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Distinguishing classical papillary thyroid microcancers from follicular-variant microcancers

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ABSTRACT

Background: Papillary thyroid microcarcinomas (mPTCs), tumors less than or equal to 1 cm, have been considered the same clinical entity as microfollicular-variant papillary thyroid microcarcinomas (mFVPTCs). The purpose of this study was to use population-level data to characterize differences between mFVPTC and mPTC.

Materials and methods: We identified adult patients diagnosed with mFVPTC or mPTC between 1998 and 2010 in the Surveillance, Epidemiology, and End Results database. Binary comparisons were made with the Student *t*-test and chi-squared test. Multivariate logistic regression was used to further analyze lymph node metastases and multifocality.

Results: Of the 30,926 cases, 8697 (28.1%) were mFVPTC. Multifocal tumors occurred with greater frequency in the mFVPTC group compared with the mPTC group (35.4% *versus* 31.7%; $P < 0.01$). Multivariate logistic regression indicated that patients with mFVPTC had a 26% increased risk of multifocality (odds ratio, 1.26; 95% confidence interval, 1.2–1.4; $P < 0.01$). In contrast, lymph node metastases were nearly twice as common in the mPTC group compared with the mFVPTC group (6.8% *versus* 3.6%; $P < 0.01$). Multivariate logistic regression confirmed that patients with mPTC had a 69% increased risk of lymph node metastases compared with patients with mFVPTC (odds ratio, 1.69; 95% confidence interval, 1.4–2.0; $P < 0.01$).

Conclusions: Multifocality is not unique to classical mPTC and occurs more often in mFVPTC. The risk of lymph node metastases is greater for mPTC than mFVPTC. The surgeon should be aware of these features as they may influence the treatment for these microcarcinomas.

1. Introduction

Thyroid cancer is one of the most rapidly increasing malignancies in the United States. The incidence rate has doubled from 7.00 per 100,000 in 1998 to 14.05 per 100,000 in 2010 [1]. Because of improved tumor detection techniques, most of this increase has been attributed to microcarcinomas, cancers the World Health Organization defines as measuring 1 cm or less [2].

Papillary thyroid microcarcinomas (mPTCs) have demonstrated a 441% increase between 1983 and 2006, whereas the incidence rate of papillary carcinomas measuring 5 cm or greater has remained almost unchanged [1]. Despite this increase in papillary microcarcinoma incidence, there is continued debate regarding the most effective treatment for these cancers, predominately because of their excellent prognosis [3,4]. Providers must weigh any potential risks of

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treatment against the risk of recurrence or metastases. Several risk factors have been identified in determining the tumor progression and prognosis of patients with mPTC. Age, race, sex, tumor size, node involvement and metastases, extrathyroidal invasion, and distant metastases were significant factors in risk stratifying patients to predict worse prognosis in patients with mPTC [3,5–8].

Among papillary thyroid carcinomas (PTCs), the most common type of thyroid malignancy, several histologic variants exist, with follicular-variant papillary thyroid carcinoma (FVPTC) accounting for 24%–33% of PTCs [9–12]. FVPTC was first described by Crile and Hazard in 1953 [13], and in 1960 Lindsay described FVPTC as a clinical entity that presents with nuclear features of classical papillary carcinomas, but with a follicular growth pattern [14]. Although some variants of PTC carry a much worse prognosis when compared with classical PTC, FVPTC is not considered to differ drastically in disease-specific survival [12,15]. Because FVPTC presents with histologic characteristics of both PTC and follicular thyroid carcinoma (FTC), it is believed to behave clinically as an intermediary between the two carcinomas [12,16].

Although FVPTC tumors greater than 1 cm have been well studied, relatively little is known about microfollicular-variant papillary thyroid microcarcinomas (mFVPTCs). Clinicians treat mPTC and mFVPTC as if they were the same clinical entity. Often studies of microcarcinomas consider all histologic variants together, with little distinction between histologic subtypes. Therefore, it remains unknown whether the factors that determine disease behavior for microcarcinomas differ by histologic type. The purpose of this study was to use population-level data to characterize differences between mFVPTC and mPTC.

2. Materials and methods

2.1. Database

A retrospective cohort study was performed using data from the Surveillance, Epidemiology, and End Results (SEER) Cancer Database maintained by the National Cancer Institute. SEER is a tumor database that currently collects cancer incidence and survival data from 17 cancer registries, representing 26% of the US population. SEER registries include the states of Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah, metropolitan areas of Atlanta, Detroit, San Francisco–Oakland, Seattle-Puget Sound, and San Jose–Monterey, and the Alaska Native Tumor Registry, rural Georgia, Greater California, and Los Angeles County. In addition to patient demographics, SEER registries routinely collect data on primary tumor site, tumor pathology, and stage at diagnosis, among other tumor characteristics. Additionally, SEER collects information on the first course of treatment [17,18]. The data set used in the present study was released in April 2013, based on the November 2012 submission.

2.2. Case definition

All patients with primary PTC or FVPTC diagnosed between 1988 and 2010 were examined, but patients diagnosed between 1988 and 1997 were excluded from the present study analysis because of variability in pathologic diagnosis of FVPTC in the earlier years. Cases were identified using primary tumor site code of C739 (thyroid) in combination with the International Classification of Disease for Oncology, third edition [19]. PTCs included 8050 (papillary carcinoma, not other specified), 8260 (papillary adenocarcinoma, not other specified), 8341 (papillary microcarcinoma), and 8343 (papillary carcinoma, encapsulated). FVPTCs included 8340 (papillary carcinoma, follicular variant).

Only patients with tumor sizes less than or equal to 1 cm were selected. Patients who did not have surgery or diagnoses made only at autopsy were excluded from this analysis.

2.3. Data analysis

After identification of the mPTC and mFVPTC cases in SEER database, we first compared the demographics, tumor features, and treatment among the patients. Significance of the differences was calculated either by the chi-square test for categorical variables or the Student *t*-test or Wilcoxon rank sum test for continuous variables.

Multivariate logistic regression was used to analyze the relative importance of histologic type in the development of lymph node metastases and multifocality. Clinically significant lymph node metastases were defined as at least two positive regional lymph nodes. Specific predictors that demonstrated significance ($P < 0.05$) in the univariate analysis were used in the multivariate analysis model. All statistical analysis was performed using STATA 12 (StataCorp 2011, College Station, TX). *P* value < 0.05 was defined to be statistically significant.

3. Results

3.1. Patient characteristics, tumor features, and treatments

Our selection criteria identified 22,229 mPTC cases (71.9%) and 8697 mFVPTC cases (28.1%). The demographics, clinicopathologic, and treatments of mFVPTC and mPTC subgroups are compared in Table 1. Individuals in the mFVPTC group were slightly older (51.4 ± 13.8; Table 1) than individuals in the mPTC group (49.8 ± 13.8; $P < 0.01$). Specifically, there was a higher percentage of cases older than 45 y in the mFVPTC group ($n = 5912$; 68.0%) compared with the mPTC group ($n = 14,086$; 63.4%; $P < 0.01$; Table 1). Most patients were female in both the mPTC ($n = 18,008$; 81.0%) and mFVPTC ($n = 7210$; 82.9%; $P < 0.01$; Table 1) groups. Most patients in both groups were Caucasian (Table 1).

The mean size of the primary tumor of mPTC was 5.3 ± 3.0 mm, slightly smaller than that of mFVPTC at 5.5 ± 3.0 mm ($P < 0.01$; Table 1). There was a significantly higher percentage of patients with multifocality in the mFVPTC group ($n = 3065$; 35.4%) than in the mPTC group ($n = 7003$; 31.7%; $P < 0.01$; Table 1). The mFVPTC group also exhibited a significantly higher number of minimally invasive tumors ($n = 317$; 3.7%) than the mPTC group ($n = 487$; 2.5%; $P < 0.01$; Table 1). Minimally invasive mFVPTC and mPTC