8 cm). A ROC curve was generated to determine the significance of the relationship between LVI and tumor diameter. Tumor size was significantly higher in men than in women (p < 0.001). The ROC curve was used to show the relationship between LVI and tumor diameter and the cut-off value for tumor diameter was determined to be 1.55 cm. While no significant association has been found between the tumor size and CI, a significant association has been observed with multifocality and LVI (Tables 2-3). The median size of metastatic lymph nodes was 1.5 cm (minimum: 0, IQR: 4.2 and maximum: 8) in men

Table 1 The pathology of patients who underwent neck lymph node dissection

N	%	Histopathology
2	1.7	Poorly Differentiated
2	1.7	Hurtle
2	1.7	NIFTP
12	10.4	Medullary
4	3.5	PTC Microcarcinoma
8	7	PTC Follicular variant
8	7	PTC Mixt variant
2	1.7	PTC Hobnail variant
4	3.5	PTC Oncocytic variant
4	3.5	PTC Tall cell variant
4	3.5	PTC Warthin variant
63	54.8	PTC Classic

Table 2 The comparison of tumor diameter and some pathological parameters

		N	Mean Rank	Test Value	p value
LVI	No	46	38.1	670	< 0.001
	Yes	69	71.3		
CI	No	37	22.9	1018	0.011
	Yes	78	63.4		
MC	No	58	66.9	1132	0.003
	Yes	57	48.9		

LVI: lymphovascular invasion, CI: capsule invasion, MC:multisentricity, N: number. Mann-Whitney U test was used.

and 1 cm (minimum: 0, IQR: 0.8 and maximum: 3.6) in women. The size of metastatic lymph nodes was significantly higher in men than in women ($p < 0.001$). It has been observed that there is a significant relationship between metastatic lymph nodal size and LVI and CI (Table 4). Besides, no significant relationship has been found between multifocality and metastatic lymph node size ($p = 0.063$). In the group that underwent BTT followed by CND, 12.2% (14) of the patients underwent prophylactic central lymph node dissection, and no lymph node metastases were detected in these patients. The pathological examination of these patients revealed that there has been multicentricity in 6 cases, capsule invasion in 6 cases, and lymph vascular invasion in 2 cases. In patients with MTC (8), 67% had a serum calcitonin level >200 ng/L and underwent bilateral CND and bilateral LND in addition to BTT. Two other patients received bilateral CND and unilateral LND in addition to BTT. Patients with lymph node metastases had an average of 6.89±8.38 lymph nodes with metastases. There is no significant relationship detected between Hashimoto's disease and the number of lymph nodes removed in CLNM and CND ($p = 0.835$, $p = 0.318$,

Table 3 The comparison of pathological parameters according to the cut-off value determined for tumor diameter after taking the ROC curve

			Tumor Diameter		Total	p value
			<1.55 cm	≥ 1.55		
LVI	No	N	40	6	46	<0.001
		%	87	13	100	
	Yes	N	28	41	69	
		%	40.6	59.4	100	
CI	No	N	28	9	37	0.013
		%	75.7	24.3	100	
	Yes	N	40	38	78	
		%	51.3	48.7	100	
MC	No	N	26	32	58	0.002
		%	44.8	55.2	100	
	Yes	N	42	15	57	
		%	73.7	26.3	100	

LVI: lymphovascular invasion, CI: capsule invasion, MC:multisentricity, N: number. Mann-Whitney U test was used.

Table 4 The comparison of metastatic tumor diameter and some pathological parameters

		N	Mean Rank	Test Value	p value
LVI	No	46	40.9	804	<0.001
	Yes	69	69.4		
CI	No	37	45.1	964	0.004
	Yes	78	64.1		

LVI: lymphovascular invasion, CI: capsule invasion, N: number. Mann-Whitney U test was used.

Table 5 The effect of neck lymph node dissection surgical approaches on IP

Neck Lymph Node Dissection Approach		N	Mean Rank	p value
Incidental Parathyroidectomy	BTT after CND	94	63.5	<0.001
	LND and/or CND after BTT	21	33.3	
	Total	115		

BTT: bilateral total thyroidectomy, CND: central neck lymph node dissection, LND: lateral neck lymph node dissection, N: number. Mann-Whitney U test was used.

Table 6 The need for re-operation after surgical approaches to neck lymph node dissection

Neck Lymph Node Dissection Approach		Reoperation		p value
		No	Yes	
BTT after CND	N	74	20	0.104
	%	78.7	21.3	
LND and/or CND after BTT	N	13	8	
	%	61.9	38.1	
Total	N	87	28	
	%	75.7	24.3	

BTT: bilateral total thyroidectomy, CND: central neck lymph node dissection, LND: lateral neck lymph node dissection, N: number. Pearson Chi-Squared test was used.

respectively). Incidental parathyroidectomy (IP) was found in pathology specimens in 47.4% (54) of patients. Among these patients, 29.8% (34) had 1 parathyroid gland removed, 14% (16) had 2 glands removed, and 3.5% (4) had 3 parathyroid glands removed. The median number of IPs was 1 (minimum: 0, IQR: 1, maximum: 3) in patients who underwent BTT followed by CND and/or LND, whereas only 1 IP was detected in patients who underwent LND and/or CND followed by BTT. It has been observed that there has been a significant reduction in the number of IPs in patients who underwent LND and/or CND followed by BTT ($p < 0.001$) (Table 5). No hypoparathyroidism occurred in patients who underwent LND and/or SND followed by BTT, whereas in patients who initially underwent BTT+CND, 12.3% (14) had transient hypoparathyroidism and 3.5% (4) had permanent hypoparathyroidism. When the need for re-operation due to the detection of central lymph node metastasis at follow-up has been evaluated, it is detected that there is no significant difference between surgical techniques ($p = 0.104$) (Table 6). While 11.55±5.15 lymph nodes were dissected in CND in patients who underwent thyroidectomy first and then thyroidectomy, 12.8±4.1 lymph nodes were dissected in patients who underwent CND first and then BTT. It has been revealed that there is no statistically significant difference between the two methods ($p = 0.104$).

Discussion

The primary result of our study was that patients who underwent thyroidectomy after lateral neck dissection or central lymph node dissection were at a lower risk of developing incidental parathyroidectomy and hypoparathyroidism than those who underwent thyroidectomy first. The secondary results of our study are that as tumor diameter increases, LVI and CI increase, while MC decreases. As the metastatic lymph node diameter increases, LVI and CI positivity increases.

Overall, CLNM in PTC typically occurs first in the central compartment, and then it spreads to the lateral compartment (29-32). Although positive CLNM is associated with a higher regional recurrence rate, it has little significance in terms of mortality. There is a consensus that therapeutic central neck lymph node dissection (CND) should be performed in CLNM-positive PTC patients, but the question of whether prophylactic CND should be performed in clinically node-negative PTC patients remains controversial (33, 34). Therefore, routine prophylactic CND has not been performed in our clinic. Prophylactic dissections performed in suspicious cases did not reveal metastatic lymph nodes. In addition, in the group that underwent LND and/or CND before BTT, all patients had lymph node metastasis in the lateral compartment, and these patients included those with lymph node metastasis detected by fine-needle aspiration biopsy before surgery. Of the patients who underwent BTT followed by CND, 12.3% (7) underwent prophylactic CND. While the impact of CND on reducing locoregional recurrence rates remains uncertain, it does increase the risk of recurrent laryngeal nerve (RLN) paralysis and hypoparathyroidism (35, 36). Permanent hypoparathyroidism is more common in patients who undergo bilateral CND than in those undergoing unilateral CND (37). Incidental parathyroidectomy is mainly due to prophylactic and therapeutic CND. However, performing more lymph node dissections during CND does not increase the incidence of IP (38).

Although IP is less common when CND is performed by experienced surgeons, it is important to carefully identify and protect the parathyroid glands during surgery (39).

Thyroidectomy performed by ligating the main trunk of the inferior thyroid artery results in a significantly higher rate of hypoparathyroidism than when the branches of the inferior thyroid artery are ligated near the thyroid capsule (40). The close connection of the thyroid arteries and veins to the thyroid capsule preserves the supply to the parathyroid gland and reduces the development of hypoparathyroidism, even in patients undergoing SND (41). In previous studies, it is thought that IP occurs as a result of the mixing of parathyroid glands with central region lymph nodes due to CND after thyroidectomy. Our study suggests that performing CND only after ligating the middle thyroid vein before BTT, together with careful identification and preservation of the parathyroid glands during BTT, can prevent IP. In this study, it has been detected that there is no statistically significant difference between the two techniques in terms of the need for a re-operation due to the detection of lymph node metastases during the postoperative follow-up period.

The retrospective design of the study can be represented as its weakness. On the other hand, the strengths of the study include its conduct in a center specializing in thyroid surgery, well-maintained records, and regular patient follow-up and monitoring.

In conclusion, similar to previous studies, in this study, it has been found that the size of the largest metastatic lymph node is associated with CI and LVI, and performing CND before BTT might prevent IP. In this area, further studies in larger series are required.

Conflict of Interest Statement
There is no potential conflict of interest.

Ethical Approval
The study has been conducted following the approval by the Ankara City Hospital Clinical Research Ethics Committee Research Ethics Committee on 21 June 2023 under decision number 3746. The study was conducted in accordance with the principles set forth in the Declaration of Helsinki.

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Availability of Data and Materials
Data availability: The datasets generated and/or analysed during the current study are available in Article metadata, and in the zenodo site, 10.5281/zenodo.10369423.

Authors Contributions
FS: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

SK: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft; Writing-review & editing.

MOY: Formal analysis; Investigation; Writing-original draft; Writing-review & editing.

AFB: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

BK: Writing-original draft; Writing-review & editing.

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