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Invasion rather than nuclear features correlates with outcome in encapsulated follicular tumors: further evidence for the reclassification of the encapsulated papillary thyroid carcinoma follicular variant[☆]

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Summary

The prognosis of the encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) and its relationship to encapsulated follicular carcinoma (EFC) and follicular adenoma (FA) is subject to controversy. All EFVPTCs, EFCs, and FAs identified at a single institution between 1981 and 2003 were analyzed microscopically. A cohort of FAs from a different hospital was also examined. EFVPTCs were subdivided into noninvasive EFVPTC (NIEFVPTC) and invasive EFVPTC (IEFVPTC) displaying capsular/vascular invasion. There were 83 EFVPTCs (57 noninvasive, 26 invasive), 14 EFCs, and 52 FAs. Similar to FA, over a median follow-up of 9.5 years, none of the NIEFVPTCs manifested lymph node metastasis (LNM) or recurred. Furthermore, with a median follow-up of 10.5 years, none of 39 NIEFVPTCs without radioactive iodine therapy recurred. Four (15%) of 26 IEFVPTCs and none of 14 EFCs harbored distant metastasis ($P = .29$). There was no difference in LNM rate and degree of vascular or capsular invasion between IEFVPTC and EFC ($P > .1$). All 4 IEFVPTCs with adverse behavior presented with distant metastasis and no LNM. Sixteen percent of IEFVPTCs had poor outcome, whereas there was none in the NIEFVPTCs ($P = .007$). In conclusion, NIEFVPTC seems to behave similarly to FA, whereas IEFVPTC can metastasize and spread like EFC. Thus, invasion rather than nuclear features drives outcome in encapsulated follicular tumors. Non-IEFVPTC could be treated in a conservative manner sparing patients unnecessary total thyroidectomy and radioactive iodine therapy. The position of the EFVPTC in the classification of thyroid neoplasia should be reconsidered.

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Keywords

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1. Introduction

Despite past and recent efforts, there are many problems and controversies in the classification of follicular cell–derived thyroid carcinomas. The most controversial class of carcinomas is the follicular variant of papillary thyroid carcinomas (FVPTC). This tumor is a common subset of papillary thyroid carcinoma (PTC) found in 9% to 22.5% of PTC patients [1–4]. This variant has less than 1% papillary formations and is composed predominantly of follicles lined by cells having the nuclear features of the PTC family of tumors [5]. Thus, FVPTC shares with follicular adenomas (FAs) and follicular thyroid carcinoma (FTC) the presence of follicles.

When FVPTC is nonencapsulated and infiltrates the surrounding thyroid parenchyma, the diagnosis of carcinoma usually poses no problem. For the encapsulated tumor without invasion of surrounding thyroid tissue, the diagnosis of malignancy relies solely on the presence of the nuclear features of PTC (eg, irregular nuclear membrane, clearing, and grooves), which can often be borderline. Therefore, the diagnosis of noninvasive, encapsulated FVPTC (EFVPTC) versus FA is subject to considerable interobserver variability [6,7].

We and others have shown that noninvasive EFVPTCs do not recur even when treated with lobectomy alone [8–10]. Furthermore, many studies have found that the molecular profile of FVPTC as a whole is much closer to FA and FTC than to classical PTC [11–13]. This is especially true for the encapsulated/well-circumscribed FVPTC that harbors a relatively high rate of *RAS* mutations and no *BRAFV600E* mutations [14,15].

Despite all this evidence, the noninvasive EFVPTC is still classified as a variant of PTC. More importantly, most clinicians and all professional societies recommend for this noninvasive variant a therapy similar to the one designed for garden-variety intrathyroidal PTC of similar size [16]. For example, based on the American Thyroid Association guidelines, a 4.1-cm FA is treated with lobectomy alone, whereas a similar sized noninvasive EFVPTC is subjected to total thyroidectomy and radioactive iodine (RAI) remnant ablation [16]. This rationale is based on the fact that PTC nuclear features (the only differential histologic finding between encapsulated noninvasive FVPTC and FA) are thought to be by themselves an indicator of carcinoma in encapsulated follicular-patterned lesions conveying the message of worse outcome than FA.

Our hypothesis is that the presence of PTC nuclei has little effect on outcome in encapsulated follicular tumors. If this is proven, then patients with encapsulated noninvasive FVPTC should have initial therapy similar to FA and spared unnecessary aggressive up-front therapy. In order to explore the prognostic value of PTC nuclei in encapsulated follicular patterned tumors, we compared the survival of a series of FA, FTC, invasive EFVPTC, and noninvasive EFVPTC.

2. Materials and methods

2.1. Histologic definitions and inclusion criteria

The institutional database was searched for all cases with a diagnosis of thyroid carcinomas treated at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1981 and 2003. All cases from MSKCC with adequate material were examined microscopically under the supervision of a head and neck pathologist with special interest in thyroid neoplasia (R. G.). A median (range) of 19 (1–48) slides per specimen were examined microscopically in the MSKCC series. A median (range) of 13 (3–48) slides were reviewed in the noninvasive EFVPTC group.

Tumors were classified as *EFVPTC* if completely surrounded by a fibrous capsule, composed predominantly of follicles with less than 1% papillary formations and containing tumor cells with the nuclear features of PTC (ie, irregular enlarged clear nuclei with grooves, pseudoinclusions, and overlapping; Table 1). The pathologists on the study had agreed before the analysis on a common set of nuclear criteria for the diagnosis of EFVPTC. Tumors with a very thin capsule or well circumscribed as well as those with multifocal nuclear features of PTC were also included under the rubric of EFVPTC. Papillary carcinomas fulfilling the cytoarchitectural criteria for all other variants of PTC including the solid, tall, or columnar cell variant of papillary carcinomas were not classified as FVPTC [17,18]. EFVPTC less than 1 cm and those associated with other foci of PTC were excluded from the analysis.

FAs were defined as encapsulated tumors composed of follicles or nests of tumor cells lacking an oncocyctic cytoplasm and the nuclear features of PTC. *Encapsulated FTCs* were defined as tumor having the cytoarchitectural features of FA but harboring capsular and/or vascular invasion. Carcinomas with high mitotic rate (≥ 5 mitosis per 10 high-power fields; ×400) and any neoplasm with tumor necrosis were excluded from the analysis.

Using the above histologic definitions, an additional cohort of FA from Salta, Argentina, were included in the study and reviewed by a pathologist with special interest in thyroid pathology (H. R. H.). Six to 10 sections per tumor were submitted for histology in the Argentinian series.

2.2. Pathology review

Tumor size was measured as the maximum diameter of the resected tumor specimen. Mitotic rate was determined by counting 10 high-power fields (×400) with an Olympus microscope (U-DO model, Olympus, Waltham, MA) in the areas of greatest concentrations of mitotic figures. *Capsular invasion* was defined as complete penetration of the capsule by tumor, and the number of these foci was recorded. The presence of vascular invasion was noted only when such foci were present within or beyond the capsule in accordance with criteria outlined by the Armed Forces Institute of Pathology fascicle [5]. Briefly, only when the invasive focus protruded into the lumen of the vessel in a polypoid manner covered by endothelial cells, or when it was attached to the vessel wall or associated with thrombus formation, was it considered true vascular invasion. Areas of vascular invasion that were closely adjacent to one another were counted as separate foci. The foci of capsular and

vascular invasion were subdivided into 2 categories: focal (<4 invasive foci) and extensive (≥ 4 foci). The presence or absence of tumor extension into the extrathyroid soft tissue stroma was documented. Microscopic resection margins were categorized as positive (tumor at the inked margin) or negative (no tumor at the inked margin). Finally, the number and metastatic status of the regional lymph nodes were also recorded.

2.3. Clinical review

The patient's medical records were reviewed for age at diagnosis, sex, type of surgery, and adjuvant therapy (RAI). In view of the fact that many cases from the 1980s did not have adequate biochemical data, the patient disease status at recurrence or follow-up was based on a combination of clinical and imaging assessments. These evaluations include history taking, physical examination, RAI scanning, cross-sectional imaging and/or positron emission tomography scanning, or histologic examination of the recurrent tumor. Thus, biochemical recurrence was not assessed. Status at last follow-up was categorized as no evidence of disease (NED), alive with disease (AWD), dead of disease (DOD), dead of unknown cause, or dead of other causes. The study was approved by the institutional review board of MSKCC.

2.4. Statistics

Descriptive statistics were used to summarize study data. Associations between categorical variables were evaluated using the Fisher exact or χ^2 test, where appropriate. In all statistical analyses, a 2-tailed *P* value less than .05 was considered statistically significant. Follow-up time was calculated from time of surgery to date of last follow-up.

3. Results

3.1. Patient population

Eighty-three EFVPTCs fulfilled the study entry criteria, of which 57 (69%) were noninvasive (Fig. 1). Fourteen encapsulated follicular carcinoma (EFCs) and 52 FAs were also included in the analysis. In order to assess interobserver variability for the diagnosis of EFVPTC, 2 of the pathologists (N. K., R. G.) relooked at the noninvasive EFVPTC cases, and there was universal agreement on all of them.

3.2. Comparison of the outcome and clinicopathological features of noninvasive EFVPTC and FA

Table 2 lists the clinicopathological features of the 57 noninvasive EFVPTCs and the 52 FAs. None of the patients in either group recurred, died of disease, or developed lymph node or distant metastasis.

3.3. Comparison of the outcome and clinicopathological features of invasive EFVPTC and EFC

Table 3 displays the clinicopathological features of the 26 invasive EFVPTCs and the 14 EFCs. Four (15%) of 26 invasive EFVPTCs and none of 14 EFCs had an adverse outcome (*P* = .29).

3.4. Clinicopathological features of patients with adverse outcome

Table 4 lists the features at presentation of those 4 patients who had a poor outcome. All were invasive EFVPTCs in patients older than 50 years lacking lymph node metastasis. Three of 4 displayed symptoms related to their distant metastasis (eg, pain). Although only 2 patients displayed vascular invasion (Fig. 2), all 4 had very high serum thyroglobulin levels and distant metastasis at presentation. Three patients died of disease. One died at 10 years and 2 months, another 5 years and 2 months, and the third 2 years and 11 months from diagnosis. The fourth patient was AWD 15 years and 1 month after diagnosis.

3.5. Outcome and clinicopathological characteristics of patients with noninvasive EFVPTC managed with conservative therapy

Table 5 shows the clinicopathological features of 39 noninvasive EFVPTCs who were not administered RAI therapy and had adequate follow-up data (>1 year). None of those patients had metastasis, recurred, or died of disease. Thirty-two individuals were operated on by lobectomy only with no RAI therapy. None of these 32 patients recurred or developed metastasis, with a median follow-up of 10 years and 3 months. Within noninvasive EFVPTC patients with adequate follow-up, there was no difference in survival, age, sex, and tumor size between those treated with RAI ($n = 13$) and those not receiving RAI ($n = 39$; $P > .2$).

3.6. Comparison of the clinicopathological features of invasive versus noninvasive EFVPTC

There were no significant differences in age, sex, mitotic rate, extent of surgery, RAI therapy, and length of follow-up between invasive and noninvasive EFVPTCs ($P > .05$). Invasive EFVPTCs were significantly larger than their noninvasive counterparts: 12 (46%) of 26 invasive tumors measured greater than 4 cm, while only 3 (5%) of 57 noninvasive EFVPTCs were greater than 4 cm in size ($P = .0001$). Adverse outcome (recurrence, DOD) was much higher in invasive EFVPTCs (4/25; 16%) than in their noninvasive counterparts (0/56; $P = .008$).

4. Discussion

In order to assess the prognostic value of PTC nuclei in encapsulated follicular tumors, we performed a comparative analysis controlling for their invasive status. Thus, we compared encapsulated noninvasive EFVPTC to FA. The results clearly show that the presence of PTC nuclei does not affect outcome in encapsulated noninvasive follicular tumors because both groups lacked recurrence or regional/distant metastasis. One could argue that noninvasive EFVPTCs had an excellent outcome similar to FAs because they were treated more aggressively with much higher rates of total thyroidectomy and RAI therapy. However, the noninvasive EFVPTC group contained 32 patients treated with lobectomy alone as well as 39 who did not receive RAI. All these noninvasive EFVPTC cases treated in a conservative manner did not recur with a median follow-up of 10 years. This length of follow-up is considered adequate because most recurrences occur within 5 years in papillary and follicular carcinomas [19].

When invasive follicular tumors are compared, invasive EFVPTC did not differ from EFC. There was no significant difference in age, sex, tumor size, mitotic rate, lymph node metastasis, extrathyroid extension, margin status, degree of capsular or vascular invasion, extent of surgery, or RAI therapy. Although 4 invasive EFVPTCs had an adverse outcome and none of the EFCs recurred, this difference was not statistically significant. The lack of recurrence in the EFC group could be attributed to their small sample size. That we collected only 14 cases of EFC in a 22-year period reflects the rarity of this diagnosis based on the current histologic classification of follicular lesions [20]. In addition, the current accepted definition of follicular carcinoma excludes poorly differentiated carcinoma that used to be categorized as follicular carcinoma in the past (eg, tumor with nested growth and tumor necrosis). Furthermore, we excluded from these series the rare follicular carcinomas growing in a follicular pattern but with necrosis and/or high mitotic activity. The exclusion of these aggressive carcinomas could also explain the indolent behavior of our cohort of EFC.

Although nuclear features do not seem to have a significant impact on outcome in encapsulated follicular tumors, invasion correlated with worse prognosis within EFVPTC. Sixteen percent of invasive EFVPTCs were alive with disease or DOD, whereas none of the noninvasive EFVPTC recurred ($P = .007$). We attempted to look for histopathologic and clinical features that correlate with invasion in EFVPTC. The only difference found related to a significantly larger size in invasive EFVPTC. Pathologists should therefore be more generous in sampling large EFVPTCs.

More interestingly, all the invasive EFVPTCs with poor outcome had aggressive features at presentation such as distant metastasis and very high serum thyroglobulin levels ($>10\,000$ ng/mL). The latter biochemical finding coupled with the frequent presence of pain related to distant disease renders the detection of aggressive EFVPTC by the clinician relatively easy. This is important because invasive EFVPTC may not display histologic signs predictive of aggressive behavior in all cases. Indeed, 2 of the invasive EFVPTCs with poor outcome displayed only focal capsular invasion and no angioinvasion. All EFVPTC patients who developed distant disease lacked regional nodal metastases. The presence of distant metastases without regional nodal disease has been reported in some EFVPTC, suggesting that their behavior is similar to follicular carcinomas rather than classical papillary carcinoma [21].

The above pathologic and outcome data reinforce the evolving concept that EFVPTC is a misclassified entity [8,22]. EFVPTC seems much closer to the follicular carcinoma/adenoma group of tumors than to classical PTC. Indeed EFVPTC does not appear to spread via lymph nodes if invasive and, more importantly, displays an extremely indolent behavior if noninvasive. This lack of recurrence in noninvasive EFVPTC reported by our group in 2006 has now been confirmed by this study as well as others [8–10,22]. The misclassification of EFVPTC is also supported by the finding that FVPTC as a whole is much closer in its molecular profile to follicular carcinoma/adenoma and different from classical PTC with a high frequency of *RAS* mutations and very low rates of *BRAF* mutations [11,12,23,24]. When one restricts the analysis of the follicular variant PTC to its encapsulated or well-circumscribed forms, their molecular profile is also very similar to the one seen in FTC and FA in 2 of 3 large studies [14,15,25].

These findings have profound clinical implications. Noninvasive EFVPTC may be treated in a conservative fashion similar to FA. However, for this change in therapy to happen, there is a need for a new nomenclature. Indeed, it will be very difficult to convince clinicians not to use the full armamentarium at their disposal if the pathology reports describe, for example, a 4-cm noninvasive EFVPTC. Based on all the molecular and clinicopathological correlations mentioned in this article, it seems logical to remove the terms “papillary” and “carcinoma” from the noninvasive EFVPTC and the term “papillary” from the invasive EFVPTC. In the year 2000, the term “follicular tumor of uncertain malignant, potential” was proposed for follicular-patterned lesions of the thyroid that cannot be readily diagnosed as benign or malignant, either because of minor nuclear changes of PTC or because of questionable/minimal capsular invasion [26]. However, that terminology was not accepted globally, especially in North America, because it created uncertainty among endocrinologists and surgeons in terms of management. The reality is that these noninvasive EFVPTCs are not tumors of uncertain malignant potential but rather of extremely low malignant potential. Instead of noninvasive EFVPTC, perhaps a designation such as “noninvasive well-circumscribed/encapsulated follicular tumor” should be used with a note stating that the nuclear clearing found in the tumor has no clinical value and that this lesion should be treated like a FA. For invasive EFVPTC, one could categorize them as EFC as they used to be diagnosed 50 years ago before Lindsay [27] coined the term FVPTC in 1960 and Chem and Rosai [28] popularized it in 1977. Again, a comment could be included in the pathology report stating the presence of clear nuclei and their lack of clinical impact. Some pathologists may still be reluctant to adopt a terminology that does not use carcinoma to describe encapsulated noninvasive follicular tumor with PTC nuclei. This reluctance is based on the extremely rarely encountered noninvasive EFVPTC that metastasizes [21]. These metastasizing noninvasive tumors could have been poorly sampled for the invasive foci to be detected. Even if these noninvasive tumors were adequately analyzed, the presence of that exceptional phenomenon does not validate the use of the term carcinoma for nonencapsulated follicular tumors with clear nuclei. Indeed, FAs were also shown to exceptionally give rise to distant metastasis and their nomenclature was not changed to carcinoma [29]. We are not unique in our position on the subject. Deleting the term *carcinoma* from a tumor with extremely low malignant potential (if any) such as noninvasive EFPVTC is getting wider acceptance today in view of the adverse effects of overtreatment. Indeed, the working group for the overdiagnosis of cancer convened by the US National Cancer Institute recommends that “the word cancer should be removed from the names of lesions thought to have a very low likelihood of progression...” [30].

If this reclassification of the EFVPTC is realized, pathologists will be spared the frustrating and subjective exercise of deciding whether an encapsulated follicular tumor has the nuclear features of papillary carcinoma. All the confusion and psychological stress related to interobserver variability and experienced by physicians and patients will hopefully decrease. More importantly, there will be less pressure to aggressively treat noninvasive encapsulated follicular tumors with PTC nuclei, sparing a considerable number of patients unnecessary total thyroidectomy and RAI therapy with its attached morbidity (ie, hypoparathyroidism, recurrent nerve injury, and salivary gland damage) and financial costs. A consensus

conference on the reclassification of EFVPTC including a large number of thyroid pathologists is urgently needed.

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Fig. 1.

Microphotographs of a 3.6-cm noninvasive EFVPTC in a 27-year-old woman treated with lobectomy only. The patient is alive and well with no recurrences 10 years and 6 months after diagnosis. A, Low-power view (hematoxylin and eosin, ×40). The tumor (T) grows in follicles and has a well-defined fibrous capsule (C) with no invasion into nonneoplastic thyroid (N). B, High-power view (hematoxylin and eosin, ×400). Tumor follicles are lined by enlarged, clear, overlapping, irregular nuclei with grooves (arrow).

Fig. 2.

Microphotographs of a 5-cm invasive EFVPTC in a 62-year-old woman who presented with lung metastasis and a serum thyroglobulin level of 13 900 ng/mL. A, Low-power view (hematoxylin and eosin [H&E], ×40). The tumor (T) grows in follicles and has a well-defined fibrous capsule (C) with a focus of vascular invasion immediately outside the capsule. B, High-power view (H&E, ×400). Tumor follicles are lined by enlarged, clear, overlapping, irregular nuclei with grooves (arrow). C, Medium-power view (H&E, ×100). Another focus of vascular invasion showing tumor thrombus (arrow) in the vessel lumen. D, High-power view (H&E, ×400). Tumor thrombus covered by endothelial cells (arrow). The latter feature indicates that this is true vascular invasion and not artifactually displaced carcinoma.

Table 1

Histologic definitions and current terminology of encapsulated follicular tumors

Current terminology	Histologic definition
Encapsulated PTC, follicular variant, noninvasive	Encapsulated follicular tumor <i>displaying nuclear features of PTC without capsular or vascular invasion</i>
Encapsulated PTC, follicular variant, invasive	Encapsulated follicular tumor <i>displaying nuclear features of PTC with capsular and/or vascular invasion</i>
Follicular adenoma	Encapsulated follicular tumor <i>lacking nuclear features of PTC without capsular or vascular invasion</i>
Encapsulated follicular carcinoma	Encapsulated follicular tumor <i>lacking nuclear features of PTC with capsular and/or vascular invasion</i>

Abbreviation: PTC, papillary thyroid carcinoma.

Table 2

Clinicopathological characteristics of noninvasive EFVPTC and FA

Characteristic	Encapsulated noninvasive FVPTC (n = 57), n (%)	FA (n = 52), n (%)	<i>p</i> ^a
Age (y)			<.001
Median (range)	48 (24–78)	37.5 (13–61)	
45	23 (40)	38 (73)	
>45	34 (59)	14 (27)	
Sex			.06
Female	42 (74)	46 (86)	
Male	15 (26)	6 (14)	
Tumor size (cm)			.0001
Median (range)	3 (1.1–7)	3.5 (1.2–9)	
<4	54 (95)	29 (55)	
4	3 (5)	23 (45)	
Thyroid surgery			.0006
<Total thyroidectomy	39 (68)	49 (94)	
Total thyroidectomy	18 (32)	3 (6)	
RAI therapy			.0001
Administered	13 (23)	0	
Not given	44 (77)	52 (100)	
LN metastases (all cases)			1
Present	0	0	
Absent	57 (100)	52 (100)	
LN metastases (cases with LN tissue)			1
Present	0	0	
Absent	18 (100)	3 (100)	
Distant metastases			1
Present	0	0	
Absent	57 (100)	52 (100)	
Recurrence ^b			1
Present	0	0	
Absent	56 (100)	51 (100)	
Status at FU ^b			1
DOD	0	0	
AWD	0	0	
NED	56 (100)	51 (100)	
FU (y)			.0001
Median	9.5	12.3	
Range	0.2–27	0.25–21	

Abbreviations: EFVPTC, encapsulated follicular variant of papillary thyroid carcinoma; FA, follicular adenoma; RAI, radioactive iodine; LN, lymph node; FU, follow-up; DOD, dead of disease; AWD, alive with disease; NED, no evidence of disease.

^aFisher exact test, 2-tailed values.

^bFollow-up was not available on 1 case of noninvasive EFVPTC and 1 case of FA.

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Table 3

Clinicopathological characteristics of invasive EFVPTC and EFC

Characteristic	Invasive EFVPTC (n = 26), n (%)	EFC (n = 14), n (%)	<i>p</i> ^a
Age (y)			.32
Median (range)	40.5 (18–75)	47.5 (27–68)	
45	16 (62)	6 (43)	
>45	10 (38)	8 (57)	
Sex			.19
Female	17 (65)	6 (43)	
Male	9 (35)	8 (57)	
Tumor size (cm)			.33
Median (range)	3.75 (1.1–6)	3.2 (1.5–8.5)	
<4	14 (54)	10 (71)	
4	12 (46)	4 (29)	
Vascular invasion			.32
Absent	15 (58)	5 (35.5)	
Focal	7 (27)	5 (35.5)	
Extensive	4 (15)	4 (29)	
Capsular invasion			.67
Absent	4 (15)	3 (21)	
Focal	15 (58)	7 (50)	
Extensive	7 (27)	4 (29)	
Mitosis			.7
Absent	21 (81)	10 (71)	
Present	5 (19)	4 (29)	
Extrathyroid extension			1
Absent	25 (96)	14 (100)	
Present	1 (4)	0	
Margins			1
Positive	0	0	
Negative	26 (100)	14 (100)	
Thyroid surgery			1
<Total thyroidectomy	14 (54)	7 (50)	
Total thyroidectomy	12 (46)	7 (50)	
RAI therapy			1
Administered	8 (31)	4 (29)	
Not given	18 (69)	10 (71)	
LN metastases			1
Present	1 (4)	0	
Absent	25 (96)	14 (100)	
Distant metastases			.28

Characteristic	Invasive EFVPTC (n = 26), n (%)	EFC (n = 14), n (%)	<i>p</i> ^a
Present ^b	4 (15)	0	.29
Absent	22 (85)	14 (100)	
Status at FU ^c			
DOD	3 (12)	0	1
AWD	1 (4)	0	
NED	21 (84)	14 (100)	
FU (y)			
Median	10.1	10.8	
Range	0.1–20.4	1.5–27.7	

NOTE: The average (range) mitotic count per 10 high-power fields (×400) is 0.36 (0–2) for FC and 0.3 (0–3) for invasive EFVPTC.

Abbreviations: EFVPTC, encapsulated follicular variant of papillary thyroid carcinoma; EFC, encapsulated follicular carcinoma; RAI, radioactive iodine; LN; lymph node; FU, follow-up; DOD, dead of disease; AWD, alive with disease; NED, no evidence of disease.

^aFisher exact test, 2-tailed values.

^bAll distant metastases in FVPTC were at presentation.

^cFollow-up was not available on 1 case of invasive EFVPTC.

Table 4

Clinicopathological features at presentation of patients with adverse outcome

Pt	Age (y)/sex	Clinical presentation	Perioperative serum TGB (ng/mL)	Histo	Tumor size (cm)	Capsular invasion (no. of foci)	Vascular invasion (no. of foci)	DM at diagnosis/ location	Surgery/ RAI TT	Outcome
1	75/M	Pain from pelvic bone met	36250 (high)	FV/PTC	4.0	Focal (1)	None (0)	Yes/Bone	TT/Yes	DOD
2	66/M	Pain from rib met	10050 (high)	FV/PTC	5.0	Extensive (6)	Extensive (8)	Yes/Bone	TT/Yes	DOD
3	62/F	Thyroid mass	13900 (high)	FV/PTC	5.0	None	Extensive (8)	Yes/Lung	CT/Yes	AWD
4	57/F	Fracture due to bone met	72200 (high)	FV/PTC	2.2	Focal (3)	None	Yes/Bone	TT/Yes	DOD

NOTE. Patient 3 had CT 13 years after lobectomy for benign disease.

Abbreviations: Pt, patient; TGB, thyroglobulin; Histo, histology; DM, distant metastasis; RAI, radioactive iodine; TT, total thyroidectomy; M, male; Met, metastasis; DOD, dead of disease; FVPTC, follicular variant of papillary thyroid carcinoma; F, female; CT, completion thyroidectomy; AWD, alive with disease.

Table 5

Outcome and clinicopathological characteristics of 39 patients with the noninvasive, encapsulated follicular variant of PTC with no RAI therapy

Characteristic	Value
Median follow-up (y)	10.5 (1.9–27)
Tumor size (cm), median range	2.9 (1.1–5.6)
Median age (y)	48 (26–78)
Female	31 (79%)/39
Lymph node/distant metastases	Absent
Outcome	No recurrence

Abbreviations: PTC, papillary thyroid carcinoma; RAI, radioactive iodine.