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Distinguishing Classical Papillary Thyroid Microcancers From Follicular-Variant Microcancers

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Abstract

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

Materials & Methods—We identified adult patients diagnosed with mFVPTC or mPTC between 1998 and 2010 in the Surveillance, Epidemiology, and End Results (SEER) database. Binary comparisons were made with the student's 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, 8,697 (28.1%) were mFVPTC. Multifocal tumors occurred with greater frequency in the mFVPTC group compared to the mPTC group (35.4% vs. 31.7%, $p<0.01$). Multivariate logistic regression indicated that patients with mFVPTC had a 26% increased risk of multifocality (OR = 1.26, 95% CI 1.2–1.4, $P<0.01$). In contrast, lymph node metastases were nearly twice as common in the mPTC group compared to the mFVPTC group (6.8% vs. 3.6%, $p<0.01$). Multivariate logistic regression confirmed that patients with mPTC had a 69% increased risk of lymph node metastases compared to patients with mFVPTC (OR 1.69, 95% CI 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.

Keywords

thyroid cancer; microcarcinoma; SEER; papillary thyroid carcinoma; follicular variant of papillary thyroid carcinoma; multifocality; lymph node metastases

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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). Due to improved tumor detection techniques, the majority of this increase has been attributed to microcarcinomas, cancers the World Health Organization defines as measuring 1 centimeter or less (2).

Papillary thyroid microcancers (mPTC) have demonstrated a 441% increase between 1983 and 2006, while 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 due to their excellent prognosis (3,4). Providers must weigh any potential risks of 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 (3,5,6,7,8).

Among papillary thyroid carcinoma (PTC), the most common type of thyroid malignancy, several histologic variants exist, with follicular-variant papillary thyroid carcinoma (FVPTC) accounting for 24–33% of PTC (9,10,11,12). FVPTC was first described by Crile and Hazard in 1953 (13), and in 1960 Lindsay described FVPTCs as a clinical entity that presents with nuclear features of classical papillary carcinomas, but with a follicular growth pattern (14). While some variants of PTC carry a much worse prognosis when compared to classical PTC, FVPTC is not considered to differ drastically in disease-specific survival (12,15). Since 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).

Even though FVPTC tumors greater than one centimeter have been well-studied, relatively little is known about micro follicular-variant papillary thyroid cancers (mFVPTC). 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 differs by histologic type. The purpose of this study was to use population-level data to characterize differences between mFVPTC and mPTC.

Materials and Methods

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 U.S. 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 current study was released in April 2013, based on the November 2012 submission.

Case Definition

All patients with primary PTC or FVPTC diagnosed between 1988 and 2010 were examined, but patients diagnosed between 1988–1997 were excluded from the present study analysis due to 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, 3rd Edition (ICD-O-3) (19). PTC included 8050 (papillary carcinoma not other specified, NOS), 8260 (papillary adenocarcinoma, NOS), 8341 (papillary microcarcinoma), and 8343 (papillary carcinoma, encapsulated). FVPTC 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.

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 chi-square test for categorical variables or student's 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.

Results

Patient Characteristics, Tumor Features and Treatments

Our selection criteria identified 22,229 mPTC cases (71.9%) and 8,697 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 were a higher percentage of cases over the age of 45 in the mFVPTC group (n=5,912; 68.0%) compared to the mPTC group (n=14,086; 63.4%, $P<0.01$, Table 1). The majority of patients were female in both mPTC (n = 18,008; 81.0%) and mFVPTC (n=

7,210; 82.9%, P<0.01, Table 1). The majority of 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 = 3,065; 35.4%) than the mPTC group (n = 7,003; 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 tumors were defined as tumors that extended into the thyroid capsule, but not beyond (SEER Codes CS Extension 400 and EOD10-Extent 40). No significant differences existed in frequency of invasive tumors or distant metastasis between mPTC and mFVPTC.

The lymph node involvement data of mFVPTC and mPTC subgroups are compared in Table 2. The incidence of lymph node metastasis in mPTC was 6.8%, nearly double the rate in mFVPTC (3.6%, P<0.01, Table 2). As expected, there were significantly more lymph nodes examined in mPTC (2.31 ± 0.05) than mFVPTC (1.65 ± 0.06; P<0.01, Table 2). There were no significant differences in positive lymph node location (central versus lateral neck) between mPTC and mFVPTC.

Total thyroidectomies were performed in 76.1% of patients with mPTC and 74.8% of patients with mFVPTC (p=0.02, Table 1). Radioactive iodine was administered to 30.4% of patients with mPTC (n = 6,748), while 32.4% of patients with mFVPTC (n = 2,817, p=0.001, Table 1) received radioactive iodine.

Multivariate Analysis for Risk Factors of Multifocality

Because significantly more patients with mFVPTC had multifocal tumors compared to mPTC, we examined the relative importance of histologic type in determining multifocality using multivariate analysis (Table 3). Interestingly, having mFVPTC histology type was significantly associated with multifocality (OR = 1.26, P<0.01, Table 3). mFVPTC histology demonstrated a 26% increased risk of multifocality compared to mPTC. Age greater than 45 years was also significantly associated with multifocality (OR = 1.22 P<0.01, Table 3).

Multivariate Analysis of Factors Associated With Lymph Node Metastases

Cases of mPTC demonstrated almost double the number of lymph node metastases than mFVPTC. To analyze this relationship further, we constructed a multivariate model to evaluate the relative importance of histologic type in determining lymph node metastases. Interestingly, mPTC histology was significantly associated with developing lymph node metastases with an odds ratio of 1.69 (P<0.01, Table 4). In other words, mPTC cases had a 69% increased risk of lymph node metastases compared to patients with mFVPTC. The other significant variables associated with lymph node metastases were extrathyroidal extension (OR = 3.08, P<0.01) and distant metastases (OR = 3.20, P<0.01, Table 4).

Discussion

As papillary thyroid mPTC are diagnosed at an increasing rate, providers are left to make difficult clinical decisions about treatment. Further complicating the issue, several histologic variants of mPTC exist, with mFVPTC representing the largest and fastest growing subtype of mPTC (9–11). Management of microcarcinomas remains controversial, and clinicians currently treat mPTC and mFVPTC as the same clinical entity. There is very limited research characterizing mFVPTC or distinguishing it from mPTC. We sought to resolve these issues using a large-scale database to characterize the differences between mFVPTC and mPTC.

Here we demonstrate clinically significant differences between mFVPTC and mPTC in terms of multifocality and lymph node metastases using population-level data. We found near double the percentage of lymph node metastases in the mPTC group than mFVPTC group (Table 2). Via multivariate analysis, we show mPTC was independently associated with lymph node metastases. Additionally, while multifocality is traditionally associated with mPTC tumors, we found an even higher percentage of multifocal tumors in the mFVPTC group (35.4%) than in the mPTC group, and mFVPTC was independently associated with multifocality in the multivariate analysis.

Current data suggest traditional FVPTC tumors greater than one centimeter, and not microcancers, behave as clinical intermediates between follicular thyroid carcinoma (FTC) and papillary thyroid carcinoma (PTC) (12,16). A study by Liu et al examined the clinicopathologic features of FVPTC tumors and found in their sample that 34% of the cases were over the age of 45, 14% exhibited extrathyroidal extension, 14% demonstrated lymph node metastases, and none demonstrated distant metastases (20). In our study of the FVTPC microcancers, we found 68% of patients were over the age of 45, double what this previous group reported in tumors greater than one centimeter, likely reflecting the increased incidence of all thyroid tumors with increasing age. 5% of our sample of mFVPTC exhibited extrathyroidal extension, 4% demonstrated lymph node metastases, and 0.5% demonstrated distant metastases. These differences indicate the overall better prognosis of microcancers compared to tumors greater than one centimeter.

Multifocality may represent spread of the tumor throughout the thyroid, while at other times multifocality arises from de novo lesions (21,22). In a previous study of mPTC tumors, multifocality was found in 15% to 16% of tumors (23). In our study, we found multifocality in 35% of mFVPTC tumors and 32% of mPTC tumors. This difference could be due to a larger overall sample size in our study and because the former study included patients from 2002–2008 in their study, while we included patients from 1998–2010. Multifocal thyroid tumor disease has been associated with high-risk tumors (24). Multifocality in mPTC has been previously reported as one of the risk factors for increased lymph node recurrence, increasing the risk 5.6 fold (25). This increase in tumor recurrence rate with multifocal thyroid tumors has been described extensively in the literature (26,27). SEER only provides data on disease specific and overall mortality, so we cannot comment on recurrence in this series.

One study on treatment of mPTC found multifocality was independently associated with increased likelihood of receiving radioactive iodine (4). Another study recommended lobectomy as the treatment of choice for patients with single focus mPTC, but total thyroidectomy for patients with multifocal mPTC tumors, given a decrease from 20% disease recurrence after lobectomy to a 5% disease recurrence after total thyroidectomy (28). These and other authors have previously recommended total thyroidectomy as the preferred treatment for patients with PTC given the high percentage of multifocality associated with PTC (25). Since we show a 26% increased risk of multifocal tumors in mFVPTC cases compared to mPTC cases, providers need to consider multifocality in mFVPTC, and not just mPTC. Multifocality may influence the decision to perform total thyroidectomy or completion thyroidectomy for patients with microcarcinomas.

Lymph node metastases have been documented as an independent prognostic marker for more aggressive papillary thyroid cancer in terms of recurrence (29). In the literature, FVPTC groups are documented to have a higher frequency of lymph node metastases than FTC, but lower than PTC groups (12). Consistent with these findings, we also demonstrated an increase in lymph node metastases in mPTC groups. Chang, H.Y et al found 34.1% PTC patients presented with lymph node or soft tissue invasion, while only 11.8% of FVPTC patients did so (30). Our study found nearly double the rate of lymph node metastases in mPTC compared to mFVPTC, while the former study found more than triple the incidence of lymph node metastases (30). This difference is likely because tumors greater than one centimeter behave more aggressively than microcancers, therefore making the differences between the tumors greater than one centimeter more pronounced.

Blanchard et al found that multifocality and tumor involvement of perithyroid tissue were each independent risk factors in predicting lymph node metastases in FVPTC tumors (31). In our multivariate analysis, we found in addition to multifocality and extrathyroidal extension, distant metastases and the mPTC histology type were independent risk factors to predict lymph node metastases. Another study found increased extrathyroidal extension in FVPTC compared to PTC (32). We, however, found no significant difference in extrathryoidal extension between the mPTC and mFVPTC groups. This difference is again likely due to the more indolent behavior of microcarcinomas.

Yamashita et al analyzed thyroid microcarcinoma prognostic factors. 93% of their sample were mPTC, 5% were micro follicular thyroid carcinomas, and the remaining 2% were distributed among other carcinoma histology types; they found lymph node metastasis was a significant indicator of disease recurrence and poor prognosis (33). Here we show patients with mPTC had a 69% increased risk of lymph node metastases compared to patients with mFVPTC, after accounting for potential confounding factors. This increase in lymph node metastases and the previously demonstrated association between lymph node metastases and disease recurrence, should be considered when making treatment decisions for mPTC patients, and emphasizes the importance of lymph node evaluation even in patients with microcarcinoma.

This study does possess some limitations. SEER is a large database, recording data from clinical centers around the nation, and so it cannot encompass all of the factors that concern

clinicians caring for thyroid cancer patients. SEER is a tumor database but not a patient database, and it does not provide detailed treatment information. For example, we do not know how many of these microcarcinomas were discovered incidentally when the thyroid was removed for other reasons. SEER does not provide recurrence data so we can only report on disease-specific survival. For differentiated thyroid carcinoma, mortality is extremely low, so this is not the ideal outcome measure for microcarcinomas whose 5-year survival approaches 100%. Another limitation is that we do not know the surgeon's intent. For example, SEER does not indicate the surgeon's intention when considering the extent of surgery – we cannot readily distinguish incidentally removed nodes from purposefully excised nodes, or prophylactic from therapeutic neck dissections. Therefore, our results may include lymph nodes that are not clinically relevant. To address this, we required at least two positive lymph nodes from SEER to consider the case as having positive lymph nodes metastases to limit patients with incidentally removed nodes. While FVPTC was originally described in 1960, it was not until 1977 that a landmark paper further characterized FVPTC (34). Since more accurate diagnosis of FVPTC pathology was not discussed until 1998, the potential for mis-diagnosis of tumor pathology exists (35). To address this issue, we chose to limit our study to 1998–2010 since the pathologic characteristics of FVPTC were better diagnosed after 1998. Preliminary analyses revealed that mFVPTC characteristics from 1998 and beyond were most similar to the most recent years (2009–2010) available.

Contrary to previous beliefs, multifocality is not unique to classical mPTC and occurs more often in mFVPTC. Although more rare than tumors greater than 1 cm, microcarcinomas may have lymph node metastases, and this is more common in patients with mPTC than mFVPTC. When a microcancer diagnosis is received post-operatively, these differences between mPTC and mFVPTC can be used to further guide clinical decision-making regarding further diagnostics or treatment. If a lobectomy was performed and the tumor was reported to be a microcancer, especially a mFVPTC, the surgeon could carefully examining the remaining lobe and consider performing a completion thyroidectomy if multifocality is suspected. If the pathology was reported as mPTC, the clinician could follow up with the patient to perform a lymph node assessment with ultrasound. These examples underscore the need for a high-quality preoperative ultrasound that assesses not only the thyroid, but also the lymph node compartments including the central and lateral neck. These differences between mPTC and mFVPTC are important clinical considerations that may influence the extent of thyroid resection or the performance of lymph node dissection in patients with microcarcinomas.

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Table 1

Demographic, clinicopathologic features, and treatment in mPTC and mFVPTC

Patient Demographics	mPTC (22,229)	mFVPTC (8,697)	P-Value
Age at diagnosis (yr ± SD)	50 ± 14	51 ± 14	<0.01
Age > 45	14,086 (63.4)	5,912 (68.0)	<0.01
Sex			<0.01
Male (%)	4,221 (19.0)	1,487 (17.1)	--
Female (%)	18,008 (81.0)	7,210 (82.9)	--
Ethnicity			
Caucasian (%)	18,714 (84.2)	7,405 (85.1)	0.04
African American (%)	1,178 (5.3)	627 (7.2)	<0.01
Others (%)	2,106 (9.5)	589 (6.8)	<0.01
Hispanic	2284 (11.2)	924 (10.6)	0.17
Tumor Features			
Tumor size (mm ± SD)	5.3 ± 3.0	5.5 ± 3.0	<0.01
Minimally invasive	487 (2.5)	317 (3.7)	<0.01
Extrathyroidal extension	1,177 (5.3)	425 (4.9)	0.15
Distant metastasis	103 (0.5)	41 (0.5)	0.93
Multifocal tumors	7,003 (31.7)	3,065 (35.4)	<0.01
Treatment			
Total thyroidectomy	16,906 (76.1)	6,504 (74.8)	0.02

Table 2

Lymph node Involvement in mPTC and mFVPTC

Characteristics	mPTC (22,229)	mFVPTC (8,697)	P-Value
Lymph nodes examined, (mean ± SD)	2.31 ± 0.05	1.65 ± 0.06	<0.01
Lymph node metastasis	1450 (6.8)	304 (3.6)	<0.01
Lymph node location			0.97
Central (%)	1218 (91.5)	256 (91.4)	--
Lateral (%)	113 (8.5)	24 (8.6)	--

Table 3

Multivariate analysis for multifocality

Dependent Variable	Odds Ratio (OR)	95% CI	P-Value
Distant metastasis	0.33	0.19–0.55	<0.01
Non-caucasian race*	--	--	--
Female	0.96	0.87–1.07	0.5
Hispanic	1.02	0.90–1.16	0.73
Size	1.05	1.04–1.07	<0.01
Year of diagnosis	1.05	1.04–1.07	<0.01
Caucasian	1.13	1.00–1.28	0.26
Lymph node metastasis	1.08	0.93–1.25	0.31
Extrathyroidal extension	1.15	1.00–1.33	0.05
Age>45	1.21	1.12–1.32	<0.01
mFVPTC	1.26	1.15–1.38	<0.01

*Omitted due to collinearity

Table 4

Multivariate analysis for lymph node metastases

Dependent Variable	Odds Ratio (OR)	95% CI	P-Value
Non-Caucasian race*	--	--	--
Female	0.56	0.48–0.66	<0.01
Age>45	0.56	0.49–0.65	<0.01
Caucasian	1.05	0.85–1.29	0.66
Size	1.22	1.09–1.15	<0.01
Hispanic	1.23	1.00–1.50	0.05
Multifocal	1.42	1.23–1.64	<0.01
mPTC	1.69	1.42–2.00	<0.01
Extrathyroidal extension	3.10	2.59–3.72	<0.01
Distant Metastasis	3.20	1.74–6.05	<0.01

*Omitted due to collinearity