Clinical Significance of Multinodularity in Patients with Papillary Thyroid Carcinoma

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Abstract. *Backgroud/Aim: To assess the clinical significance of nodules in multinodular thyroid if one nodule is diagnosed as papillary carcinoma (PC), we investigated 97 patients with a multinodular thyroid and histopathological diagnosis of PC. Patients and Methods: We assessed the following variables: age and gender, fine-needle aspiration diagnosis, PC nodule size and dominance, intraglandular dissemination (ID), regional lymph node (RLN) status, and distribution of diagnoses of the other nodules. Results: Among 97 patients with PC, additional diagnoses were: nodular goiter (NG) in 64 patients, ID in 28, Hashimoto's thyroiditis (HT) in 26, and follicular or Hürthle cell adenoma in seven. Conclusion: Patients with ID, and without NG or HT more often had RLN metastases. Lower rates of RLN metastases in patients with NG and HT are probably due to smaller PC nodule sizes found during routine follow-up of these benign diseases.*

Thyroid nodules are extremely common in the general population, being identified in 5% of patients by palpation and up to 50% by ultrasound (US) examination (1, 2). By contrast, thyroid carcinoma is uncommon. The lifetime risk of being diagnosed with thyroid carcinoma is less than 1% (3). Thyroid cancer is thought to be related to a number of environmental and genetic predisposing factors, but significant uncertainty remains regarding its causes (4). Every patient with a palpable or incidental thyroid nodule should undergo further investigation to rule-out a possible malignancy. To determine if fine-needle aspiration (FNA) is warranted, serum thyroid-stimulating hormone (TSH) level and thyroid US should be obtained. A nodule that appears either iso- or hypofunctioning on radionuclide scan should be considered for FNA. If the FNA reveals that the nodule is malignant, surgery is generally recommended.

The accuracy of detection of early thyroid neoplasms may be influenced by prior thyroid disease events. Thyroid nodules and other thyroid conditions may call for closer medical surveillance, increasing the likelihood of being diagnosed with thyroid cancer (5). The aim of the present study was to investigate characteristics and clinical significance of nodules in multinodular thyroid if one nodule is diagnosed as papillary carcinoma (PC).

Patients and Methods

We retrospectively analyzed data of a total of 227 patients with PC who were examined at high-volume thyroid University Hospital Center during a period of 10 years (between year 2000 and 2009). Thyroid nodes were evaluated with a neck US, FNA, and, when indicated, by tissue pathology. We assessed the following variables: age, gender, FNA diagnosis, PC nodule size and dominance, intraglandular dissemination (ID), regional lymph node (RLN) status, and distribution of diagnoses of other nodules. The Iargest nodule (assessed by US preoperatively, and by histopathology after surgery) was defined as the dominant nodule, and ID was defined as a presence of PC micrometastasis inside thyroid.

Statistical analysis. Medians, means and standard deviations are used to summarize quantitative variables, while frequencies and percentages are used to summarize qualitative data. Statistical analysis was performed with Fisher's exact test, χ^2 test, and logistic regression test. A probability of $p<0.05$ was considered statistically significant.

Results

Out of 227 patients, 44 (19.4%) had solitary nodule in the thyroid gland registered by neck US, 97 (42.7%) had multinodular thyroid, and in 86 (37.9%) patients, data regarding nodularity were not available. Inclusion criteria were multiple thyroid nodes and histopathological diagnosis of PC, and 97 patients remained eligible for the statistical analysis. In 41 out of these 97 patients, histopathological data for the RLN status were available. Among 97 patients with multinodular thyroid and histopathological diagnosis of

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PC in one of the nodules, there were 87 females and 10 males. Patients' characteristics are shown in Table I. No statistically significant difference in mean age was observed between female and male patients in our cohort of patients (p=0.0885).

FNA diagnosis was PC or suspicion of PC in 95 patients, suspicion of follicular neoplasm in one patient, and inadequate material in one patient. The mean diameter of the nodule with confirmed PC was 14±11 mm (median=10; range=2-60 mm). Nodules with confirmed PC were found to be larger in male patients (22±14 mm) than in females (13±2 mm), but the difference was not statistically significant (p=0.0976). Nodules with confirmed PC were also the dominant nodes in 64 of our patients, while in 33 of them, another diagnosis was confirmed in the dominant nodule. The difference was statistically significant (p<0.01). The size of dominant nodules with confirmed PC was significantly larger than the size of nondominant nodules with PC (p<0.01). The mean size of dominant nodules was 17±12 mm (median=13; range=5-60 mm), while in non-dominant nodules it was 8±5 mm (median=7; range=2-25 mm).

Additional diagnoses, confirmed in other nodules are shown in Table II. A significant proportion of patients had more than one additional diagnosis, and only in one patient was no additional nodule found by histopathological examination. The relationship between additional diagnosis and nodule dominance is shown in Table III. The ratio of dominant to non-dominant PC nodules was highest in patients with ID, where most of the PC nodules were dominant, whereas in nodular goiter (NG), the number of dominant and nondominant nodules with confirmed PC was approximately the same.

Besides PC, in 26 patients diagnosis of Hashimoto's thyroiditis (HT) was also established, and these patients had a lower risk of RLN metastases than those without HT (Table IV). The difference was statistically significant (p<0.05). Patients with diagnosis of HT also had a lower rate of ID when compared to patients without HT, but the difference did not reach a statistical significance (p=0.1551).

ID itself was found in 28 of our patients. It was most commonly located in the contralateral lobe of the thyroid (with regard to the PC nodule) – 17 patients (60.7%) had ID in the contralateral, four in the ipsilateral, and seven in both lobes (bilaterally). Among patients with ID, eight of them also had NG, five HT, and two follicular adenoma (FA). Both mean and median nodule diameter were slightly larger in patients who had diagnosis of ID, when compared to patients without ID (16 mm *vs*. 13 mm, and 13 mm *vs*. 10 mm, respectively). The difference did not reach a statistical significance (p=0.1551). The vast majority of patients with confirmed ID were also found to have RLN metastases (85%), while the same was found in 50% of patients who did not have ID (Table IV). This observed difference was statistically significant (p<0.05).

Table I. *Distribution of patients by sex and age.*

Patients' characteristics		N (%)
Male (M),		10 (10.3%)
Female (F)		87 (89.7%)
M:F ratio		1:8.7
Age (years)		
All patients	Mean (SD)	51±13
	Median	52
	Range	15-80
Males	Mean (SD)	56±8
	Median	57.5
	Range	41-66
Females	Mean (SD)	51±13
	Median	52
	Range	15-80

SD: Standard deviation.

In patients with NG, a lower rate of ID was recorded when compared to patients without diagnosis of NG (p<0.01). RLN metastases were also more common in patients without NG compared to patients with additional diagnosis of NG (p<0.05) (Table IV).

ID was more common in patients with a dominant PC nodule (24 out of 64 patients, 37.5%) compared to patients with PC in a non-dominant nodule (four out of 33 patients, 12.1%) (p<0.01). Although RLN metastases were also more common in patients with a dominant PC nodule than in those with a non-dominant nodule (21 out of 31 *vs*. out of 10), the difference was not statistically significant (p=0.1175). Patients with additional NG or additional HT had a smaller average PC nodule size than patients without these diseases (13.2 mm or 12.9 mm *vs*. 15.2 mm) but the difference was not found to be statistically significant (for patients with NG, p=0.2399; for patients with HT, p=0.1839). Logistic regression test has shown that PC nodule size positively correlated with the presence of RLN metastases (p<0.05).

Discussion

The study was undertaken to investigate characteristics and clinical significance of nodules in multinodular thyroid if one nodule is diagnosed as PC. Thyroid cancer is a relatively rare tumor but it represents the most frequent form of malignant tumor found in the endocrine glands, with PC being its most common variety. Co-existence of PC and other abnormalities of the thyroid is known to be present in a significant proportion of patients, and was investigated in several former studies. However, the clinical significance of other nodules in patients with multinodular thyroid and confirmed PC in one of the nodules is not yet fully understood. In our study, additional diagnoses that were confirmed in other nodules

Table II. *Additional diagnoses in female and male patients.*

Additional diagnosis	Female patients, N (%)	Male patients, N (%)	All patients, N (%)
None	1 (1.1%)	0 (0%)	1 (1%)
Adenoma	6 (6.9%)	1 (10%)	7 (7.2%)
Follicular adenoma	4 (4.6%)	1 (10%)	5 (5.2%)
Hürthle cell adenoma	2 (2.3%)	0 (0%)	2 (2.1%)
Intraglandular dissemination	16 (18.4%)	3 (30%)	28 (28.9%)
Metastatic carcinoma	20 (23%)	2 (20%)	22 (22.7%)
Microcarcinoma	5 (5.7%)	1 (10%)	6 (6.2%)
Hashimoto's thyroiditis	25 (28.7%)	1 (10%)	26 (26.8%)
Nodular goiter	57 (65.5%)	7 (70%)	64 (66%)
Multiple diagnoses	26 (29.9%)	2 (20%)	28 (28.9%)

were NG (66%), ID (29%), HT (27%), and adenoma (7%).

HT is a frequent inflammatory thyroid disease and the main cause of hypothyroidism, characterized by the infiltration of the thyroid gland by inflammatory cells (6). The clinical importance of co-existing HT in patients with PC was investigated in several former studies, especially since it is known that the prevalence of HT is significantly higher in patients with PC (7-9). Our results show that in these patients the risk of RLN metastasis is significantly lower than in those without HT ($p<0.05$). Kim and colleagues separately analyzed different regions of affected lymph nodes, and concluded that only central lymph node metastases were found at lower frequency in patients without HT, while the difference in involvement of lateral lymph nodes was not statistically significant between study and control groups (10). These results are in accordance with the results of Singh and associates, which confirmed positive correlation between HT and disease-free (DFS) and overall (OS) survival of patients with PC, since metastasis in lymph nodes place a patient in higher disease stage than in cases without lymph node involvement, and the presence of coexistent HT does not affect the diagnostic evaluation or management of PC (9). Pisanu *et al*. also investigated the frequency of co-existence of HT and differentiated thyroid cancer, and the impact of HT on the management of differentiated thyroid cancer in 44 patients with HT, and concluded that an adequate follow-up of patients with HT may permit an early diagnosis of differentiated thyroid cancer and its appropriate management (11). Thus, regular follow-up of patients with confirmed HT may be one of the reasons for prolonged DFS and OS in these patients. Another study reviewed the medical records of 195 consecutive patients with PC who underwent total thyroidectomy and bilateral central lymph node dissection (12). In this study, a large proportion of patients with PC were found to have coexisting HT (28.7%), and these patients had smaller tumor size, lower incidence of capsular invasion and central lymph node metastases than patients without HT. Compared to patients without HT, patients with HT were younger, with a female predominance, which are the most important and well-known prognostic variables for thyroid cancer mortality. This is in accordance with our results, which confirmed smaller average PC nodule size in patients with PC and co-existing HT or NG than in patients without these diseases (although the difference did not reach statistical significance), as well as positive correlation of PC nodule size and the presence of RLN metastases. Although the role of the inflammatory-immune cells is not yet fully understood, more favorable course of PC in the presence of lymphocytic infiltration may also be due to immune reaction which controls tumor growth and proliferation (13, 14).

Table III. *Relationship between additional diagnosis and nodule dominance.*

Additional diagnosis	Number of dominant PC nodules	Number of non-dominant PC nodules
None	1	0
Adenoma	5	2
Follicular adenoma	4	1
Hürthle cell adenoma	1	1
Intraglandular dissemination	24	4
Metastatic carcinoma	21	1
Microcarcinoma	3	3
Hashimoto's thyroiditis	19	7
Nodular goiter	33	31

NG is a very common thyroid disorder. In our patients with PC and additional diagnosis of NG, a smaller average PC nodule size was observed than in patients without NG (13.2 mm *vs*. 15.2 mm), probably due to regular routine follow-up of patients with diagnosed NG. Again, PC nodule

Table IV. *Correlation of additional diagnosis, regional lymph nodes metastasis (RLN) and intraglandular dissemination (ID).*

	RLN metastasis		ID	
Additional diagnosis	Positive, N (%)	Negative, N (%)	Positive, N (%)	Negative, N (%)
Hashimoto's thyroiditis				
Yes	7 (41%)	10 (59%)	5 (19%)	21 (81%)
No	18 (75%)	6 (25%)	23 (32%)	48 (68%)
Intraglandular dissemination			N/A	N/A
Yes	11 (85%)	2 (15%)		
No	14 (50%)	14 (50%)		
Nodular goiter				
Yes	9 (45%)	20 (55%)	8 (12.5%)	56 (87.5%)
No	16 (76%)	5 (24%)	20 (61%)	13 (39%)

N/A: Not applicable.

size was positively correlated with the presence of RLN metastases, consequently making RLN metastases less common in patients with additional diagnosis of NG ($p<0.05$). These results are in correlation with a former study by Cheng *et al*., who also reported smaller tumor size in patients with PC and additional diagnosis of NG (15). In that study, the difference in tumor size between the two groups was even larger (14.2 mm *vs*. 22 mm). When comparing HT and NG, the former results indicate that the frequency of PC is significantly higher in combination with HT than with NG, and is associated with increased levels of serum TSH (16). Similar results were obtained in our cohort of patients, since 66% of them had NG, and only 27% HT. However, although NG may harbor cancer, it cannot be considered as a condition predisposing to cancer, and there is no reason to consider the surgical treatment of NG as prophylaxis of PC (17, 18). Association of NG and PC is variable, and surprisingly a high occurrence of malignancy in patients with NG has been reported in several studies (19-21), while other studies did not confirm such a strong association (22). One teaching hospital reported a high prevalence of malignancy in patients with NG (1/7), although follicular carcinoma was found to be the prevalent histological type (19). The results were consistent with the findings elsewhere in endemic goitrous regions. Considering these results, although many of these cases appear to remain clinically silent, and factors predisposing micro PCs to evolving from a sub-clinical to a clinically apparent form are still not recognized (20), it is recommended to value the dominant nodule in patients with NG as if it were a solitary nodule in an otherwise normal gland (21, 22). Our results also show the necessity of closely following-up not only the dominant nodule, but also other nodules, since the number of dominant and non-dominant PC nodules in patients with co-existing NG was approximately the same. By evaluation of only the dominant nodule, the true occurrence of PC in these patients might be under-estimated. One study reported that the cancer risk is similar for patients with one or two nodules larger than 1 cm, and decreases with more than two thyroid nodules (23). In contrast, one Center reported a markedly low frequency of carcinoma in NG (only 0.25%), while it was found in 42% of patients with solitary thyroid nodules, with PC being the most common variety (24). Problems arising in patients with co-existence of PC and NG were also studied in several former studies, since a significant discrepancy between the clinical impression and the FNA biopsy diagnosis may occur, leading to the suspicion that a false-positive FNA diagnosis was obtained (25).

In conclusion, patients with PC and additional NG or HT less often had RLN metastases, probably due to smaller PC nodule size found during routine follow-up of these benign diseases, and patients with NG also had lower rates of ID, while patients with ID had more often RLN metastases. In our cohort of patients, results show that PC was more commonly confirmed in the dominant nodule. Nevertheless, in a significant proportion of patients, PC was confirmed in the non-dominant nodule. Thus, careful follow-up of all registered nodes in patients with multinodular thyroid is mandatory. Our study group suggests US for follow-up, and in the case of newly detected suspicious nodes, or nodes that become suspicious over time (and were not assessed by FNA before), FNA is indicated.

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Conflicts of Interest

The Authors report no conflicts of interest.

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