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ORIGINAL ARTICLE – ENDOCRINE TUMORS

The Effect of Thyroiditis on the Yield of Central Compartment Lymph Nodes in Patients with Papillary Thyroid Cancer

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ABSTRACT

Background. In patients who have undergone thyroidectomy and central compartment neck dissection (CCND) for papillary thyroid cancer (PTC), visualization of enlarged lymph nodes may lead to more extensive CCND. This study sought to determine the effect of patient age and the presence of thyroiditis on the number of malignant and total lymph nodes resected in patients who underwent CCND for PTC.

Methods. This retrospective review examined a prospective database of patients who underwent total thyroidectomy and CCND for PTC between April 2009 and June 2013 and had thyroiditis on the final pathology. The patients were categorized into age groups by decade (18–29, 30–39, 40–49, 50–59, and ≥60 years) and compared with a control group of patients matched by age, gender, and tumor size.

Results. Of 74 patients with thyroiditis, 64 (87 %) were women. The median age of the patients was 47.5 years (range 18.2–72.0 years). The patients with thyroiditis had more lymph nodes resected than those without thyroiditis (median 11 vs 7; $p < 0.01$). However, these patients had fewer malignant lymph nodes (median 0 vs 1.5; $p = 0.06$), resulting in a lower lymph node ratio (0 vs 0.18; $p = 0.02$) for the entire cohort, but particularly for the youngest (18–29 years) and oldest (≥60 years) age groups.

Conclusions. Patients with thyroiditis and PTC who underwent CCND had more lymph nodes resected but a had lower proportion of metastatic lymph nodes than those without thyroiditis. Given the relatively low yield of malignant cervical lymphadenopathy, a more judicious approach to CCND might be considered, particularly for the youngest and oldest patients with PTC and thyroiditis.

Central compartment lymph node metastases occur in approximately 40–70 % of patients with papillary thyroid cancer (PTC).[1–3] The central compartment is defined by the hyoid bone superiorly, the carotid arteries bilaterally, and the level of the innominate artery inferiorly.[4]

Patients who undergo thyroidectomy for PTC and have clinically evident lymph node metastases, shown by either physical examination or ultrasonography, should receive a therapeutic, compartment-oriented lymph node dissection.[5] The role of prophylactic central compartment lymph node dissection (CCND) for patients who are clinically node-negative is controversial. Consensus has not been reached on the potential risks associated with more extensive surgery versus the value of such surgery for reducing cervical recurrence with or without adjuvant radioactive iodine (RAI) treatment.[6–10]

Thyroiditis refers to thyroid disorders marked by an inflammatory process, most commonly due to an autoimmune mechanism that demonstrates a lymphocytic infiltration on histopathology. Hashimoto's thyroiditis, a form of autoimmune thyroiditis, is the most common type of thyroiditis in the United States.[11] Chronic autoimmune thyroiditis has local structural effects on the thyroid gland

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as well as the surrounding lymph nodes, and cervical lymphadenopathy occurs in approximately 23 % of patients with thyroiditis.[12] Lymphadenopathy identifiable on ultrasonography more frequently occurs in patients with benign chronic autoimmune thyroiditis than in patients without thyroiditis, primarily in the lateral neck (levels 2–4).[13]

Few studies have evaluated how patient age and the presence of enlarged, benign lymph nodes secondary to thyroiditis in adult patients with PTC may affect the surgical approach to CCND at the time of thyroidectomy. We hypothesized that in the setting of thyroiditis, identification of a greater number of enlarged lymph nodes would heighten concern for the presence of central compartment metastases, leading to more extensive surgery, particularly in younger adults. Therefore, this study aimed to determine how the presence of thyroiditis influences the number of malignant and total lymph nodes resected in patients who have undergone CCND for PTC and whether patient age influences these results.

MATERIALS AND METHODS

This retrospective review examined a prospective database of patients who underwent total thyroidectomy and CCND (prophylactic or therapeutic; unilateral or bilateral) by one of four endocrine surgeons at the Medical College of Wisconsin between April 2009 and June 2013. The study was approved by the institutional review board. The study cohort consisted of patients 18 years of age or older who underwent total thyroidectomy and CCND for PTC and whose surgical pathology report also demonstrated thyroiditis. Patients were excluded from the cohort if they had undergone previous thyroid/parathyroid surgery and/or if PTC was an incidental finding on the final pathology not related to the index nodule or nodules.

All the patients underwent preoperative comprehensive ultrasonography of the thyroid and the central and lateral neck compartments. Patients were considered clinically node-negative if there was no evidence of metastatic lymphadenopathy at physical examination, ultrasonography, or intraoperative inspection. On ultrasonography, suspicious lymph node characteristics included calcifications, cystic changes, loss of a fatty hilum, hypervascularity, and other abnormal morphology.

The majority of the patients underwent fine-needle aspiration (FNA) of suspicious lateral neck lymph nodes, but FNA was not performed if the results would not change the operative approach. Intraoperative suspicion of metastatic lymphadenopathy included the presence of enlarged or pigmented lymph nodes. Prophylactic CCND was performed for the majority of patients with a preoperative diagnosis of PTC at our institution. The decision to perform a uni- or bilateral CCND was at the discretion of the surgeon based on tumor size, location, and multifocality. Intraoperative frozen section was not used to determine the extent of CCND.

The study cohort was matched in a 1:1 manner by age, gender, and tumor size to a control group of patients who also underwent total thyroidectomy and CCND for PTC but had no mention of thyroiditis in the pathology report.

The data collected included patient demographics and results of preoperative imaging and diagnostic studies including preoperative FNA biopsy, extent of surgery, final pathology, and postoperative complications (e.g., recurrent laryngeal nerve (RLN) injury or hypoparathyroidism). Postoperative laryngoscopy was used to document RLN injury if the patient reported postoperative voice changes. Hypoparathyroidism was defined as a postoperative serum parathyroid hormone (PTH) level lower than 10 pg/mL the morning after surgery and considered to be transient if postoperative calcium, calcitriol supplementation, or both had a duration shorter than 6 months, after which it was considered permanent.

For each patient, the total number of lymph nodes resected within the central compartment and the total number of malignant lymph nodes resected from the central compartment were collected from the pathology report. From these values, the lymph node ratio (number malignant/total lymph nodes resected) was calculated. Lymph nodes resected from a lateral neck compartment were not included in this analysis because the focus of this study was on the potential local effect that thyroiditis might have within the central compartment.

The primary outcome measured was a comparison of the total number of malignant lymph nodes resected, the total lymph nodes resected, and the lymph node ratio between the thyroiditis and nonthyroiditis patients. The secondary outcome was an evaluation of these same factors as they related to patient age. The patients were divided into age groups by decade as follows: 18–29, 30–39, 40–49, 50–59, and 60 years or older. The patients in the thyroiditis cohort were compared by age group with their matched controls.

Statistical analysis was performed with SPSS version 21 software (SPSS, Chicago, IL, USA). Significance, defined as a p value lower than 0.05, was assessed using the Kruskal–Wallis and Mann–Whitney tests.

RESULTS

Of the 328 consecutive patients who underwent total thyroidectomy and CCND for PTC, 74 (23 %) had mention of thyroiditis in their final pathology report. The majority (86 %) were women, and the median age of the cohort was

TABLE 1 Patient characteristics

Parameter	Thyroiditis present ($n = 74$) n (%)	Thyroiditis absent ($n = 74$) n (%)	p Value
Median age: years (range)	47.5 (18.2–72.0)	48.5 (26.4–71.7)	
Male	10 (14)	10 (14)	1.00
Female	64 (86)	64 (86)	
Type of central compartment neck dissection			0.87
Prophylactic	47 (64)	48 (65)	
Therapeutic	27 (36)	26 (35)	
Extent of central compartment neck dissection			0.32
Unilateral	40 (54)	46 (62)	
Bilateral	34 (46)	28 (38)	
Median tumor size: cm (range)	1.4 (0.3–6.5)	1.5 (0.15–7.5)	0.73
T stage			0.88
1a	21 (28)	21 (28)	
1b	26 (35)	25 (34)	
2	11 (15)	11 (15)	
3	15 (20)	15 (20)	
4	1 (1)	2 (3)	
N stage			0.13
pN0	37 (50)	25 (34)	
pN1a	21 (28)	31 (42)	
pN1b	14 (19)	16 (22)	
pNx	2 (3)	2 (3)	
Extrathyroidal extension			0.54
Absent	61 (82)	58 (77)	
Present	13 (18)	16 (22)	
Focality			0.86
Unifocal	43 (58)	44 (59.5)	
Multifocal	31 (42)	30 (40.5)	
Histologic variant			0.04
Classical	45 (61)	59 (80)	0.01
Follicular	15 (20)	11 (15)	0.39
Oncocytic	10 (14)	1 (1)	<0.01
All others (tall cell, diffuse sclerosing, Hobnail features, Hurthle)	4 (5)	3 (4)	0.70

47.5 years (range 18–72 years). A preoperative diagnosis of thyroiditis was suspected for 35 patients (47 %) based on a preoperative diagnosis by the endocrinologist (19 patients), hypothyroidism requiring thyroid hormone supplementation (8 patients), elevated antibodies/thyroid peroxidase levels (6 patients), and features of thyroiditis on ultrasound (2 patients) or preoperative cytology (2 patients).

The 74 thyroiditis patients were matched 1:1 for age, gender, and tumor size with 74 control patients (Table 1). The presence of multifocal disease or extrathyroidal extension did not differ between the thyroiditis and nonthyroiditis groups. However, a difference in the histologic variants of PTC was identified on the final pathology. The classical variant was present less often in the patients with thyroiditis ($n = 45$, 61 %) than in the control group ($n = 59$, 80 %) ($p = 0.01$). Although the number of patients was small, the oncocytic variant of PTC was present more often in the patients with thyroiditis ($n = 10$, 14 %) than in those without thyroiditis ($n = 1$, 1 %) ($p < 0.01$).

Of the 148 CCNDs performed, 86 were unilateral and 62 were bilateral. The thyroiditis and nonthyroiditis groups were similar in the proportion of patients who underwent uni- or bilateral CCND and prophylactic or therapeutic

TABLE 2 Comparison of central compartment lymph nodes resected by presence of thyroiditis

	Thyroiditis present	Thyroiditis absent	*p* value
Median no. of lymph nodes resected (range)	11 (0–50)	7 (1–26)	<0.01
Median no. of malignant lymph nodes resected (range)	0 (0–25)	1.5 (0–21)	0.06
Median ratio of malignant:total lymph nodes resected (range)	0 (0–1)	0.2 (0–1)	0.02

CCND (Table 1). Furthermore, the presence of central (N1a) or lateral (N1b) neck lymph node metastases did not differ between the two groups (Table 1). However, as shown in Table 2, the patients with thyroiditis had a median of 11 central compartment lymph nodes resected compared with 7 lymph nodes in the patients without thyroiditis ($p < 0.01$). Interestingly, the median number of malignant lymph nodes was higher in the patients without thyroiditis (0 vs 1.5; $p = 0.06$). This resulted in a lower lymph node ratio in the patients with thyroiditis (0 vs 0.2; $p = 0.02$).

When the patients with thyroiditis and those with no thyroiditis were compared by age group, no differences were found in the number of lymph nodes resected, the number of malignant lymph nodes, or the lymph node ratio among the patients ages 30–39, 40–49, or 50–59 (Table 3). However, among the patients ages 18–29 years, those with thyroiditis had a higher median number of lymph nodes resected than those without thyroiditis (17 vs 7; $p = 0.02$), although there was no difference in the median number of malignant lymph nodes resected. The patients ages 18–29 years showed a trend for the median lymph node ratio to be lower among those with thyroiditis than among those without thyroiditis (0.06 vs 0.86; $p = 0.05$). Among those age 60 years or older, although no difference was observed in either the total number lymph nodes or the number of malignant lymph nodes resected, there was a trend toward a lower median lymph node ratio in the patients with thyroiditis than in those without thyroiditis (0 vs 0.19; $p = 0.05$).

The overall rate for iatrogenic permanent RLN injury was 1.3 %. Permanent hypoparathyroidism was present in 5 % of the patients. The groups did not differ statistically in terms of RLN injury or transient or permanent hypoparathyroidism.

DISCUSSION

Enlarged central compartment lymph nodes identified at the time of thyroidectomy may represent lymph node metastases from a primary thyroid cancer or inflammatory lymph nodes from a benign process such as thyroiditis, a distinction not easily made at the gross, macroscopic level. This study demonstrated that among the patients with PTC who underwent CCND, those with thyroiditis had a greater number of lymph nodes resected but a lower lymph node ratio than the patients with no thyroiditis. The greater number of resected lymph nodes in the thyroiditis group may have been due to a larger number of enlarged lymph nodes attributed to a locoregional inflammatory process created by the thyroiditis rather than strictly because of a malignant process. Patients with thyroiditis do not demonstrate an increased number of malignant central compartment lymph nodes, particularly younger (<30 years) and older (≥60 years) patients.

These findings suggest that patients with known or suspected thyroiditis who are undergoing prophylactic CCND have a low risk for metastatic lymphadenopathy, even in the presence of what may be interpreted as enlarged lymph nodes. This information is important for the surgeon struggling to preserve parathyroid tissue in situ, or for the surgeon dealing with the challenging anatomy of a RLN that appears to be surrounded by lymph nodes.

Previous findings have shown that patients with thyroiditis have an increased number of enlarged lymph nodes. In one study, cervical ultrasonography was performed for 106 patients with chronic autoimmune thyroiditis and 70 control patients who had no thyroiditis, with comparison of the number, topographic distribution, and morphology of neck nodes.[13] The total number of lymph nodes with a long-axis diameter greater than 10 mm was higher in the thyroiditis group (mean 3.7 ± 2.4) than in the control group (mean 0.8 ± 1.3; $p < 0.001$). In the central compartment specifically, however, the two groups did not differ in the mean number of lymph nodes identified (0.8 ± 0.3 vs 1.0 ± 0.5; nonsignificant difference) or in the long- or short-axis diameter of the lymph nodes. However, the study did not include patients with PTC, making it difficult to determine how the presence of lymphadenopathy might be interpreted for patients with thyroiditis and PTC.

Previous studies also have suggested that patients with thyroiditis and PTC have a lower rate of central compartment lymph node metastases than those without thyroiditis. Although the etiology is unclear, it has been suggested that the inflammatory process of thyroiditis confers a protective effect.[14–18] In one recent study of 495 patients who underwent thyroidectomy with nodal excision (defined as ≥1

TABLE 3 Comparison of lymph nodes resected, by presence of thyroiditis and age

Age groups (years)	Median no. of lymph nodes resected (range)	*p* value	Median no of malignant lymph nodes resected (range)	*p* value	Median lymph node ratio (range)	*p* value
18–29 ($n = 14$)						
Thyroiditis ($n = 7$)	17 (5–31)	0.02	1 (0–12)	0.24	0.06 (0–0.44)	0.05
No thyroiditis ($n = 7$)	7 (4–7)		6 (0–7)		0.86 (0–1)	
30–39 ($n = 38$)						
Thyroiditis ($n = 19$)	12 (4–37)	0.45	2 (0–16)	0.56	0.11 (0–0.94)	0.30
No thyroiditis ($n = 19$)	11 (2–18)		3 (0–17)		0.18 (0–1)	
40–49 ($n = 28$)						
Thyroiditis ($n = 14$)	10 (1–22)	0.06	0.5 (0–5)	0.83	0.02 (0–0.83)	0.59
No thyroiditis ($n = 14$)	7.5 (1–17)		1 (0–5)		0.20 (0–0.6)	
50–59 ($n = 40$)						
Thyroiditis ($n = 20$)	11 (0–25)	0.39	0 (0–10)	0.50	0 (0–1)	0.77
No thyroiditis ($n = 20$)	7 (1–26)		0.5 (0–21)		0.03 (0–1)	
≥60 ($n = 28$)						
Thyroiditis ($n = 14$)	10 (1–30)	0.85	0 (0–25)	0.12	0 (0–0.833)	0.05
No thyroiditis ($n = 14$)	7 (1–23)		2 (0–8)		0.19 (0–1)	

central compartment lymph node on the final pathology) for PTC, 226 patients (46 %) had chronic lymphocytic thyroiditis. In the univariate analysis, when stratified by age, the patients with thyroiditis were more likely to have central compartment lymph node metastases than those without thyroiditis, both those age 45 years or older (33 vs 49 %; $p = 0.01$) and those younger than 45 years (37 vs 57 %; $p = 0.002$). However, multivariate analysis demonstrated that patients with thyroiditis were less likely to have central compartment lymph node metastases (odds ratio 0.61, 95 % confidence interval 0.38–0.99; $p = 0.046$) after adjustment for age, gender, tumor size, histopathologic subtype, and presence of lymphovascular invasion.[14]

Despite these findings, more extensive surgery may be performed for patients with thyroiditis and PTC. In a study of 269 patients, Ahn et al.[19] compared PTC patients with thyroiditis (22 %) and those without thyroiditis (78 %). The patients with thyroiditis showed a trend toward a lower incidence of lymph node metastasis than the patients without thyroiditis (12 vs 30 %; $p = 0.06$) but were more likely to have undergone a CCND at the time of thyroidectomy than those without thyroiditis (22.4 vs 10.9 %; $p = 0.02$). Similarly, in a study comparing 254 patients with PTC but no thyroiditis and 146 patients with thyroiditis who underwent therapeutic CCND, those with thyroiditis were less likely to have central compartment lymph node metastases (28.8 vs 39.4 %; $p = 0.033$) and more likely to have a greater number of lymph nodes resected (13.2 vs 9.2; $p < 0.001$). This resulted in a lower lymph node ratio (11.4 vs 18.2 %; $p = 0.003$).[15] The results of our study corroborate this finding of a lower lymph node ratio in patients with thyroiditis.

The lower lymph node ratio may occur because patients with thyroiditis are more likely to have enlarged lymph nodes, thus prompting the surgeon to perform a more extensive CCND at the time of thyroidectomy. Previous studies have shown that the lymph node ratio may affect disease recurrence or disease-specific mortality. In a study of adult patients from the Surveillance, Epidemiology, and End Results (SEER) database, Schneider et al.[16] demonstrated that patients with a lymph node ratio of 0.42 or greater had a higher disease-specific mortality rate than those with a ratio lower than 0.42 (1.72 vs 0.65 %; $p < 0.01$). In a separate institutional study, a central neck lymph node ratio threshold of 0.86 was suggestive of a higher disease recurrence rate. In our study, only younger patients with no thyroiditis approached the threshold of 0.86, suggesting that these patients may be at a higher risk for recurrent disease and may require closer surveillance.

Our study was limited by its retrospective nature, its lack of randomization, and its small sample size. We compared the cohort of interest with an age- and gender-matched control group of patients, but additional matching by type of CCND (prophylactic or therapeutic) was not feasible. In addition, the number of lymph nodes examined was dependent not only on the extent of surgery but also on the lymph node retrieval performed at the time of gross inspection of the operative specimen. The study also was limited by its lack of preoperative diagnosis of thyroiditis for all the patients in the study cohort and by its lack of histologic confirmation by a second pathologist for the presence or absence of lymphocytic infiltration in the surgical specimen.

In conclusion, patients with thyroiditis and PTC appear to undergo a more extensive CCND, presumably due in

part to the presence of grossly enlarged lymphadenopathy identified at the time of thyroidectomy. However, our study did not find these patients to have more extensive metastases to the central neck, as evidenced by the lower median number of malignant lymph nodes resected and the lower lymph node ratio. This was particularly true in the youngest and oldest patient subsets. Therefore, although a CCND can be performed with low rates of morbidity for patients with underlying thyroiditis, an overly aggressive dissection that may compromise the normal function of the RLN or nerves or risk permanent hypoparathyroidism is not necessary. Patients without histologically documented cervical lymph node metastases, despite intraoperative findings of enlarged lymphadenopathy, as well as those at either end of the age spectrum may not warrant an overly aggressive approach. Awareness of the effect that thyroiditis has on patients undergoing thyroidectomy for PTC should be incorporated into the surgeon's perioperative patient counseling and intraoperative decision making.

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