

The risk of hypoparathyroidism after central compartment lymph node dissection in the surgical treatment of pT1, N0 thyroid papillary carcinoma

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Abstract. – OBJECTIVE: The role of central compartment lymph node dissection (CCLND) in the treatment of papillary thyroid carcinoma (PTC) is still controversial. The benefits of CCLND should be weighed against its potential risks. We aim to evaluate the positivity of central lymph nodes in pT1, N0 PTC and to establish the complication rates of total thyroidectomy (TT)+CCLND.

PATIENTS AND METHODS: This is a retrospective study on prospectively collected data over a 45-month period. A total of 329 patients were included. Total thyroidectomy was performed in 130 (39.5%) of these patients due to benign thyroid pathologies, and 199 (60.5%) pT1, N0 PTC patients had TT+CCLND. Our TT technique was applied in the same way in both groups. Central lymph node positivity, the number of lymph nodes removed during CCLND and the operative complications were evaluated. T-test and chi-square analysis were conducted in independent groups for statistical evaluation.

RESULTS: The rate of central lymph node positivity in TT+CCLND group was 38%. The average number of lymph nodes removed by CCLND is 10.2 (1-36). Complication rates between TT and TT+CCLND groups were statistically significant (3.8% vs. 11.1%, respectively) ($p < 0.05$). The difference was found to be particularly more pronounced for transient hypocalcemia. Although there was no significant relation between the number of lymph nodes removed during CCLND and the number of parathyroid glands detected in the pathology specimens ($p > 0.05$), the relation between the development of symptomatic hypocalcemia and the number of the parathyroid glands removed during surgery was significant ($p < 0.05$).

CONCLUSIONS: Central compartment lymph node metastasis in PTC is common. CCLND may increase the rate of transient hypocalcemia.

Key Words:

Papillary thyroid carcinoma, Total thyroidectomy, Central compartment lymph node dissection, Hypoparathyroidism.

Introduction

Papillary thyroid carcinoma (PTC) constitutes one of the most widespread type of differentiated thyroid carcinomas, and primary place of metastasis happens to be central compartment lymph nodes. Surgical procedure usually involves total thyroidectomy (TT) ± central compartment lymph nodes dissection (CCLND). The requirement and scale of CCLND are not a settled matter yet. Although central neck dissection is indicated in clinically node-positive disease, it remains controversial with regards to the patients with no clinical evidence of nodal metastasis. The actual benefits of CCLND in improving survival would not be easily demonstrated¹. Besides, CCLND does carry risks, especially for hypoparathyroidism². Level VI of the neck or central compartment signifies the region located inferior to the innominate artery or the sternal notch, and superior to the hyoid bone, and anterior to the superficial layer of the deep cervical fascia, and posterior to the deep layer of the deep cervical fascia, and lateral to the carotid arteries³. The central compartment is where pretracheal and bilateral paratracheal lymph nodes, and prelaryngeal (Delphian nodes) are contained.

Despite the excellent prognosis of PTC, cervical lymph node metastases are common, occurring in 20 to 50% of patients^{1,2,4-11}. Micrometastases are even more common and may be found in 90% of

patients^{1,2,8,9,12}. Nodal metastases are associated with an increase in recurrence rate, and may negatively impact survival^{1,5,8,13,14}. Some authors^{2,12,13,15-20} recommend routine CCLND in order to prevent a future recurrence, citing the high risk of positive lymph nodes, the accuracy of staging, better outcomes, reduced postoperative thyroglobulin (Tg) levels, and a lower morbidity rate associated with the first operation, whereas others^{1,5,9,12,15,16,19,21,22} suggest that this procedure increases the rate of complications, without any demonstrable benefits in terms of long-term survival.

The primary aim of this study is to evaluate the positivity of central lymph nodes and to establish the complication rates of TT+CCLND in patients with pT1, N0 PTC.

Patients and Methods

We retrospectively analyzed the data of 329 patients collected prospectively from January 2012 to November 2015 in our Endocrine Surgery Department in Ankara Guven Hospital. All patients with pathologically proven pT1, N0 PTC treated with TT+CCLND (n=199, 60.5%) and TT performed for benign thyroid pathologies (n=130, 39.5%) were included. All procedures were performed by two senior endocrine surgeons. Patient demographic data, complications, histopathology reports and postoperative calcium levels were collected.

A total thyroidectomy was performed by extra capsular dissection to remove both thyroid and pyramidal lobes in all cases regardless of the benign or malign pathology. We prefer to identify the recurrent laryngeal nerve (RLN) immediately caudal to the point where it crosses the inferior thyroid artery, and to dissect it in both directions: caudally to the mediastinum and cranially to the cricothyroid junction. Nerve monitoring was used in all cases. After the thyroid gland had been mobilized medially, the connective tissue on the tracheoesophageal space was dissected to identify the nerve. All vessels, particularly the branches of the inferior thyroid artery, were ligated close to the thyroid gland. Non-viable parathyroid glands were auto-transplanted immediately. Where the diagnosis of PTC was confirmed through cytopathologic examination before the operation or confirmed with frozen section intraoperatively, bilateral CCLND was performed. Bilateral CCLD involves removal of prelaryngeal, pretracheal and both the left and the right paratracheal nodal basins.

The pathology reports were reviewed for pathological staging and presence of incidental parathyroid gland in the resected specimen.

The postoperative vocal cord examination was performed whenever any voice change occurred. Permanent RLN palsy was defined as persistent postoperative vocal cord paralysis when it lasted more than 6 months after surgery. A vocal cord paralysis that healed within 6 months was considered transient. A permanent hypoparathyroidism was defined as postoperative serum parathyroid hormone level below normal value, with an albumin-adjusted serum calcium level below 8.0 mg/dL and requiring more than 6 months of calcium and vitamin D supplementation. Hypoparathyroidism that healed within 6 months was considered transient.

Statistical Analysis

The correlation between two variables was tested with Pearson correlation test. Comparison of the means between two unrelated groups was conducted with independent sample *t*-test. Where the groups were more than two, one-way ANOVA analysis was performed. Statistical analysis of the variables between two categories was performed with Chi-square test or Fisher's exact test. Statistically significant levels were presented as *p*-values, and observed differences were considered statistically significant where $p \leq 0.05$. SPSS 20.0 (SPSS Inc., Chicago, IL, USA) for Windows was used for data analysis.

Results

Table I illustrates demographic data of the patients and the complication rates. Central compartment lymph node metastasis was found in 89 patients (38%) in TT+CCLND group. Complication rates between TT and TT+CCLND groups were statistically significant (3.8% vs. 11.1%, respectively) ($p < 0.05$). The difference was found to be particularly more pronounced for transient hypoparathyroidism. There was no hypoparathyroidism in TT group. Permanent RLN palsy was not available in either of the groups, and the difference between TT and TT+CCLND groups by means of transient RLN palsy was not significant (2.3% vs. 3%, respectively).

Looking into the correlation between the numbers of lymph nodes removed during CCLND and the number of parathyroid glands detected in the pathology specimens, we could not find any

Table I. Demographic features of the patients and complication rates of each operative procedure.

	TT Group n (%)	CCLND Group n (%)
Number of patients	130	199
Mean age	48.1	41.3
Female/Male	99/31	168/31
Temporary RLN palsy	3 (2.3%)	6 (3%)
Permanent RLN palsy	-	-
Temporary hypoparathyroidism	-	12 (6%)
Permanent hypoparathyroidism	-	3 (1.5%)
Hematoma	2 (1.5%)	1 (0.5%)
Serum calcium level <8 mg/dl	3 (2.3%)	31 (15.6%)
Serum calcium level >8 mg/dl	127 (97.7%)	168 (84.4%)

TT: Total thyroidectomy; CCLND: Central compartment lymph node dissection.

significant relation (Table II). However, there is a significant relation between the patients who had symptomatic hypoparathyroidism and those whose parathyroid glands were removed (Subgroup analysis by Tukey test, $p < 0.5$, Table II).

Table III presents the number of parathyroid glands detected in the pathology specimens in the TT+CCLND group.

Discussion

Surgery must be a part of overall multidisciplinary treatment strategy and follow-up plan in

PTC. Lymph node metastases in level VI nodes are common. Macroscopically positive nodal disease is present in 10 to 30% of patients^{9,23,24}, and the incidence of the subclinical disease is reported in 40 to 70% of patients^{9,13,25}. However, the impact of CCLND on the prognosis of PTC is unclear⁹. In some retrospective studies^{5,9,16,26,27}, central lymph node metastasis has been shown to be associated with an increased risk of locoregional recurrence but not with overall survival. However, others^{17,20} found that microscopically positive subclinical lymph nodes do not appear to progress to recurrence. Other reports^{5,9,16,27} indicate that nodal dissection in differentiated thyroid cancer can advantageously decrease locoregional recurrence and improve survival. Another advantage of CCLND is that it provides information about the use of adjuvant RAI²⁸⁻³¹. It may improve the post-treatment thyroglobulin (Tg) levels^{10,32} and decrease the need for repeated RAI treatments^{8,20,29,33-39}.

In this study, 89 (38%) of the patients would have residual metastatic neck lymph nodes post-operatively if we did not perform CCLND. This group of patients may develop neck lymph node recurrence and face the morbidity of reoperation. Our central lymph node positivity rate is very similar to the published data.

The average number of lymph nodes that were removed during CCLND was 10.2 (min: 1 – max: 36), which is an appropriate number in order to assess the central compartment. Comparing the relation between the number of extracted lymph nodes during CCLND and the number of parathyroid glands found in the pathology specimens, we

Table II. The comparison of the number of central lymph nodes and parathyroid glands removed during CCLND and the complication rates.

		N	Average	Standart deviation	F	p
The number of lymph nodes	X	177	10,00	6,42	0,894	0,445
	RLN palsy	6	12,17	4,45		
	Hypoparathyroidism	15	12,40	5,74		
	Hematoma	1	8,00	-		
	Total	199	10,24	6,33		
The number of parathyroid glands	X	302	0,40	0,65	3,400	0,018*
	RLN palsy	9	0,67	0,71		
	Hypoparathyroidism*	15	0,93	0,88		
	Hematoma	3	0,33	0,58		
	Total	329	0,43	0,67		

*Significant only for hypoparathyroidism.

Table III. The number of parathyroid glands detected in the pathology specimens.

		Parathyroid glands in the pathology specimens							
		n=0		n=1		n=2		n=3	
		n	%	n	%	n	%	n	%
Operation	TT	109	83.8	19	14.6	2	1.5	0	0
	TT+CCLND	109	54.7	62	31.2	26	13.1	2	1.0

TT: Total thyroidectomy; CCLND: Central compartment lymph node dissection.

found no statistical significance ($p>0.05$). However, the relation between symptomatic hypoparathyroidism and the number of removed parathyroid glands was significant (Table II, $p<0.05$).

The most important complications of thyroid surgery are RLN palsy and hypoparathyroidism. In several studies, CCLND increased the likelihood of temporary morbidity. One of the largest series in the literature was published by Giordano et al¹⁶ about the complications of CCLND in 1087 patients over a 30-year period. They found that bilateral CCLND had a significantly higher rate of transient (51.9% vs. 27.7%, respectively) and permanent hypoparathyroidism (16.2% vs. 6.3%, respectively) than total thyroidectomy alone. Likewise, bilateral CCLND had significantly higher rates of transient hypoparathyroidism than total thyroidectomy alone.

We do not have any permanent RLN palsy in both groups, and the rate of transient RLN palsy in TT+CCLND group is very similar to the previously published data. The only significant complication of CCLND is transient hypoparathyroidism^{13,40,41}. The incidence of hypoparathyroidism varies among centers^{10,13,37,42}. The most common definition of hypocalcemia is a serum calcium level below 8 mg/dl (2 mmol/l) on the first day after surgery, and its prevalence ranges from 16 to 55%^{2,3}. Our transient and permanent hypoparathyroidism rates are much lower compared to the results of previous studies^{10,25,43-46}. Biochemical hypocalcemia (<8 mg/dl) was observed in 34 patients, and symptomatic hypocalcemia was observed in only 12 of these patients.

Central compartment dissection can be achieved with low morbidity by experienced thyroid surgeons^{8,30,47}. In our previous study where we compare the thyroidectomy techniques in the treatment of multinodular goiter, we demonstrated that 30% of patients had transient hypocalcemia in TT group, whereas only one patient (0.4%) suffered permanent hypoparathyroidism,

and 5 patients (1.9%) had temporary RLN injury but none of them remained permanent⁴⁸. After 10 years of added experience, we do not have any hypoparathyroidism complication in TT group in this study, and we have the results of serum calcium levels at the first postoperative day, and none was below 8.0 mg/dl. We think that CCLND adds more experience to the surgeon in order to find and recognize the parathyroid glands during surgery, which might help to decrease our hypocalcemia rate after TT.

A recent study⁴¹ found that routine postoperative treatment of patients undergoing TT and CCLND with calcium and vitamin D reduced the risk of transient hypocalcemia without causing parathyroid hormone inhibition. In most of the subjects who underwent TT+CCLND, we also followed a similar procedure.

The damage to three or more parathyroid glands is what usually causes the occurrence of hypoparathyroidism⁴⁹. Sitges-Serra et al (50) showed that the extent of surgery does not influence the number of parathyroid glands identified, and those, which are autografted or left *in situ*. Thus, the most likely mechanism linking extended surgery with hypocalcemia is an impaired function of the glands remaining *in situ* owing to devascularization. This finding is quite similar to our observation. None of the permanent hypoparathyroidism patients had parathyroid glands removed during surgery. As clear from Table III, at least one parathyroid gland is removed in 45.3% of the TT+CCLND group, but the ratio of symptomatic hypoparathyroidism is very low in this group.

Conclusions

Our data showed that the central compartment lymph node metastasis in PTC is common. The central compartment dissection is a safe proce-

ture to be performed by experienced endocrine surgeons. However, the transient hypoparathyroidism is the most serious problem after CCLND. We recommend the use of CCLND to stage accurately the disease and to avoid the possible morbidity of reoperation for lymph node recurrence.

Conflicts of interest

The authors declare no conflicts of interest.

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