THYROID MALIGNANCY RISK OF INCIDENTAL THYROID NODULES IN PATIENTS WITH NON-THYROID CANCER

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Abstract

Context. Thyroid incidentaloma is a common disorder in endocrinology practice. Current literature regarding the risk of thyroid cancer in incidentalomas found in patients with non-thyroid cancer is limited.

Objective. The aim of the present study was to investigate the frequency of thyroid malignancy in thyroid incidentalomas detected in patients with non-thyroid cancer.

Design. Case control study.

Subjects and Methods. The database of 287 thyroid nodules from 161 patients with a history of non-thyroid cancer followed between 2008 and 2014 were retrospectively evaluated.

Results. From 287 thyroid nodules, 69.7 % had a benign final cytology. Thyroid cancer detected in one nodule while follicular neoplasia detected in 4 nodules, atypia of unknown significance (AUS) detected in 10 nodules, Hurthle cell neoplasia detected in 5 nodules and suspicious for malignancy detected in 6 nodules according to fine needle aspiration biopsy results. Metastasis of the non-thyroid cancer to the thyroid gland was detected in 4 nodules. Twenty seven nodules from 15 patients were removed with surgery. There were 3 malignant nodules found after surgery (1 papillary, 1 follicular and 1 medullary cancer). In addition to these three thyroid cancers, two patients with benign nodules had co-incidental thyroid cancer detected after surgery. Finally, 11.1 % of thyroid nodules which underwent thyroid surgery had malignant histopathology except for co-incidental and metastatic cancers.

Conclusions. The frequency of thyroid malignancy seems not to be substantially increased in incidental thyroid nodules detected in patients with non-thyroid cancer when these patients were evaluated in nodule-based approach.

Key words: thyroid cancer, non-thyroid cancer, thyroid nodules.

INTRODUCTION

Thyroid incidentaloma can be defined as an asymptomatic thyroid lesion detected during the radiological imaging methods including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET/CT) for reasons unrelated to the thyroid gland (1). The frequency of thyroid nodules detected by USG ranges between 30-67 % (2, 3). So that, thyroid incidentalomas are frequently seen and to rule out the malignancy is the main problem (4). The rate of thyroid cancer has been reported as 12 % in thyroid nodules incidentally found by US (5).

The increased frequency of secondary cancers has been observed in patients with thyroid cancer in observational studies (6-8). Also, a previous study from Turkey suggested that the occurrence of multiple primary tumors is common in patients with differentiated thyroid cancer (9). However, the literature associated with the risk of thyroid malignancy in patients with non-thyroid cancers is few (7, 10). All of these studies included heterogeneous groups with respect to cancer types of non-thyroid cancer. Also, study designs (nodule based, patient based) and end-points (cytology, histopathology) were different in the literature. So, interpretation of these studies leads to confusing results. Also, current data regarding the evaluation of the thyroid fine needle aspiration biopsy (FNAB) results in thyroid incidentalomas in patients with non-thyroid cancer with an endocrine perspective is limited.

In the present study, we aimed to investigate the frequency of thyroid malignancy based on the results of cytology and histopathology from thyroid nodules found incidentally in patients previously diagnosed with non-thyroid cancer retrospectively.

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MATERIAL AND METHODS

FNABs of 287 thyroid nodules from 161 patients with a history of non-thyroid cancer were retrospectively evaluated. Ultrasonography guided FNABs (US-FNABs) were performed by experienced endocrinologists in our institution between January 2008 and February 2014. The study protocol was approved by the local ethic committee.

The maximal diameters of the nodules, cytology results of FNABs, and the types of primary tumors were recorded. FNAB results from all patients and histopathology results of the nodules which underwent thyroid surgery were recorded.

The indications for FNABs in the first visit and follow-up were size of the nodule (nodule maximal diameter > 10 mm), or any suspicion of thyroid malignancy (rapid growth of the nodule), physical examination findings like fixed nodule or suspicious findings detected by ultrasonography (micro calcifications, central vascularity or irregular border). US-FNABs were performed under the guidance of continuous real time US with a 22-gauge needle attached to a 10-mL disposable plastic syringe without local anesthesia. Each nodule was aspirated at least twice. Materials obtained from FNABs were

immediately smeared on glass slides after aspiration and fixed by air-drying. Thyroid FNAB results were categorized according to Bethesda classification. In the context of insufficient results or atypia of unknown significance (AUS), repeated biopsies were performed. Final cytology was defined as the cytology result of the last biopsy performed for that nodule.

RESULTS

Of the 161 patients included in the study, 72.7 % of patients were female and mean age of the patients was 57.6 ± 10.8 years. Of the 287 nodules, mean of the maximal diameter of the nodules biopsied was 17.0 ± 9.6 mm. The distribution of the non-thyroid cancers were listed in Table 1. Breast cancer was the most common primary malignancy.

There were 356 biopsy séances from 287 nodules. The reasons of repetitions were insufficient biopsy results, biopsies resulted as AUS or growth of the nodule. Final cytology results of nodules from non-thyroid cancer patients as well as according to non-thyroid cancer types were shown in Tables 2 and 3. From 287 thyroid nodules, 69.7 % had a benign final cytology while 19.9 % of the nodules had insufficient cytology despite repetitions. One

Table 1. The distribution of non-thyroid cancers

	n (%) (nodule distribution)	n (%) (patient distribution)
Breast Cancer	94 (32.8)	53 (32.9)
Hematologic Cancer	79 (27.5)	41 (25.5)
Gastrointestinal Cancer	27 (9.4)	15 (9.3)
Gynecologic Cancer	18 (6.3)	10 (6.2)
Lung Cancer	17 (5.9)	12 (7.5)
Genitourinary Cancer	17 (5.9)	11 (6.8)
Skin Cancer	15 (5.2)	9 (5.6)
Other	20 (7.0)	10 (6.2)
Total	287(100)	161 (100)

Table 2. Final cytology results of nodules from non-thyroid cancer patients

	n (%)
Benign	200 (69.7)
Follicular Neoplasia	4 (1.4)
AUS	10 (3.5)
Hurthle cell neoplasia	5 (1.7)
Suspicious for malignancy	6 (2.1)
Malignant	1 (0.3)
Metastasis	4 (1.4)
Insufficient	57 (19.9)
Total	287 (100)

Table 3. Final cytology results according to non-thyroid cancer types

	Breast cancer	Lung cancer	GU cancer	Gynecologic cancer	GIS cancer	Skin cancer	Hematologic cancer	Other
Benign	76 (80.9)	10 (58.8)	11 (64.7)	11 (61.1)	16 (59.3)	10 (66.7)	54 (68.4)	12 (60.0)
Follicular neoplasm	0 (0)	0 (0.0)	1 (5.9)	0	0	0	3 (3.8)	0
AUS	3 (3.2)	1 (5.9)	1 (5.9)	1 (5.6)	3 (11.1)	0	0	1 (5.0)
Hurthle cell neoplasia	1 (1.1)	0 (0.0)	0	1 (5.6)	0	0	2 (2.5)	1 (5.0)
Suspicious for cancer	2 (2.1)	0 (0.0)	0	0	0	0	3 (3.8)	1 (5.0)
Malignant	0 (0)	0 (0.0)	1 (5.9)	0	0	0	0	0
Metastasis	0 (0.0)	2 (11.8)	0	0	0	0	2 (2.5)	0
Insufficient	12 (12.7)	4 (23.5)	3 (17.6)	5 (27.7)	8 (29.6)	5 (33.3)	15 (19.0)	5 (25.0)

Data were expressed as n (%), AUS, atypia of unknown significance; GU, genitourinary; GIS, gastrointestinal system.

Table 4. Results of cytology and histopathology of nodules surgically removed

	Histopathological Results			
	Benign	Papillary cancer	Follicular cancer	Medullary cancer
Benign Cytology	13	0	0	0
Follicular neoplasia	1	0	0	0
AUS	2	0	0	0
Suspicious Cytology	4	0	1	0
Hurthle cell Cytology	1	0	0	0
Malignant Cytology	0	0	0	1
Insufficient	3	1	0	0
Total	24	1	1	1

nodule had a malignant cytology, 4 nodules follicular neoplasia, 10 nodules AUS, 5 nodules Hurthle cell neoplasia, 6 nodules suspicious for malignancy in FNABs. Metastasis of the non-thyroid cancer to the thyroid gland was detected in 4 nodules. Two of 4 had a history of lung cancer and the other two had a history of hematologic cancer. None of the patients with a metastatic cytology underwent thyroidectomy, all of them were treated with chemotherapy targeting the primary cancer.

As seen in Table 4, twenty seven nodules from 15 patients were removed with thyroid surgery. Seven nodules with a final cytology of AUS, one nodule with a final cytology of suspicious for papillary thyroid cancer and four nodules with a final cytology of Hurthle cell neoplasia could not be removed by surgery or re-biopsied because of patients' poor general health or unwillingness to thyroidectomy. There were 3 malignant nodules found after surgery (1 papillary, 1 follicular and 1 medullary cancer). One nodule with insufficient cytology was papillary cancer, one nodule with suspicious cytology was follicular cancer and one nodule with malignant cytology was medullary cancer in histopathology results. In addition to these three thyroid cancers, two patients with benign nodules had co-incidental thyroid cancer detected after surgery. After all, we found that 11.1 % of thyroid nodules (3 of 27 nodules) had malignant pathology except co-incidental thyroid cancer.

DISCUSSION

Endocrinologists frequently face with the evaluation of thyroid nodules in non-thyroid cancer patients as a result of aging of the population, increasing cancer rates and imaging modalities. Nevertheless, the frequency of thyroid cancer in incidentally found thyroid nodules in these patients is still not fully known. As far as we know, there are a limited number of studies on the prevalence of primary thyroid cancer

in non-thyroid cancer patients in the literature (10-22).

In the present study, we showed that the frequency of thyroid malignancy in incidentally found thyroid nodules during the imaging studies performed for the investigation of non-thyroid cancer who underwent surgery was 11.1 % when we exclude co-incidental thyroid cancers and metastasis to the thyroid gland, although malignancy risk was even lower in the whole group (3 thyroid cancers detected in 267 nodules). According to our data, non-thyroid cancer patients may not have substantially increased risk for thyroid malignancy when nodule based approach was performed. In the study of Wilhelm *et al.* (11), the presence of a thyroid cancer in patients who have another primary malignancy and referred to a surgery clinic for incidental thyroid nodule was found as 24.3%. But, they included co-incidental thyroid cancer and metastasis to thyroid in the ratio of thyroid malignancy. The difference between Wilhelm's study and ours was the ratio of patients who need surgery. Such that, 57% of the referred patients had atypical biopsy results (not described in detail) warranting surgery in their study group whereas this ratio was lower in our study group. In the study of Cohen *et al.* (12), only 15 of 102 patients with thyroid incidentalomas detected on FDG-PET/CT were evaluated with FNAB, 7 of whom had a diagnosis of thyroid cancer according to FNAB results. As the number of patients who were histopathologically evaluated in their study group, it was hard to decide the thyroid cancer rates of the whole study group. This phenomenon can be attributed to most of the studies evaluating thyroid incidentalomas detected on FDG-PET/CT. King *et al.* (23) reported that all of the 22 thyroid incidentalomas found on FDG-PET/CT were evaluated with FNAB and thyroid cancer (when co-incidental thyroid cancers were excluded) was detected in 14 % of the incidentalomas. Kim *et al.* (22) found that thyroid malignancy rate was 24.3 % according to FNAB results in a large number of incidentalomas found on FDG-PET/CT. But, the histopathology results were

not discussed in the article. The atypical thyroid FNAB results (Bethesda category IV and V) were reviewed in the study of Duskova *et al.* (15). Eleven of the 21 patients with a history of malignancy had metastasis of the initial malignancy whereas 8 of the 21 patients had thyroid cancer most of which was undifferentiated thyroid cancer. As a result, there are different ratios for thyroid malignancy risk in incidentalomas found in non-thyroid cancer patients in the literature. This difference may come from the departments where studies were conducted such as endocrinology, surgery or oncology; availability of FNABs, thyroid surgery and existence of metastasis or co-incidental thyroid cancer in the evaluation of thyroid malignancy risk in non-thyroid cancer patients. In our study, only 3 nodules of whole study group were diagnosed as thyroid malignancy. This result may be related to our selection of only high risk patients for thyroid surgery who had already have a primary cancer as well as unwillingness or unhealthiness of the patients to surgery. Therefore, the other reason of discordant results in terms of thyroid malignancy rates in the previous studies may be related to the selection criteria of the patient group or the determination of end-points. A selection bias in non-thyroid cancer patients in the literature may exist like in patients with autoimmune thyroiditis who have different thyroid cancer rates according to surgical or cytological series (24).

In our study, the distribution of FNAB cytology results from different non-thyroid cancers seems to be similar although breast cancer was the most frequent non-thyroid cancer type. The distribution of non-thyroid cancers was different in previous studies (11, 18, 22, 25, 26). Indeed, the possible effects of the specific types of the non-thyroid cancer on the malignancy rates of thyroid incidentalomas is not known. In population-based epidemiological studies, the risk of subsequent thyroid cancer differed between various cancer types (10, 16). Lal *et al.* showed that there is increased subsequent thyroid cancer risk in almost all non-thyroid cancer types except bladder and uterus cancers (16). Also, subsequent thyroid cancer risk in patients with renal and breast cancers remained high for 10 years. Different previous studies had different spectrum of non-thyroid cancer types such as gynecologic cancers were predominant in the study of Gavriel *et al.* (25), gastrointestinal cancers in the study of Wilhelm *et al.* (11), head and neck cancers in the study of Nam *et al.* (27) and lung cancers in the study of Ishimori *et al.* (18). Some other studies did not mention the types of primary cancers (12, 28). On the other

hand, Fanti *et al.* (26) selected thyroid incidentalomas from primary melanoma patients and they did not find any thyroid malignancy among 102 incidentally found thyroid nodules. Moreover, no significant effect of non-thyroid cancer type in the risk of thyroid cancer in thyroid incidentalomas detected on FDG-PET/CT was observed in the study of Kim *et al.* (22). Taken together, the idea that non-thyroid cancer type is an important factor for the risk of thyroid malignancy in incidentally found thyroid nodules needs further evaluation.

Incidental thyroid nodule is defined as the detection of a thyroid nodule with imaging studies performed for any reason which is unrelated with thyroid nodule. These nodules can be detected with US, CT, MRI or FDG-PET/CT. Recent publications mostly targeted the incidental thyroid nodules found with FDG-PET/CT performed for non-thyroid cancer (12-14, 21, 22, 28, 29). However, we included thyroid incidentalomas detected with either of all imaging studies as Wilhelm *et al.* did in their study (11). The imaging technique using for staging primary cancer differs between cancer types and sometimes between activities of the cancer. Especially, FDG-PET/CT imaging is used in relatively aggressive cancers. So, including thyroid incidentalomas identified by only one imaging method cannot cover all the cancer types. This may partly explain the relatively high cancer rates detected from thyroid incidentalomas identified by FDG-PET/CT imaging and also low cancer rates found in our study as we included thyroid incidentalomas from all kinds of detection methods.

Co-incidentally found thyroid carcinoma out of the suspected nodule is not so rare. Therefore, malignancy rate should be defined according to the cancers found in the nodule which was investigated. Thus, it is reasonable to define the malignancy risk as nodule-based instead of patient-based especially in a study group with multiple nodules which we did in our study as the important feature of the present study. We think that future large-scale studies which consider nodule-based approach for the investigation of thyroid cancer risk in non-thyroid cancer patients are needed.

In our study, there are a relatively high number of patients with thyroid incidentalomas who could not be evaluated with further tests (re-biopsy, operation) because of poor health status. Therefore, the limitations of the present study were that the number of our patients who undergo thyroidectomy for the suspicion of thyroid cancer was small and the repetitions of the FNABs could not be done as expected especially in patients with primary cancer which is not in remission.

Poor general health in some patients or unwillingness to thyroid operation were the reasons of a low number of thyroidectomies in these patients. However, these problems also apply to the previous studies which had a small number of patients for final diagnosis. The other limitation was the relatively higher rate of insufficient FNAB results. It may come from our approach that we performed FNAB even in smaller thyroid nodules. Nevertheless, our insufficient FNAB ratio is in accordance with the other groups reporting as 5-20 % (30).

In conclusion, our study is a large study group which is evaluating incidentalomas found in non-thyroid cancer patients all with FNAB and indicates that frequency of thyroid malignancy seems not to be substantially increased when these patients were evaluated in nodule-based approach. Future studies are needed to compare the thyroid malignancy risk in thyroid incidentalomas from non-thyroid cancer patients with the incidentalomas from healthy subjects.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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