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Synchronous and antecedent malignancies in patients with papillary thyroid carcinoma

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ABSTRACT

Objective. This study aimed to evaluate concurrently detected second primary malignancy in the patients who underwent surgery for papillary thyroid carcinoma. ***Methods***. In this study, we retrospectively analyzed the files of the patients who underwent surgery for papillary thyroid carcinoma between 2000-2017. A total number of 601 patients with papillary thyroid carcinoma were evaluated. Among these patients, 48 patients were found to have secondary primary tumors. Preoperative and postoperative laboratory examination findings of the patients were retrospectively recorded. ***Results***. Among 601 patients with papillary thyroid cancer evaluated with respect to radiation exposure, the second primary tumor with breast cancer was found to be the most common tumor. Renal cell carcinoma, malignant melanoma and stomach cancer were found to be more frequent when evaluated regardless of radiation effect. Furthermore, when molecular genetic results were evaluated, BRAF mutation rate was found to be more frequent than in other secondary tumors, especially in patients with renal cell carcinoma. ***Conclusions***. The importance of epidemiological and experimental studies of multiple cancers is obvious. Although it is known that the impact of radiation is considerable among the ones with concurrence of breast cancer and papillary thyroid carcinoma, we suggest that further studies on common molecular genetic characteristics and development of targeted treatment for detected molecules are required in the patients with renal cell carcinoma in whom papillary thyroid carcinoma is diagnosed regardless of radiation effect.radiation effect.

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Keywords: Papillary thyroid carcinoma, second primary carcinoma, carcinogenesis, renal cell carcinoma

Introduction

The incidence of papillary thyroid carcinoma has been increasing in the recent years. It constitutes about 85% of all differentiated thyroid cancers. Papillary thyroid carcinoma is a slow-growing tumor with

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favorable prognosis which is more common in women aged 20-50 years, 20-year survival rates are being around 90% [1]. Multiple primary tumors develop in the same patient at the same or different time points. The relationship between the development of multiple primary cancers and smoking is well known in humans. Nutritional deficiencies due to alcohol abuse may be an integral factor for multiple cancers. Applying radiotherapy for another cancer may also be responsible for the development of a second primary cancer. A possible explanation for the development of multiple cancers in different organs may also be a similar response to common etiological agents [2]. There are few studies in the literature on multiple malignancies with papillary thyroid carcinoma. In this study, we aimed to evaluate clinical, histopathological and molecular genetic characteristics in patients who have second primary tumor with thyroid cancer.

Methods

In this study, a total number of 601 patients with papillary thyroid carcinoma were evaluated. Among these, we retrospectively evaluated a total number of 48 cases who were diagnosed with concurrent second tumors and papillary thyroid carcinoma in our hospital between 2000-2017. All patients with concurrent tumors whose data were available were included in the study. Data on demographic features, cigarette and alcohol consumption, radiation exposure, family history and BRAF mutation status were recorded. Codon 600 (exon 15) and codon 464-469 (exon 11) mutations of the BRAF gene were examined by extracting DNA from paraffinized tissue. We defined synchronous cancers as those occurring within 6 months of the first primary cancer, while antecedent cancers were defined as those occurring more than 6 months later. Tumor types most frequently seen together with papillary thyroid carcinoma were identified. Local ethics committee approval was obtained.

Statistical Analysis

Descriptive statistics were expressed as number or percentage distributions and mininim-maximum range.

Results

A total number of 601 patients with papillary thyroid carcinoma were evaluated. Among these, 48 patients with secondary primary tumors were evaluated. The most common malignancy was breast cancer which was present in 12 patients as metachronous tumor, diagnosed within 17 years. History of radiotherapy was present in 9 of 12 patients at the breast cancer group. All patients were female (F:12/12) and the mean age was 53 years (range, 51-62 years). The average time to the diagnosis of thyroid cancer after breast cancer diagnosis was 2.9 years (min-max: 1-16 years), while it was 3.75 years (min-max: 1-16 years) after radiotherapy. Renal cell carcinoma was the most common secondary tumor when patients who received radiotherapy near the thyroid region were excluded. Besides renal cell carcinoma, malignant melanoma (4 patients), gastric cancer (3 patients), lung cancer (2 patients), parathyroid cancer (2 patients), dermatofibrosarcoma (2 patients) and lymphoma (2 patients) were also detected (Table 1).

Furthermore, colon cancer, bladder cancer, prostate cancer, basal cell carcinoma, squamous cell neck tumor, pancreas cancer, endometrium cancer, over cancer, nasopharynx cancer, malignant giant cell tumor of tendon and leukemia were all identified each in 1 patient. For all tumor types, the mean age at the

Table 1. Second primary tumor with thyroid papillary cancer cases

Type of Cancer	n	Mean Age	Gender (M/F)	Cigarette (n)	Hashimato (+)	BRAF (+)	RT
Breast cancer	12	53	0/12	6	7	1	9
Renal cell cancer	10	56	8/2	6	-	5	-
Malignant melanoma	4	64	2/2	-	-	2	-
Gastric cancer	3	62	2/1	2	-	-	-
Lymphoma	2	53	2/0	1	-	-	2
Dermatofibrosarcoma	2	57	1/1	1	-	-	-
Parathyroid cancer	2	69	0/2	1	-	-	-
Lung cancer	2	60	1/1	2	-	-	-

F = female, M = male, n = the number of patients, RT = radiotherapy

Table 2. Synchronous and antecedent malignancies in patients with papillary thyroid carcinoma

Type of Cancer	n	Synchronous (n)	Antecedent (n)
Breast cancer	12	0	12
Renal cell cancer	10	8	2
Malignant melanoma	4	2	2
Gastric cancer	3	0	3
Lymphoma	2	0	2
Dermatofibrosarcoma	2	0	2
Parathyroid cancer	2	2	0
Lung cancer	2	0	2

time of second tumor diagnosis was 56 years (min: 28, max: 76). Thyroid papillary carcinoma was determined as metachronous in 9 patients, detected within 1-16 years after the diagnosis of breast cancer. Papillary thyroid carcinoma was determined to be synchronous in 8 patients with renal cell carcinoma. Furthermore, papillary thyroid carcinoma was diagnosed in 1 patient 3 years after the diagnosis of renal cell carcinoma and papillary thyroid carcinoma was detected in 1 patient 2 years prior to the diagnosis of renal cell carcinoma (Table 2). Five patients with renal cell carcinoma were determined to be BRAF positive at molecular pathological investigation. One of these cases with micropapillary thyroid carcinoma aggressively progressed and metastasized to lymph nodes. Therefore, lymph node excision was applied. This patient died after recurrence and metastasis of renal cell carcinoma. Second patient with BRAF positivity had papillary thyroid carcinoma recurrence and wide-spread metastatic renal cell carcinoma.The second most common cancer with BRAF mutation was determined to be malignant melanoma by molecular pathology.

Discussion

Developments in the diagnosis and treatment of various malignancies and increased survival have increased the rate of secondary cancers in recent years. In one study, the rate of non-thyroid malignancy was 13.9% in the subjects with papillary thyroid carcinoma. Breast cancer, prostate cancer, malignant melanoma, leukemia and lymphoma were determined to be the most common secondary cancers, all of which were thought to be related to radiation exposure [3]. In our study, non-thyroidal malignancy rate was 7.9% among the subjects with papillary thyroid carcinoma. Breast cancer was determined to be the most common second primary tumor among the subjects with papillary thyroid cancer exposed to high levels of radiation. The possible association between breast and thyroid cancer was found to be significant with respect to radiotherapy. Early stage breast cancer is typically treated by breast conserving surgery and postoperative radiation therapy. Following treatment, breast cancer survivors are 10-50% more likely to develop a second primary breast cancer than the general population. Therefore, long-term effects of therapies such as radiation therapy among cancer survivors are important. Furthermore, the most common tumor was determined to be renal cell carcinoma independent of radiation exposure. Multiple primary tumors, developing at the same time or at different time points, have been reported to occur in 0.7%-7.7% of all carcinomas [4-6]. There are various theories on the development of multiple tumors, but the exact mechanisms are not fully understood. These theories include; “field cancerization” theory of being exposed to carcinogenic substances like alcohol and cigarette, “cancer prone” theory of having multiple tumors in different anatomical regions, and “common clonal origin” theory for explaining cases with multiple tumors by current molecular studies. In addition, underlying genetic and immunological deficiency in a patient may reflect treatment related damage or exposure to carcinogens. Long-term follow-up is important for the observation of the development of new neoplasms or the recognition of developing secondary malignancy that has been skipped before [7-17].

In our study, BRAF mutation was determined to be more frequent in renal cell carcinoma which was the most common tumor regardless of radiation. For this reason, further studies are required to detect a common genetic mutation. Multiple primer tumors are usually divided into two groups as synchronous and metachronous. We defined synchronous cancers as those occurring within 6 months of the first primary

cancer, while metachronous cancers were defined as those occurring more than 6 months later [18]. In our study, papillary thyroid carcinoma was determined to be metachronous in patients with breast cancer. In addition, it was determined to be both synchronous and metachronous in patients with renal cell carcinoma and malignant melanoma. Patients with a primary tumor have 1.29 times higher risk of a new cancer than healthy individuals [19]. Prevalence of multiple primary tumors reaches up to 36% at advanced ages [20]. According to the World Health Organization's age classification, multiple primary tumors are more common in the older age group (> 65 years). This information suggests that aging is a risk factor for the development of cancer. Immune system failure and lack of resistance to carcinogens may explain increased incidence of tumors among elderly [21]. Median age of our study subjects was 56 years (min: 28 - max: 76), being lower than WHO data. Some environmental and individual factors, such as exposure to intensive chemical carcinogens, previous treatments, genetic factors and family history could have caused this situation [22-24]. In multiple primary cancers, the likelihood of developing other cancers in the same place with primary cancer is high, called as field effect. The field effect can be summarized as cancer development in different organs due to exposure to the same carcinogenic agents or genetic alterations. This relationship was found to be statistically significant for oral cavity cancers, pharyngeal cancer, colorectal cancer and malignant melanoma in both genders. Furthermore, field effect may be relevant for women with breast and bladder cancer [25]. In our study, malignant squamous cell neck tumors and parathyroid cancers developed as a result of field effect in the patients with papillary thyroid cancer. However, the association between papillary thyroid cancer and renal cell carcinoma, which was the most common tumor regardless of radiation, requires further studies.The importance of epidemiological and experimental studies on multiple cancers is clear. Investigation of environmental factors playing role in the etiology is important for better understanding of the mechanisms of multiple cancer development. With the information obtained through such researches, development of multiple primary cancers can be minimized by defining high-risk group of patients. Probability of developing a second primary tumor is higher in the subjects with a known malignancy than in normal patients. Therefore, it is suggested that follow-up period should be long enough in the subjects treated for cancer. When multiple tumoral lesions are detected in a patient, the clinician should consider metastasis, recurrence and as well as a second primary tumor in the differential diagnosis.

Conclusions

As a result of this study, renal cell carcinoma was detected to be the most frequent malignancy in the patients with papillary thyroid carcinoma independent of radiation effect. In this respect, further work is needed to explain the link between these two tumors. This field needs further studies to explain common molecular mechanisms. In addition, higher frequency of BRAF mutation in those subjects may be important for unknown genetic mutations.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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