Synchronous and Antecedent Nonthyroidal Malignancies in Patients with Papillary Thyroid Carcinoma

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BACKGROUND: There is a known association between the development of papillary thyroid cancer (PTC) after a primary nonthyroidal cancer (NTC). However, the prevalence of synchronous or antecedent NTCs in patients with PTC is undetermined, as are the clinicopathologic characteristics of PTC in these patients.

STUDY DESIGN: A review was performed of our prospectively maintained PTC database between January 1995 and December 2010. Information collected included patient and tumor characteristics, medical history, PTC presentation, and treatment modality.

RESULTS: Four hundred and thirty-three adult patients underwent thyroid resection and had PTC on final pathology. Sixty-seven cases of synchronous or antecedent NTCs were observed in 60 patients (13.9%). The most commonly associated antecedent NTCs were breast (n = 11), prostate (n = 8), and melanoma (n = 5), whereas renal cell carcinoma (n = 3) and melanoma (n = 3) were the synchronous NTCs most observed. Compared with patients without an NTC, those with an NTC were older (56.4 ± 15.5 years vs 44.9 ± 14.2 years; $p < 0.0001$), had experienced radiation exposure (35.0% vs 3.5%; $p < 0.001$), and more commonly presented with a thyroid mass incidentally on imaging (41.7% vs 9.1%; $p \leq 0.001$). Papillary thyroid cancer tumor characteristics were similar between groups, except that NTC patients presented at a more advanced stage. However, when analyzed independently, primary tumor size, and nodal and distant metastases were comparable.

CONCLUSIONS: The prevalence of synchronous or antecedent NTCs in patients surgically treated for PTC is 13.9%. These patients present with PTC tumor characteristics similar to those without additional NTCs, and should therefore be managed equivalently. In addition, surgeons should be aware of the frequency of synchronous PTC with these types of tumors and consider evaluation of the neck at the time of NTC diagnosis. (J Am Coll Surg 2013;216:1174–1180. © 2013 by the American College of Surgeons)

Thyroid cancer is the most common endocrine malignancy, and the annual incidence has risen nearly 50% since the 1970s.[1,2] The 2005–2009 age-adjusted annual incidence rates are 17.3 per 100,000 women and 5.9 per 100,000 men according to the Surveillance, Epidemiology, and End Results cancer registry.[1] The incidence of follicular, anaplastic, and medullary thyroid cancer has not changed substantially over time, and virtually all of the observed increase is attributable to a rise in papillary thyroid cancer (PTC).[2]

Papillary thyroid cancer is the most common form of thyroid cancer, constituting nearly 90% of all thyroid malignancies.[2] Known risk factors for PTC include exposure to ionizing radiation at a young age and a history of thyroid disease, primarily benign thyroid nodules, and potentially Hashimoto thyroiditis.[3-5] Familial cancer syndromes such as Cowden syndrome and familial adenomatous polyposis are also associated with PTC.[6,7] Numerous causes have been proposed for the rise in PTC incidence and include hormonal factors, changes

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Abbreviations and Acronyms
IQR = interquartile range
NTC = nonthyroidal cancer
PTC = papillary thyroid cancer
SIR = standardized incidence ratio

in histologic criteria, and increased diagnostic scrutiny.[2,8-11] In addition, several studies have reported an increased incidence of thyroid cancer after a primary malignancy at multiple sites.[12-15] This association might be related to treatment effects of the primary malignancy, specifically radiation therapy; however, some studies have noted an increased risk of thyroid cancer as a second primary after other cancers in patients without earlier radiation therapy.[12,16,17] In addition, many studies have reported an increased rate of secondary malignancies among thyroid cancer survivors, suggesting a 2-way positive association.[12-14,18-20]

The majority of existing literature on this topic focuses on the risk of various cancers developing after a primary thyroid cancer and, to a lesser extent, the risk of thyroid cancer after an earlier nonthyroidal malignancy. However, to our knowledge, no studies have examined the clinicopathologic characteristics of PTC in patients with an additional malignancy. Therefore, to advance our understanding of this association, the objectives of this study were the following: determine the prevalence of an additional synchronous or antecedent nonthyroidal cancer (NTC) in patients surgically treated for PTC and compare the clinicopathologic characteristics of PTC between patients with and without an additional synchronous or antecedent NTC.

METHODS

All patients who undergo thyroid surgery at our institution are documented in a prospectively maintained database. The current study is an Institutional Review Board-approved retrospective review of patients that underwent a thyroid resection at our institution between January 1995 and December 2010 and had PTC on final pathology. Exclusion criteria included patients younger than 18 years of age and patients with a history of thyroid resection for PTC before their presentation at our institution, unless the detailed pathologic information for their initial surgery was available in our electronic medical record. If this were the case, the pathology from the initial surgery was used for analysis. Patients with follicular variant PTC were included. In addition, patients with a history of antecedent non-PTC thyroid cancer (n = 7) were included but were considered part of the "without NTC" group during analysis.

Information contained in our database and used for this study included the following: patient demographics; medical history, including synchronous or antecedent malignancies; surgical history; previous radiation exposure; clinical presentation of PTC; indication for thyroidectomy; pathologic information; treatment intervention(s) for PTC; length of follow-up; and survival. Papillary thyroid microcarcinoma was defined as the largest focus of PTC in the pathologic specimen measuring $\leq$1 cm in diameter. The TNM staging system of the American Joint Committee on Cancer was used for tumor classification of PTC.[21] Similar to earlier studies, it was assumed that patients without evidence of lymph node metastases on preoperative ultrasound, pathologic analysis, or iodine 131 post-therapy scintigraphy were negative for lymph node metastases (N0).[22,23]

Synchronous malignancy was defined as the diagnosis of an NTC within 6 months of PTC diagnosis. Antecedent malignancy was defined as the diagnosis of an NTC more than 6 months before PTC diagnosis. The latency period between the 2 diagnoses was calculated from the date of primary NTC diagnosis to the date of PTC diagnosis by fine-needle aspiration. If the date of diagnostic fine-needle aspiration biopsy was unknown, or if the patient did not have a preoperative diagnosis of PTC, the date of thyroid resection was used as the date of PTC diagnosis. If a patient had multiple antecedent NTCs, only the initial cancer was used for latency analysis. The follow-up period for all patients in the series was calculated from the time of thyroid surgery to the most recent clinic visit by either the operating surgeon or the endocrinologist.

Data were analyzed using Stata software version 12 (Stata Corp) and are expressed as mean (SD) for continuous, normally distributed variables or as median with interquartile range (IQR) for non-normally distributed variables. Comparisons of continuous variables were made using Student's *t*-test and comparisons of categorical variables were performed using chi-square or Fisher's exact test when appropriate. Values of $p < 0.05$ were used to determine statistical significance.

RESULTS

Clinicopathologic characteristics of papillary thyroid cancer in patients with synchronous or antecedent malignancy

A total of 433 patients with PTC were included in this analysis. The mean age was 46.5 $\pm$ 14.9 years and 73.7% (n = 319) were female. Sixty patients (13.9%) had either a synchronous or antecedent NTC. Table 1