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Encapsulated FVPTC: Are These Tumors Really Benign?

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Abstract

OBJECTIVE—Recent studies suggest that the encapsulated form of follicular variant papillary thyroid cancer (eFVPTC) behave more similarly to benign lesions and can be treated with thyroid lobectomy alone instead of total thyroidectomy. To distinguish aggressive cancers from more benign lesions more clearly, the objective of this study was to determine if the eFVPTC behaves less aggressively than the non-encapsulated variant (neFVPTC).

METHODS—A prospectively collected endocrine surgery database in our institution was reviewed for all patients with FVPTC on surgical pathology from 1999 to 2012. Samples were re-reviewed to determine if the tumor was eFVPTC or neFVPTC, which were correlated with patient outcomes.

RESULTS—Of the 68 patients, 59 (87%) had eFVPTC and 9 (13%) had neFVPTC. The mean age was 48 years and 63% were female. Fifty-four out of 64 patients (84%) who had a total thyroidectomy received radioactive iodine. The eFVPTC group had lower rates of cervical LN involvement (5% vs 22%, $p=0.2504$). The median follow-up time was 3 years (0–13y) and only 2 patients had recurrence, one with eFVPTC and one with neFVPTC. None of the patients had distant metastasis or died of their disease.

CONCLUSION—eFVPTCs appear to have a lower rate of cervical lymph node metastases compared to neFVPTCs, but recurrent disease may be seen in both subtypes. These findings suggest eFVPTC can be managed more conservatively.

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Author contributions:

Zviadi Aburjania collected the clinical data with assistance of Samuel Jang. Ricardo Lloyd and Celina Montemayor-Garcia reviewed the pathology slides. Rebecca Sippel, David Schneider, Dawn Elfenbein, Samuel Jang and Zviadi Aburjania contributed to the interpretation of the data. Herbert Chen guided the interpretation of findings. Dawn Elfenbein carried out the statistical analysis, guided the interpretation of findings and provided overall supervision.

INTRODUCTION

The incidence of thyroid cancer has tripled since 1975.¹ Most of the rise is attributed to the increase in the diagnosis of papillary thyroid carcinoma (PTC), a differentiated thyroid cancer with a 10-year disease specific survival of 97%.² The exact cause for the increased incidence of PTC is unknown, however many attribute it to the improved sensitivity of ultrasound to identify thyroid nodules,³ as well as potential environmental factors.⁴ Furthermore, it is possible that some of the rise is due to some lesions previously classified as follicular adenomas now being classified as follicular variant PTC (FVPTC). Mehrazad et al. compared the changes in the incidence of FVPTC to the changes in the incidence of follicular adenoma (FA).⁵ The study showed that the incidence of FVPTC was increasing while the incidence of FA was decreasing.

Interestingly, even though the incidence of thyroid cancers dramatically increased, the mortality has remained the same. We may be diagnosing smaller, more indolent cancers that would not cause symptoms or death, which is leading to overtreatment.¹ It is crucial that we seek factors that can help identify the lack of aggressive features of these cancers so that the side effects of the treatment such as recurrent laryngeal nerve injury, wound infection, hypothyroidism, hypoparathyroidism can be avoided.^{6–8} Recent research shows that encapsulated form of FVPTC without invasion has an excellent prognosis with virtually no recurrence.^{9–11} This observation lead to the change of FVPTC classification – non-invasive, encapsulated FVPTCs with certain additional features were reclassified to be “noninvasive follicular thyroid neoplasm with papillary-like nuclear features, or NIFTP”.⁹ To provide more details about different histological variants, we retrospectively analyzed data. Outcomes of the clinical characteristics of encapsulated vs. nonencapsulated FVPTC (eFVPTC and neFVPTC, respectively) were recorded.

Prior to the introduction of the newest ATA guidelines¹² where solitary thyroid cancers up to 4cm may be treated with lobectomy alone, most FVPTC larger than 1cm were managed similarly to classic PTC with a total thyroidectomy. However, several recent studies suggest that the 2 histological variants of FVPTC behave differently, with eFVPTC acting more like a benign lesion, and thus may be managed differently.^{10,11,13} It has been shown that not only histological phenotype but molecular signatures are also different.¹⁴ The objective of this study was to determine if the encapsulated FVPTC (eFVPTC) behaves less aggressively than the nonencapsulated (neFVPTC) to justify the proposed differences in management. Additionally, we further looked at the eFVPTC to determine if there were other features of aggressiveness, such as vascular or capsular invasion.

METHODS

Database review and patient selection

We reviewed our prospectively maintained thyroid surgery database between 1999–2012 at University of Wisconsin after IRB approval. It is important to note that this time period was prior to the introduction of new guidelines suggesting that tumors smaller than 4 cm may be managed with lobectomy alone.¹² We selected PTC cases with tumors identified as FVPTC with or without follicular adenoma by pathology report. After searching the electronic

database, 141 patients were found to have a diagnosis of FVPTC. We excluded the cases where patients had a second tumor with more aggressive thyroid cancer features such as follicular, conventional papillary, or anaplastic thyroid cancer (68) and cases where initial surgery was done in other institutions so the complete pathology was unavailable to us (2). The remaining 71 H&E slides were re-reviewed by two pathologists (RVL and CM) with expertise in thyroid cancer who were blinded to the clinical data. Two cases were reclassified as PTCs and 1 case was reclassified to be a benign adenoma and were excluded. Sixty-eight patients were included in the study.

Pathology and patient characteristics

Size was measured at the largest diameter. Tumor encapsulation, surgical margins, penetration of tumor capsule, lymphovascular invasion, thyroid capsule invasion, and tumor spread within the thyroid gland was recorded. Regional lymph nodes or distant metastasis was identified by reviewing medical records. Demographic features included age and gender. Treatment was either lobectomy or total thyroidectomy with or without central neck dissection and radioactive iodine (RAI) ablation.

Statistical analysis

Chi-squared test and Welch two sample t-test were used to compare the difference between categorical and continuous variables. All the statistical analyses were done with the use of R software (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>), and p-values 0.05 or less were considered significant.

RESULTS

Patient characteristics

The clinical characteristics of study patients are described in Table 1. Mean age of the patients at diagnosis was 48 years (range: 13–81 years) with standard deviation of 15 years. Only 1 patient was <18 years old. Total thyroidectomy was done in 41 patients and 27 patients had an initial lobectomy. Among those who received lobectomy, 23 (85%) received completion thyroidectomy, again reflecting the older guidelines that cancers > 1cm should all be treated with total thyroidectomy. Majority of the patients (84%) with total or completion thyroidectomy received radioactive iodine treatment. None of the patients with lobectomy had RAI therapy. As expected, there were more females than males (43 vs. 25) identified in our cohort.

Histopathologic features

Histopathologic features of study patients are summarized in Table 2. In our cohort, 59 (87%) of the tumors were eFVPTC and 9 (13%) were neFVPTC. The average size of the tumors was 2.5cm (range: 0.2–6cm), 30 (44%) of the tumors were multifocal and 26 (38%) were bilateral. The sizes of tumors, focality, and laterality were not significantly different among the FVPTC histological subtypes. Only 2 patients (3%) had extrathyroidal extension of the tumor, and both had neFVPTC. The biggest distance from the surgical margin was noted, and the tumors were divided into two groups with the cutoff of 1mm. Only 4 (6%) of

the tumors were closer than 1mm to the margins. We routinely perform ultrasound examination of the central neck to determine the need for therapeutic neck dissection, and also perform therapeutic neck dissection if positive nodes are identified at the time of surgery. We did not routinely perform prophylactic central neck dissections, and only 8 patients (12% of the study group) had any lymph nodes removed. Five of the 8 had positive lymph nodes (Table 3). Two of those patients had just one lymph node removed, likely indicating it was not an intentional therapeutic nodal dissection. The 3 that underwent intentional central nodal dissection had 5 positive out of 33, 29 out of 55 and 1 positive out of 3 lymph nodes resected. The mean age of the patients who had central lymph nodes removed at the time of surgery was 45 years (SE: 5.4, range:26–65) with the lymph node positive group being significantly younger than the lymph node negative group (34 years vs. 62 years, $p=0.001$). There was no difference in lymph node involvement between eFVPTC vs. neFVPTC groups ($p=0.2504$). One patient with non-invasive eFVPTC had 29 positive lymph nodes out of 55. The patient is 37 year-old male who was found to have one focus of eFVPTC in left lobe and 2 foci of eFVPTC in right lobe. The largest cancer was 2.5 cm. He underwent total thyroidectomy with bilateral central neck dissection followed by radioactive iodine ablation. Notably all the primary tumor foci in thyroid were FVPTC, while all metastatic nodal tumors were PTC. The size of the tumors ranged from 0.2cm to 0.7 cm. The patient remained asymptomatic for 2.7 years at the last follow-up.

Tumor encapsulation and invasion of tumor capsule were analyzed for differences in demographics and histological variables. 27 (40%) patients who had encapsulated tumors with no vascular or capsular invasion were compared to patients who had nonencapsulated tumor or those with capsular and/or vascular invasion (neFVPTC and invasive eFVPTC) ($n=41$). There was no significant difference found between groups when compared by demographic or histologic variables. With the median follow-up time of 3 years (range:0–162 months) recurrence occurred in only 2 patients (3%): 1 with neFVPTC and 1 with invasive eFVPTC. The characteristics of the patients with recurrence are described below.

Patient 1—28-year-old male with multifocal bilateral eFVPTC with the largest size of 3.5 cm. The tumor was encapsulated but with tumor capsule invasion. There was no evidence of lymph node or distant metastasis at the time of initial thyroidectomy. Patient received RAI treatment. He had recurrent thyroid bed mass in 9 months and underwent resection revealing 3 cm and 1 cm focus of PTC.

Patient 2—38-year-old male with a single 1.2 cm neFVPTC invading thyroid capsule. 5 of 33 lymph nodes were positive for tumor metastasis. Patient received RAI treatment following total thyroidectomy with central lymph node dissection. Thyroglobulin level was 6.0 ng/mL at 6-month follow-up, and he was found to have increased radiolabeled tracer uptake in the mediastinum revealed by PET scanning. Patient was scheduled for biopsy.

Table 4 shows the different surgical treatments based on histologic type. The majority of the patients with neFVPTC underwent total thyroidectomy (88.9%). Most of the patients who had eFVPTC tumor underwent either upfront total thyroidectomy or lobectomy followed by completion thyroidectomy regardless the invasion status of the tumor capsule. Again, this likely reflects our adherence to the pre-2016 ATA guidelines. Only 4 patients underwent

lobectomy alone: 1 with non-invasive eFVPTC, 2 with eFVPTC with capsular invasion, and 1 neFVPTC. None of these patients who underwent lobectomy alone had recurrence.

DISCUSSION

Local invasion and ability to metastasize are among the most defining features of tumor malignancy. The results of the present study show that FVPTC can be both locally invasive and metastasize to regional lymph nodes. These features can be characteristic of unencapsulated or encapsulated cancers, with or without thyroid capsular invasion. In our cohort, 2 (3%) of all eFVPTCs had extrathyroidal extension, 27 (46%) had multifocal FVPTCs and 3 out of 8 patients who had lymph nodes removed (5% of total population) had regional lymph node metastasis.

Although the study showed that the patients with lymph node positive cancers were much younger than those without (34 vs 62, $p<0.001$) and that there is no difference in lymph node status between eFVPTC or neFVPTC (50% vs 100%, $p=0.6733$), the findings can be biased as the lymph node resection was not randomized and only 8 patients (12%) had their lymph nodes examined. Another caveat in the interpretation of the results of the study is the few cases where patients had only lobectomy (6%). It is worth noticing that we observed no recurrence in neFVPTC or eFVPTC with capsular invasion in the patients who had only lobectomy. Since it is difficult to draw any significant conclusions from the few patients who received lobectomy only, there is a need to define the exact utility of lobectomy alone in patients with FVPTC. After analyzing 52,173 cases of PTC, Bilimoria et al. showed that patients with >1 cm tumors who underwent total thyroidectomy had less recurrence and better survival rates compared with lobectomy.¹⁶ In our study all patients with lobectomy alone had less than 1 cm unifocal FVPTCs. We would benefit from a larger study where the patient number with lobectomy is much larger.

Importantly, recurrence occurred only in unencapsulated (neFVPTC) and encapsulated tumors that had tumor capsule invasion (invasive eFVPTC). This finding is in accordance to previous findings, which suggest that there is virtually no recurrence in fully encapsulated FVPTC without capsular or vascular invasion.^{10,14,15,17} NIFTP is the new entity that was recently proposed to reclassify a group of FVPTCs with histologic features that was observed to be benign.⁹ The authors suggested the name NIFTP (“noninvasive follicular thyroid neoplasm with papillary-like nuclear features”) to underscore the benign nature of this neoplasia. We analyzed three out of six diagnostic criteria of NIFTP – tumor encapsulation, no vascular/capsular invasion, no tumor necrosis.⁹ The results of our study – no recurrence in noninvasive eFVPTC and recurrence in invasive eFVPTC and neFVPTC agree with the changes suggested by Nikiforov et al. The importance of tumor encapsulation and its capsular/vascular invasion makes it crucial to meticulously examine the tumor encapsulation and invasion to guide management.

The growing evidence of benign nature of encapsulated noninvasive FVPTC led to the change of its name to “noninvasive follicular thyroid neoplasm with papillary-like nuclear features” (NIFTP) that has strictly defined histologic characteristics.⁹ Our study adds more supporting evidence to this change, although we did not examine all six of the criteria to call

our eFVPTC group NIFTP. Since the tumor encapsulation and its invasion status can only be examined post-excision, it is still unclear whether this new classification will alter management for a significant number of patients. Patients with noninvasive eFVPTC on pathologic diagnosis may be reassured, however, that recurrence risk is low and discussion about subsequent completion thyroidectomy can be individualized to each particular patient.

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Table 1

Clinical characteristics of study patients

Characteristic	Encapsulated				Nonencapsulated n=9	
	Total n=68	Total n=59	Without invasion n=27	With invasion n=32		
Sex [n(%)]						
Female	43 (63)	39 (66)	21 (78)	18 (56)	4 (44)	
Male	25 (37)	20 (34)	6 (22)	14 (44)	5 (56)	
Age						
Mean	48	47	48	47	52	
Range	13–81	13–76	13–72	21–76	33–81	
Type of surgery [n(%)]						
Lobectomy	4 (6)	3 (5)	1 (4)	2 (6)	1 (11)	
Total Thyroidectomy	41 (60)	33 (56)	16 (59)	17 (53)	8 (89)	
Lobectomy with completion	23 (34)	23 (39)	10 (37)	13 (41)	0	
Radioactive iodine [n(%)]						
Yes	54 (79)	47 (80)	20 (74)	27 (84)	7 (78)	
No	14 (21)	12 (20)	7 (26)	5 (16)	2 (22)	

Histopathologic features of study patients

Table 2

Characteristics	Encapsulated				p-value
	Total n=59	Without invasion n=27	With invasion n=32	Nonencapsulated n=9	
Size (cm)					
Mean	2.1	1.8	2.3	1.2	0.08269
Range	0.2 – 6.0	0.2 – 5.8	0.2 – 6	0.6 – 1.6	
Multifocality [n(%)]					0.7345
Yes	27 (46)	12 (44)	15 (47)	3 (33)	
No	32 (54)	15 (56)	17 (53)	6 (67)	
Bilaterality [n(%)]					1
Yes	23 (39)	10 (37)	13 (41)	3 (33)	
No	36 (61)	17 (63)	19 (59)	6 (67)	
Extrathyroid extension [n(%)]					1
Yes	2 (3)	0	2 (6)	0	
No	57 (97)	27 (100)	30 (94)	9 (100)	
Margin status [n(%)]					0.9643
Positive	4 (7)	0	4 (13)	0	
Negative	55 (93)	27 (100)	28 (87)	9 (100)	

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Table 3

Lymph node status in study patients

	LN positive	LN negative	p-value
Age			
Mean	34	62	0.001
Range	26–38	56–65	
Histology			
eFVPTC	3	3	0.2504 ^b
With invasion	2	2	
Without invasion	1	1	
neFVPTC	2	0	

^aIncluded are patients who had lymph nodes examined

^bp-value is comparing encapsulated and nonencapsulated group

Table 4

Surgical management and recurrence of FVPTC subtypes.

Surgery	Encapsulated		Nonencapsulated (n=9)
	Without Invasion (n=27)	With Invasion (n=32)	
Total Thyroidectomy	16	17*	8*
Lobectomy + completion	10	13	0
Lobectomy only	1	2	1
Mean Follow-up [‡]	4 years	3.3 years	4.2 years

* Recurrence in 1 patient from this group

[‡] p-value = 0.645