Title

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Journal

Annals of Surgical Oncology, 22(1)

ISSN

1068-9265

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Publication Date

2015

DOI

10.1245/s10434-014-3964-3

Peer reviewed

Published in final edited form as:
Ann Surg Oncol. 2015 January ; 22(1): 158–163. doi:10.1245/s10434-014-3964-3.

Lymph Node Metastases Do Not Impact Survival In Follicular Variant Papillary Thyroid Cancer

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Abstract

INTRODUCTION—Follicular variant of papillary thyroid cancer (FVPTC) is the most common and fastest growing subtype of papillary thyroid cancer (PTC) with features of both PTC and follicular thyroid cancer (FTC). The purpose of this study was to determine the patient and tumor features associated with lymph node metastases (LNM) in FVPTC.

METHODS—This was a retrospective review of adult (≥18) patients with histologically confirmed diagnoses of FVPTC within the SEER database between 1988 and 2009. LNM were defined by at least two lymph nodes with metastatic disease. To determine factors associated with LNM, we constructed a multivariate logistic regression model from significant variables ($p<0.05$) identified on univariate analysis. Similarly, we used a Cox proportional hazards model to understand the relative importance of LNM in determining disease specific mortality (DSM).

RESULTS—Of the 20,357 cases of FVPTC with lymph node data available, 1,761 (8.7%) had LNM. 61.1% of these LNM were located in the central neck and 38.9% were in the lateral neck. Extrathyroidal extension (OR 2.6, 95% C.I. 2.2–3.0, $p<0.01$) and multifocality (OR 3.0, 95% C.I. 2.5–3.6, $p<0.01$) were the strongest predictors of LNM. Importantly, LNM did not independently predict DSM ($p = 0.52$). Tumor size > 4 cm (HR 5.3, 95% C.I. 2.2–12.8, $p<0.01$) and extrathyroidal extension (HR 8.2, 95% C.I. 3.0–22.0, $p<0.01$) were the strongest predictors of DSM.

CONCLUSIONS—LNM occur in less than 10% of patients with FVPTC but do not impact DSM. Instead, DSM in FVPTC is related to size and local invasion.

Introduction

Follicular variant of papillary thyroid cancer (FVPTC) is the most common and fastest growing subtype of papillary thyroid cancer (PTC), accounting for 24–33% of all PTCs (1, 2). It was first described by Crile and Hazard in 1953 as aveolar variant of papillary thyroid carcinoma (3). In 1960 Lindsay confirmed this entity and used the term “follicular variant” of PTC to describe a thyroid tumor with nuclear features of PTC but with a follicular growth

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Disclosures: The authors have no relevant financial disclosures

pattern (4). Grossly, these tumors look like a follicular neoplasm, and the diagnosis hinges on the identification of nuclear features of PTC (i.e, nuclear clearing, grooves, and pseudoinclusions) so that FVPTC is not confused with either follicular adenoma or follicular thyroid cancer (FTC) (5, 6). Although there remains significant variation in diagnosing FVPTC, imunohistochemical markers such as HBME-1 and molecular markers like BRAF have improved its recognition (6, 7).

Clinically, FVPTC displays intermediate behavior between that of PTC and FTC. In a large population-based study comparing FVPTC to PTC and FTC cases, survival from FVPTC was similar to classical PTC, but extrathyroidal extension and distant metastases among FVPTC were more similar to rates seen in FTC (8). Interestingly, the incidence of lymph node metastases (LNM) in FVPTC (16%) was roughly half the incidence in PTC (34%) but much greater than FTC (2%) (8). This makes intuitive sense since PTC spreads via lymphatic channels while FTC spreads locally or via the bloodstream (9, 10).

LNM remain a significant burden of disease for patients with all types of differentiated thyroid cancer since they are associated with a higher recurrence rates (11–13). Recurrence often requires re-operation that carries a risk of higher complication rates, especially if the recurrence is located in the central neck (14, 15). The impact of LNM on survival for differentiated thyroid carcinoma remains controversial, but a growing number of population-based studies demonstrate a small but significant decline in disease-specific survival (16, 17). In one such study, Zaydfudim and colleagues found that cervical LNM conferred an increased risk of disease-specific mortality (DSM) in all patients with FTC and older (≥45 years old) patients with PTC (16).

Data on LNM in FVPTC are currently lacking. Although the incidence of LNM falls between that of PTC and FTC, it is unclear which patients with FVPTC are likely to have LNM. Knowing this information can assist the clinician in determining which patients should undergo additional diagnostic workup and/or therapeutic interventions such as lymphatic mapping or lymph node dissection. The purpose of this study was to determine the patient and tumor features associated with lymph node metastases (LNM) in FVPTC.

Methods

This was a retrospective review using the Surveillance, Epidemiology and End Results (SEER) database between 1988 and 2009. Data from all SEER registries were queried for adult (≥18) patients with histologically confirmed diagnoses of FVPTC (International Classification of Disease for Oncology, 3rd Edition Code 8340). Cases that did not undergo surgery or diagnoses made only at autopsy were excluded from this analysis. In order to limit our analysis to clinically significant disease in the lymph nodes, LNM were defined by at least two lymph nodes with metastatic disease. We defined and divided extrathyroidal extension into two different types: 1) minimally invasive and 2) widely invasive. Minimally invasive was defined by the SEER CS Extension code 400 (into the capsule, but not beyond) or the SEER extent of disease (EOD) code 70/80 (through capsule of gland but not beyond). Widely invasive extrathyroidal extension was defined by the SEER CS Codes 450, 480, 500, 520, 550, 560, 600, 620, 650, 700, 800, 810 or EOD codes 72–99 (extension beyond thyroid

capsule into peri-capsular soft tissue/connective tissue, muscles, nerves, esophagus, larynx, cricoid cartilage, trachea, blood vessels, mediastinal tissues, or prevertebral fascia).

To determine factors associated with LNM, we constructed a multivariate logistic regression model from significant variables ($p<0.05$) identified on univariate analysis. Similarly, we used a Cox proportional hazards model to understand the relative importance of LNM in determining disease specific mortality (DSM). For the purposes of multivariate analysis, continuous variables such as age, tumor size, and diagnostic year were converted into categorical variables. Binary comparisons were made using the student's t-test, Chi-squared test, or Wilcoxon rank sum test where appropriate.

All analyses were performed using STATA v. 12.1 (StataCorp, College Station, TX). The University of Wisconsin's Institutional Review Board approved this study.

Results

Baseline Patient and Tumor Characteristics

Of the 25,492 cases of FVPTC between 1988–2009, 20,357 had lymph node data available, and this cohort was used for all further analyses.

The mean age was 48.7 ± 14.7 years old and 59% were older than 45 (Table 1). As expected, 78.7% of all patients were female. Over 80% of all subjects were Caucasian (Table 1). The median tumor size was 16.5 ± 5 mm (Table 1).

3,803 tumors exhibited extrathyroidal extension, and this was sub-classified as either minimally invasive (into thyroid capsule, but not beyond) in 2,143, and widely invasive (extension beyond thyroid capsule into peri-capsular soft tissue/connective tissue, muscles, nerves, esophagus, larynx, cricoid cartilage, trachea, blood vessels, mediastinal tissues, or prevertebral fascia) in 1,660 (Table 1). Multifocality was present in 5,254 tumors (Table 1).

1,761 patients (8.7%) had LNM. More than two-thirds of these LNM were located in the central neck, 27.2% were located in the lateral neck, and 4.2% were labeled as mediastinal LNM (Table 1). Distant metastases were quite rare, occurring in 1.1% of cases (Table 1).

Factors associated with LNM

We used multivariate analysis to analyze patient and tumor factors associated with LNM. After selecting significant predictor variables from univariate analysis, we constructed a final multivariate model. Extrathyroidal extension (OR 2.6, 95% C.I. 2.2–3.0, $p<0.01$) and multifocality (OR 3.0, 95% C.I. 2.5–3.6, $p<0.01$) were the strongest predictors of LNM when controlling for all other patient and tumor features (Table 2). Tumor size was not independently associated with LNM.

Demographic features were also associated with LNM. Older age (>45 years old) was protective against LNM (OR 0.51, 95% C.I. 0.43–0.59, $p<0.01$, Table 2). Female gender was also protective against LNM (OR 0.51, 95% C.I. 0.43–0.61, $p<0.01$, Table 2).

The relationship between LNM and these tumor and demographic features were analyzed further with binary comparisons. 45.4% of patients with LNM were older than 45, but 60.3% of patients without LNM were over 45 ($p<0.01$). The two groups differed in mean age by 4.5 years (44.6 ± 0.38 with LNM vs. 49.1 ± 0.11 without LNM, $p<0.01$). As the multivariate analysis suggested, significantly fewer females suffered LNM (66.3% vs. 79.9%, $p<0.01$). Multifocal tumors occurred more commonly in patients with LNM (56.6%) compared to those without LNM (33.3%, $p<0.01$). Extrathyroidal extension (widely invasive) was nearly four times more common in those with LNM (25.7%) compared to those without LNM (6.5%, $p<0.01$). Although minimally invasive extrathyroidal extension was not significant on univariate analysis, it was present in 10.2% of cases with LNM and 10.5% of those without LNM ($p = 0.64$). Among patients with LNM, multifocality and extrathyroidal extension rarely occurred together (4.0% of patients with LNM).

Survival

323 patients died from thyroid cancer for a disease-specific mortality rate of 1.6%. The median survival time was 60 months (IQR 53.8 months).

Of the 323 thyroid cancer-specific deaths, 237 patients (78.4%) had LNM and 86 (26.6%) did not have LNM ($p = 0.39$). For patients with LNM, the median survival time was 59 months (IQR 57.2 months), while those without LNM had a median survival time of 56 months (IQR 58.6 months, $p = 0.21$).

Multivariate Analysis

To analyze the relative influence of LNM on disease-specific mortality, we constructed a multivariate model using items significant ($p<0.05$) on univariate analysis. The final model is shown in Table 3. Tumor size > 4 cm (HR 5.3, 95% C.I. 2.2–12.8, $p<0.01$) and extrathyroidal extension (HR 8.2, 95% C.I. 3.0–22.0, $p<0.01$) were the strongest predictors of DSM (Table 3). Female gender was protective against mortality (Table 3). Importantly, LNM did not independently predict DSM ($p = 0.52$, Table 3).

Subset Analyses

Since LNM were previously shown to impact DSM among patients older than 45 with FTC (16), we repeated this analysis, but limited the cohort to patients with an age over 45 (n = 12,051). Again, LNM did not independently impact DSM (HR 0.57, 95% C.I. 0.31 – 1.04, $p = 0.07$) when controlling for all other predictors.

Because the classification of FVPTC likely changed over time, we performed further analyses to determine if the year of diagnosis impacted the disease characteristics. Although the results reported above controlled for year of diagnosis in the models, we wanted to insure that misdiagnosis of FVPTC as either PTC or follicular cancers in the earlier years did not impact our results. After subdividing the entire study period into three or four-year groups, we compared the tumor characteristics of each time period to the most recent three year period. We found that tumors diagnosed before 1998 were the most different when compared to the most recent period. Therefore, we repeated our analyses on the subset diagnosed after 1998. The results were nearly identical to the overall cohort. As with the

subset of patients older than 45, lymph node metastases did not independently influence DSM in the cohort diagnosed after 1998 (HR 0.69, 95% C.I. 0.24 – 2.00, p = 0.50).

Discussion

Using a large, national cancer registry, we found that less than 10% of patients with FVPTC experienced LNM. FVPTC with either multifocality or extrathryoidal extension are more likely to be associated with LNM. However, LNM did not independently influence DSM in FVPTC. Instead, tumor size >4 cm and frank extrathyroidal extension were predictors of DSM.

This study extends our previous work on FVPTC in which we demonstrated its intermediate behavior between PTC and FTC (8). Here, we have defined LNM more strictly (≥2 positive nodes) so as not to include incidental or clinically insignificant LNM. Nonetheless, the incidence of LNM (8.7%) remains less than ranges typically reported for PTC (20–40%), but more than that reported for FTC (2–3%) (8, 17–19). This intermediate rate of LNM agrees with other, single institution studies comparing FVPTC to PTC and FTC (20).

Others have divided FVPTC into encapsulated and nonencapsulated subtypes (21, 22). For example, Liu et al. found that the encapsulated variant behaved similar to FTC with rare LNM while the nonencapsulated subtype displayed more frequent LNM, behaving more like classical PTC (21). Other series have shown the opposite; in one such example, none of the encapsulated tumors had LNM (23).

Unfortunately, SEER does not capture encapsulation. LNM are usually not present in encapsulated FVPTC, and encapsulation will likely affect future classification and risk stratification of FVPTC (24). Instead of encapsulation, we can look at pathologic features characteristic of either PTC or FTC. Multifocality, a feature typically associated with PTC (25, 26), conferred an increased risk of LNM. This makes sense since a greater density of intratumoral lymphatics leads to a greater propensity for both multifocality and LNM in PTC (26). However, the other pathologic feature that predicted LNM in FVPTC was extrathyroidal extension (widely invasive). Features such as local invasion or angioinvasion are associated with FTC (27, 28), but we found it was also associated with LNM. Notably, poorly differentiated forms of PTC can also display this type of extrathyroidal extension (29). Among patients with FVPTC, features historically associated with either PTC (multifocality) or FTC (local invasion) were *both* independently associated with LNM, a feature historically aligned with PTC. Therefore, our results do not support this paradigm for FVPTC to either behave strictly like PTC or FTC.

Demographic features also predicted both LNM and disease-specific mortality in FVPTC. Male gender and younger age (<45 years old) were associated with LNM. Previous single institution series of FVPTC have not demonstrated these findings, but the issue of LNM was not examined in detail (21–23). However, there are now several reports on the diffuse follicular variant (of FVPTC) that strikes younger patients and is characterized by LNM, multifocality, extrathyroidal extension, and mortality (30–32). This could explain why younger age was associated with LNM in this study, although SEER does not contain the

histology code for the diffuse follicular variant. However, these three features (LNM, multifocality, and extrathyroidal extension) rarely co-existed in the same tumors, so the diffuse follicular variant cannot explain all cases with LNM. Long-considered a poor prognostic indicator in differentiated thyroid cancer, many staging or scoring systems include male gender (33, 34). Therefore, our finding that male gender predicts both LNM and DSM in FVPTC is consistent with these broader risk stratification models for differentiated thyroid carcinoma.

These results can assist clinicians caring for patients with FVPTC for several reasons. A recent long-term follow-up study by Grogan and colleagues found that FVPTC histology independently predicted recurrence among all patients with PTC (35). Similarly, LNM remains a significant risk factor for recurrence among all patients with DTC (11). Here, we identify the demographic and tumor features associated with LNM. Notably, male gender was associated with LNM and DSM. Therefore male patients, especially those with multifocality or extrathyroidal extension should undergo careful evaluation and surveillance of the lymph node compartments of the neck so that LNM can be identified and treated as needed. Since these features may only become known postoperatively, this information will help determine follow-up and scheduling of surveillance ultrasounds and/or labs. This also underscores the importance of a thorough preoperative ultrasound. Although LNM impact recurrence, they do not influence survival in patients with FVPTC. Although the relationship between LNM and survival remains controversial for PTC, it is helpful to provide patients with FVPTC the reassurance that LNM do not necessarily affect their lifespan, but LNM should be considered in the context of all other prognostic features when assessing any given patient's individualized risk.

This study has several limitations. First, one cannot determine the surgeon's intention from SEER. Excision of lymph nodes can occur incidentally with the thyroid, or purposefully in either a therapeutic or prophylactic fashion. Furthermore, the surgeon's technique and approach to cervical lymph nodes is unknown, and SEER likely contains wide variation with respect to surgical approach. We defined LNM as ≥2 positive lymph nodes in an attempt to focus our analysis on clinically significant LNM. Although this was unlikely to completely eliminate such variability, this hopefully improves upon previous studies that consider *any* positive LNs. Historically, FVPTC was a difficult pathologic diagnosis, and much variation existed between pathologists (25, 36). We have limited our analysis to 1988 – 2009 in order to eliminate misclassification, and performed subset analyses on a more recent cohort. Since the results did not change, we do not feel misdiagnosis of FVPTC impacts our major findings. Missing data within SEER is also problematic, but hopefully the very large numbers (>20,000) and exclusion of earlier years helped dampen the effects of missing data or misdiagnosis. Finally, SEER does not yet contain data on molecular markers such as BRAF. Molecular analysis of cytologic specimens for markers such as BRAF will likely impact the surgical approach since BRAF negative tumors likely represent less aggressive, encapsulated variants (37).

In summary, LNM occur in less than 10% of patients with FVPTC but do not impact DSM. Instead, DSM in FVPTC is related to size and local invasion. These factors provide specific

data regarding FVPTC that furthers our understanding of this entity and can help inform follow-up and surveillance.

Acknowledgments

This study was supported by NIH T32 CA009614-23 and the NIH National Center for Advancing Translational Sciences (NCATS) grant UL1TR000427.

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Table 1

Patient and Tumor Characteristics (n = 20,357)

Variable	# (%)
Age	48.7 ± 14.7
Age > 45 y/o	12,051 (59.0)
Female gender	16,084 (78.7)
Race	
Caucasian	16,942 (82.9)
Hispanic	2,546 (12.5)
Asian/Pacific Islander	1,681 (8.2)
Black	1,522 (7.5)
American Indian/Alaska Native	97 (0.5)
Unknown	187 (0.9)
Median tumor size (mm)	16 ± 5
Extrathyroidal extension	3,803 (24.4)
Minimally invasive	2,143 (13.7)
Widely invasive	1,660 (10.6)
Multifocality	5,254 (35.3)
Metastatic lymph nodes	1,761 (8.7)
Central	1,040 (68.6)
Lateral	413 (27.2)
Mediastinal	63 (4.2)
Distant Metastases	155 (1.1)

Data are expressed as a mean ± standard error of the mean for continuous variables and the count with the percentage in parentheses for categorical variables. Hispanic is listed under race, but does not represent a mutually exclusive race category. Extrathyroidal extension, was sub-classified as either minimally invasive (into thyroid capsule, but not beyond) in 2,143, and widely invasive (extension beyond thyroid capsule into peri-capsular soft tissue/connective tissue, muscles, nerves, esophagus, larynx, cricoid cartilage, trachea, blood vessels, mediastinal tissues, or prevertebral fascia).

mm = millimeters

Table 2

Factors Associated with Lymph Node Metastases

Variable	Odds Ratio	95% C.I.	p value
Age > 45 y/o	0.51	0.43 – 0.59	<0.01
Female gender	0.51	0.43 – 0.61	<0.01
Tumor size > 4 cm	1.13	0.88 – 1.46	0.36
ETE – widely invasive	2.55	2.18 – 2.97	<0.01
Multifocality	2.98	2.50 – 3.56	<0.01

Multivariate model comprised of significant ($p<0.05$) factors from univariate analysis. Other controls in the model include diagnostic year, # of lymph nodes examined, and extent of surgery performed (lobectomy vs. total thyroidectomy).

C.I. = confidence interval.

Table 3

Multivariate Analysis: Disease-Specific Mortality

Variable	Hazard Ratio	95% C.I.	p value
Age > 45 y/o	1.23	0.87 – 2.90	0.39
Female gender	**0.27**	**0.11 – 0.69**	**<0.01**
Non-white race	0.28	0.04 – 2.20	0.23
Tumor size > 4 cm	**5.26**	**2.16 – 12.82**	**<0.01**
ETE – widely invasive	**8.16**	**3.03 – 21.99**	**<0.01**
LNM	0.34	0.11 – 1.02	0.52

Multivariate Cox proportional hazards model with disease-specific mortality as the dependent variable. Additional controls included in the model include diagnostic year, extent of surgery (lobe vs. total), and number of lymph nodes examined. Significant predictor variables are in **bold** font.

C.I. = confidence interval, *ETE* = extrathyroidal extension, *LNM* = lymph node metastases