

Encapsulated Malignant Follicular Cell-Derived Thyroid Tumors

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Abstract Encapsulated malignant follicular cell-derived thyroid tumors are subject to considerable controversies. This group includes encapsulated follicular variant of papillary carcinoma (FVPTC) and encapsulated (so-called minimally invasive) follicular carcinoma (EFC). FVPTC usually presents as an encapsulated tumor and less commonly as a partially/nonencapsulated infiltrative neoplasm. The encapsulated form rarely metastasizes to lymph node, whereas infiltrative tumors often harbor nodal metastases. Encapsulated FVPTC have a molecular profile very close to follicular adenomas/carcinomas (high rate of *RAS* and absence of *BRAF* mutations). Infiltrative follicular variant has an opposite molecular profile closer to classical papillary thyroid carcinoma than to follicular adenoma/carcinoma (*BRAF*>*RAS* mutations). Noninvasive encapsulated FVPTC are extremely indolent even if treated with lobectomy without radioactive iodine therapy. Although most EFC are thought to have an excellent outcome, there are cases of EFC that recur and metastasize. EFC with angioinvasion, especially if extensive, have a significant rate of distant recurrence. Encapsulated FVPTC have a molecular profile and a clinical behavior very similar to the follicular adenoma/carcinoma class of tumor. If noninvasive, encapsulated FVPTC should be treated in a very conservative fashion. EFC with angioinvasion, especially if extensive, should not be termed minimally invasive in order to prevent undertreatment of the patient.

Keywords Thyroid · Carcinoma · Follicular · Papillary · Follicular variant · Minimally invasive · Follicular carcinoma · Encapsulated · Infiltrative · *BRAF* · *RAS*

Introduction

Despite past and recent efforts, there are many problems and controversies in the classification of thyroid carcinomas of follicular cell origin. These controversies have an impact on the prognosis and therapy of thyroid carcinomas patients as well as on the development of robust cutting edge research aimed at better outcome and quality of life. The most controversial class of carcinomas is encapsulated malignant follicular cell-derived tumors. This group of carcinoma include frequently encountered tumors such as the follicular variant of papillary thyroid carcinomas and encapsulated (so-called “minimally invasive”) follicular carcinomas as well as rare neoplasms such as encapsulated poorly differentiated and anaplastic carcinomas. This article will focus on the two most common and problematic entities: the follicular variant of papillary thyroid carcinoma and encapsulated “minimally invasive” follicular carcinoma.

Follicular Variant of Papillary Thyroid Carcinoma

The follicular variant of papillary thyroid carcinoma (FVPTC) is the most common subset of papillary carcinoma and is found in 9% to 22.5% of patients with papillary thyroid carcinoma (PTC) [1–4]. This variant is composed entirely or almost completely of follicles, which are lined by cells having the nuclear features of papillary carcinoma [5]. Thus, FVPTC shares with follicular adenoma (FTA) and carcinoma (FTC) the presence of follicles. When

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FVPTC is nonencapsulated and infiltrates the surrounding thyroid parenchyma or diffusely involves the thyroid, 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 (e.g., nuclear clearing, overlapping, grooves, pseudoinclusions), which can often be borderline. Therefore, the diagnosis of noninvasive, encapsulated FVPTC versus follicular adenoma is prone to considerable interobserver variability [6, 7]. This diagnostic dilemma has very important therapeutic implications. Indeed, if an FVPTC measures ≥ 1.5 cm, many physicians in the USA will recommend completion thyroidectomy followed by radioactive iodine therapy (RAI) [8]. Some authors have suggested that patients with encapsulated, noninvasive FVPTC have an excellent prognosis and, thus, believe that only a lobectomy is needed [5]. However, there are no outcome data with long median follow-up from a large number of patients with FVPTC. More importantly, to our knowledge, there has been no study in which tumor behavior was analyzed according the histologic “subvariants” of FVPTC [i.e., nonencapsulated (infiltrative/diffuse) vs. encapsulated] that can serve as the basis for a conservative treatment approach for encapsulated, noninvasive FVPTC. In addition, there is some controversy regarding the classification of FVPTC as a member of the PTC group versus the FTA/FTC group. Indeed, Baloch and LiVolsi showed that some encapsulated FVPTCs metastasize to distant sites in the absence of lymph node metastases, mimicking the behavior of FTC [9]. Other authors reported that FVPTC has a significantly lower metastatic lymph node rate and more often is encapsulated than classic PTC [10, 11]. Several groups have attempted to analyze FVPTC at the molecular and chromosomal levels [10, 12, 13]. All of those studies concurred that the molecular profile of the FVPTC seems to be closer to the FTA/FTC group than to classic PTC, supporting further consideration of the classification of FVPTC.

To assess the behavior of FVPTC (especially its encapsulated form) and to shed more light on its true position in the classification scheme of well-differentiated thyroid carcinoma, we undertook a clinicopathologic study of all patients with FVPTC who were seen at Memorial Sloan-Kettering Cancer Center between 1980 and 1995 [14]. FVPTC tumors were classified according to histologic growth patterns as encapsulated versus nonencapsulated (infiltrative/diffuse) neoplasms. The encapsulated subset was subdivided further according to the presence or absence of invasion in a manner similar to that used to differentiate FTA from FTC. The encapsulated FVPTCs outnumbered their infiltrative/diffuse counterparts (only 17 tumors were diffuse or infiltrative vs. 61 encapsulated

FVPTCs). This rarity of infiltrative/diffuse (i.e., nonencapsulated) FVPTC seems to be concordant with the first detailed article on FVPTCs by Chem and Rosai [15].

In our study, patients who had infiltrative/diffuse FVPTC had a significantly greater frequency ($P < .0001$) of marked intratumoral fibrosis, extrathyroid extension, and positive margins than patients who had encapsulated FVPTC [15]. This superior potential of nonencapsulated FVPTCs in invading the thyroid and extrathyroid stroma was reflected by its higher rate of total thyroidectomy and especially by its rate of regional lymph node metastases. Indeed, patients with nonencapsulated (infiltrative/diffuse) FVPTCs had a metastatic lymph node rate of 65% compared with 5% for patients with encapsulated FVPTCs ($P < .0001$). This difference in lymph node disease could not be explained by differences in tumor size, gender, or age at presentation because the latter two variables were similar between the patients in the encapsulated group and the nonencapsulated group. In our study, the metastatic lymph node rate of encapsulated FVPTCs (5%) was much closer to that reported in follicular carcinomas (on the order of 5–10%), whereas infiltrative/diffuse FVPTCs had a metastatic lymph node rate within the range reported for classic papillary carcinomas (on the order of 45–65%). Our overall metastatic lymph node rate in FVPTCs (18%) was slightly higher than that reported by Zhu et al. (13%) but lower than the frequency of lymph node disease reported by Zidan et al. and Tielens et al. (22%) [3, 10, 16]. The latter difference may be explained by the observation that those investigators allowed up to 20% of papillae in their FVPTCs [3]. Their tumors will be now classified as classic PTC by most authors because the modern and now universally accepted description of FVPTC indicates that the tumor must be entirely or almost completely follicular in pattern [17].

With regard to prognosis, patients who had invasive tumors, whether encapsulated or not, had a rare but real potential for adverse outcome [14]. One patient who had an encapsulated FVPTC with capsular and vascular invasion developed a recurrence in the cervical lymph nodes 2 years after surgery. With a median follow-up of almost 11 years, overall, 6% of patients who had invasive tumors, whether encapsulated or not, had adverse outcomes, whereas none of the 42 patients who had noninvasive, encapsulated FVPTCs developed recurrences/metastases, or died of disease. All 31 patients who had noninvasive, encapsulated FVPTC and underwent lobectomy alone had good outcomes and no lymph node metastases (median follow-up, 11.1 years, median tumor size of 2.3 cm; Table 1). These data confirm the view that patients with noninvasive, encapsulated FVPTC have an excellent prognosis [5]. Eight of the noninvasive, encapsulated FVPTCs had multifocal distribution of the nuclear features of papillary carcinoma. We classified the entire tumor as FVPTC according to the

recommendation of Baloch and LiVolsi with the understanding that some pathologists may count the foci with atypical nuclei and report the lesion as multifocal PTC [9]. Others may use alternative terminology, such as “tumor of uncertain malignant potential” [30]. Whatever position the investigator takes regarding the nuclear features of FVPTC, the current results seem to point to the importance of invasion rather than nuclear features for predicting outcomes in patients who have encapsulated FVPTC. Indeed, encapsulated FVPTC seems to have a behavior much closer to that of follicular tumors (i.e., FTA and FTC) rather than classic PTC. This is reflected by the lack of adverse outcomes in patients with noninvasive lesions and the rarity of lymph node metastases. These morphologic and clinical data are supported, as mentioned earlier, by several publications pointing to a molecular profile of FVPTC much closer to the FTA/FTC group than to classic PTC.

Indeed, Zhu et al. have shown a low frequency of rearranged in transformation (RET)/PTC rearrangement (3%) and a high frequency of *RAS* mutations in FVPTC (43%), very similar to follicular carcinoma [10]. Adeniran et al. confirmed these findings and showed that within PTC, *RAS* mutations occur only in FVPTC and are associated with a low level of lymph node metastases [18]. Moreover, BRAF mutations were found to be absent in FVPTC and FTC while present in 53–56% of classical PTC [18, 19]. When we genotyped FVPTC according to its encapsulated and infiltrative form, we found that encapsulated FVPTC

have a molecular profile similar to follicular adenoma/carcinoma harboring *RAS* mutations in 36% of cases and no BRAF or RET/PTC alteration [20] (Fig. 1). In contrast, infiltrative FVPTC had a somewhat opposite profile displaying BRAF V600E mutations in 26% of the tumors while *RAS* mutations and RET/PTC rearrangement were present each in 10% of the cases (Fig. 2). The molecular profile of infiltrative FVPTC is in between FTA/FTC and classical PTC, albeit closer to the latter.

The histopathologic, clinical, and molecular data gathered to date strongly argues for FVPTC being two diseases (Fig. 3): (1) encapsulated FVPTC with a genotypic, invasive, and behavioral profile similar to follicular adenoma/carcinoma and (2) infiltrative FVPTC with invasive and behavioral features very close to classical PTC and a molecular profile closer to classical PTC than to FTA/FTC. The total lack of recurrence in our group of patients with noninvasive FVPTC who underwent lobectomy alone suggests that noninvasive, encapsulated FVPTC may be managed by lobectomy only, as recommended by Rosai et al. in the last Armed Forces Institute of Pathology fascicle on thyroid tumors [5]. Larger studies with longer follow-up than the current series will be needed to refine therapy for patients with noninvasive, encapsulated FVPTC. If the current findings are confirmed, then strong consideration should be given to reclassifying encapsulated FVPTC as an entity that is close to the FTA/FTC class of tumors. The same criteria that were used to decide whether follicular tumors are biologically benign or malignant (i.e., capsular and vascular invasion) would be applied to the evaluation of encapsulated FVPTCs. In practical terms, lack of capsular or vascular invasion should denote a benign clinical behavior in encapsulated FVPTC. If this reclassification is realized, then it will have a major impact on the diagnosis and management of patients with FVPTC. In noninvasive, encapsulated FVPTC, pathologists will be spared the frustrating and subjective exercise of deciding whether a tumor has the nuclear features of papillary carcinoma. More importantly, countless numbers of patients with noninvasive, encapsulated FVPTC will be spared unnecessary and aggressive therapy with its attached morbidity (i.e., hypoparathyroidism and recurrent nerve injury) and financial costs.

Encapsulated Follicular Carcinoma

Follicular carcinomas of the thyroid gland, including its oncocyctic variant (so-called Hurthle cell carcinoma), are subdivided into minimally invasive and widely invasive tumors [5]. The minimally invasive carcinoma, also termed encapsulated, is totally surrounded by a fibrous capsule and displays capsular invasion and/or foci of vascular invasion. It is unusual for these foci of invasion to be detected grossly

Table 1 Outcome and clinicopathologic characteristics of 31 patients with the noninvasive, encapsulated follicular variant of papillary thyroid carcinoma with adequate follow-up who underwent lobectomy only with no radioactive iodine therapy

Characteristic	Value
Median follow-up	11.1 years
Median tumor size	2.3 cm
Median age	43.4 years
Male/female ratio	1:5.2
Lymph node metastases	Absent
AJCC stage (no. of patients) ^a	
Stage I	21
Stage II	8
Stage III	2
Outcome	No recurrence

AJCC indicates American Joint Committee on Cancer

^a Patients were classified with stage I disease if they had either any T, any N, M0, and age <45 years, or T1 (tumor ≤2 cm), N0, M0, and age ≥45 years; they were classified with stage II disease if they had T2 (tumor measuring >2 cm but <4 cm), N0, M0, and age ≥45 years; and they were classified with stage III disease if they had T3 (tumor measuring >4 cm), N0, M0, and age ≥45 years (reprinted with permission from Liu J et al. 14)

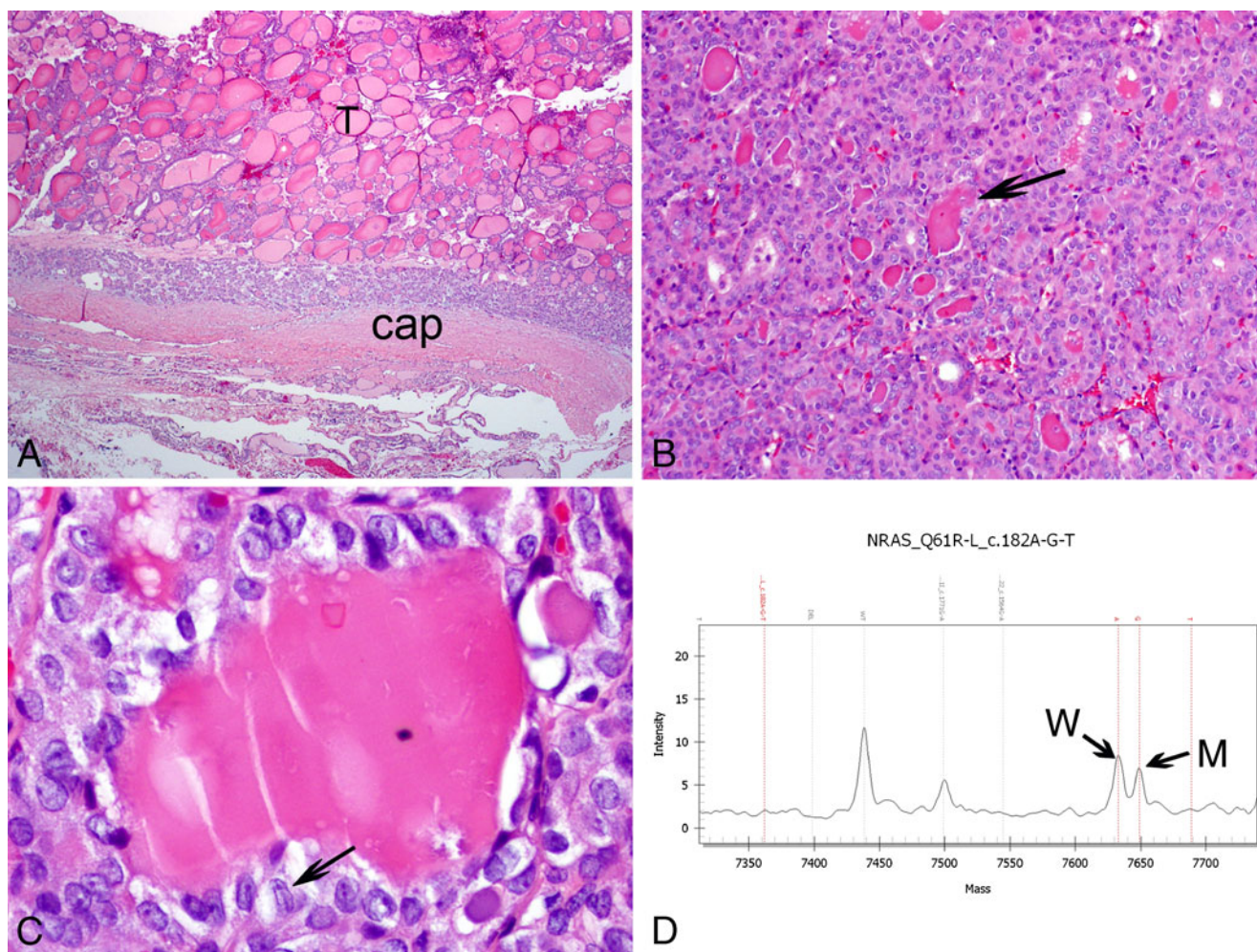


Fig. 1 Encapsulated follicular variant of papillary thyroid carcinoma. **a** Low-power view showing tumor (*T*) surrounded by its capsule (*cap*) with no invasion. **b** Medium-power view revealing follicular growth with densely eosinophilic colloid characteristic of papillary thyroid carcinoma follicular variant. **c** High-power view of the nuclear

features of papillary thyroid carcinoma: hypochromatic, irregular, overlapping nuclei with grooves (the latter indicated by an *arrow*). **d** Mass spectrometry traces for *NRAS* codon 61 mutation from the tumor. Note the mutant *NRAS* 182G (indicated by *M*) and wild-type (*W*) peaks (reprinted with permission from Rivera et al. [20])

[5]. In contrast, widely invasive follicular and Hurthle cell carcinoma are defined by extensive areas of invasion at both the macroscopic and microscopic level [5]. This classification correlates very well with outcome, such that minimally invasive tumors have an overall excellent prognosis, whereas widely invasive tumors have a much poorer outcome [5]. However, there are cases of encapsulated minimally invasive follicular carcinoma that recur and metastasize [21, 22]. Identifying these cases at the time of diagnosis is crucial because a minimally invasive tumor will be treated by lobectomy alone followed by observation in some centers, even if the follicular tumor is of the oncocyctic (Hurthle cell) category. This approach will risk undertreating those few minimally invasive tumors with a poor outcome. At variance with this minimalist surgical approach, many surgeons will perform a total thyroidectomy for any minimally invasive follicular carcinoma,

especially those of the oncocyctic category, most likely overtreating a large number of cases. In order to detect those “minimally invasive” cases that recur, some authorities limit the use of the minimally invasive term to those carcinomas with capsular invasion only since their metastatic rate is close to 0 [23, 24].

The designation “grossly encapsulated angioinvasive follicular carcinoma” has been suggested for encapsulated tumors with any foci of vascular invasion in view of their perceived higher risk of recurrence [25]. These authors feel that the presence of vascular invasion, even in one or a few endothelial-lined vessels, negates a diagnosis of “minimal invasion” as these carcinomas, once gaining access to any vessel, have the capacity to behave in a more aggressive manner than those carcinomas with only capsular invasion [25]. Other authors base their definition of minimally invasive carcinoma on the number of foci of invasion

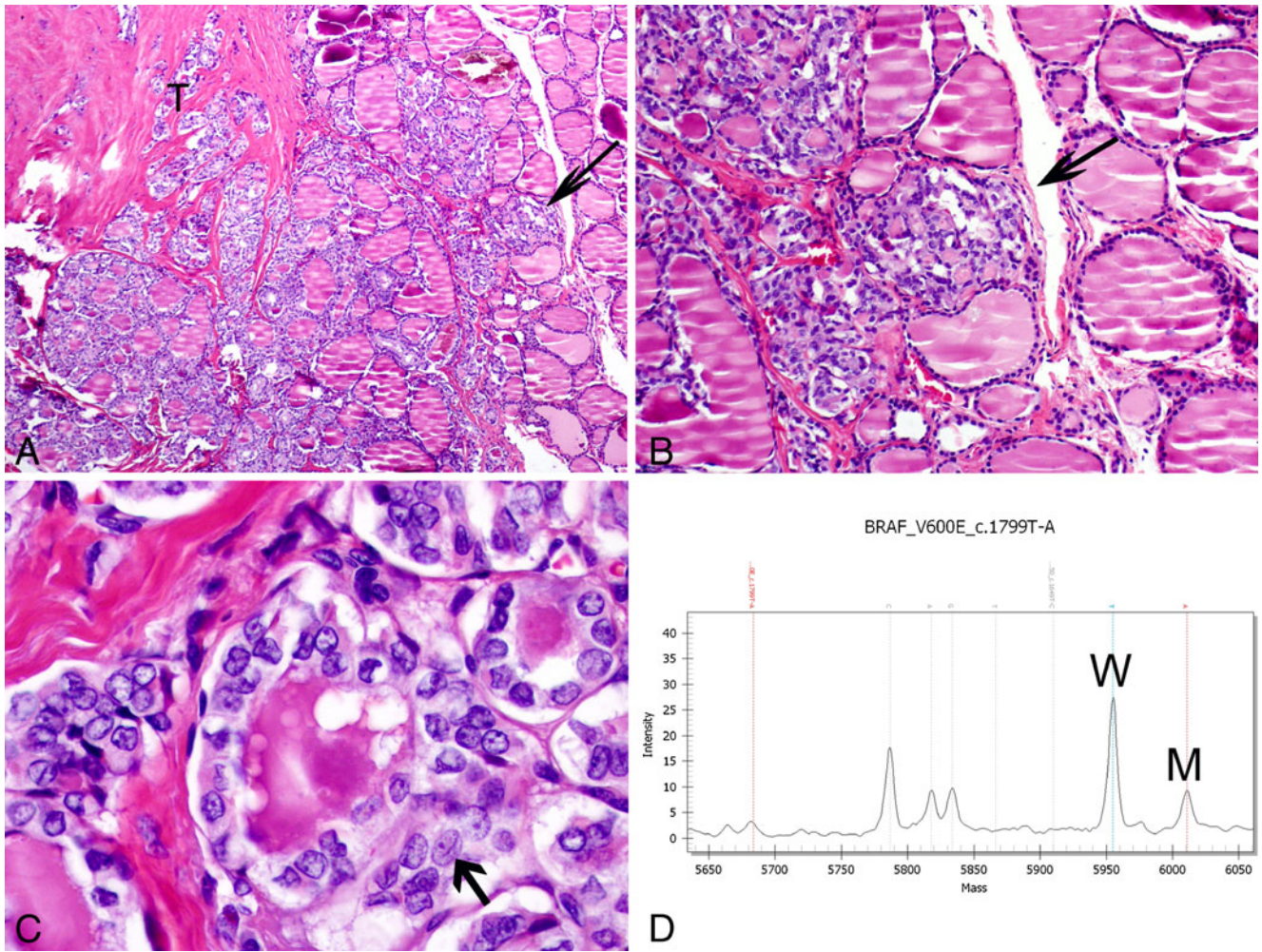


Fig. 2 Infiltrative follicular variant of papillary thyroid carcinoma. **a** Low-power view showing tumor (*T*) growing in a follicular pattern with marked fibrosis and an infiltrating advancing front (*arrow*). **b** Medium-power showing tongues of tumor infiltrating non-neoplastic thyroid without interposition of a capsule (*arrow*). **c** High-power view

of the nuclear features of papillary thyroid carcinoma: hypochromatic, irregular, overlapping nuclei with grooves (the latter indicated by an *arrow*). **d** Mass spectrometry traces for *BRAF* mutation from the tumor. Note the mutant *BRAF_T1799A* (indicated by *M*) and wild-type (*W*) peaks (reprinted with permission from Rivera et al. [20])

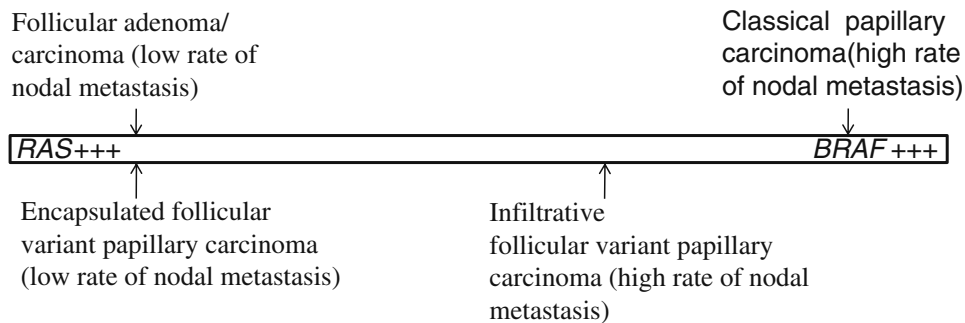


Fig. 3 *BRAF* and *RAS* mutational patterns of follicular variant of papillary thyroid carcinoma according to its encapsulated and infiltrative subtypes. The mutational pattern of encapsulated papillary thyroid carcinoma follicular variant is similar to follicular adenoma/carcinoma while infiltrative papillary thyroid carcinoma follicular

variant has a *BRAF* and *RAS* genotype in between follicular adenoma/carcinoma and classical papillary carcinoma, albeit closer to the latter. The mutational patterns of encapsulated and infiltrative papillary thyroid carcinoma follicular variant parallel their lymph node metastatic rate (reprinted with permission from Rivera et al. [20])

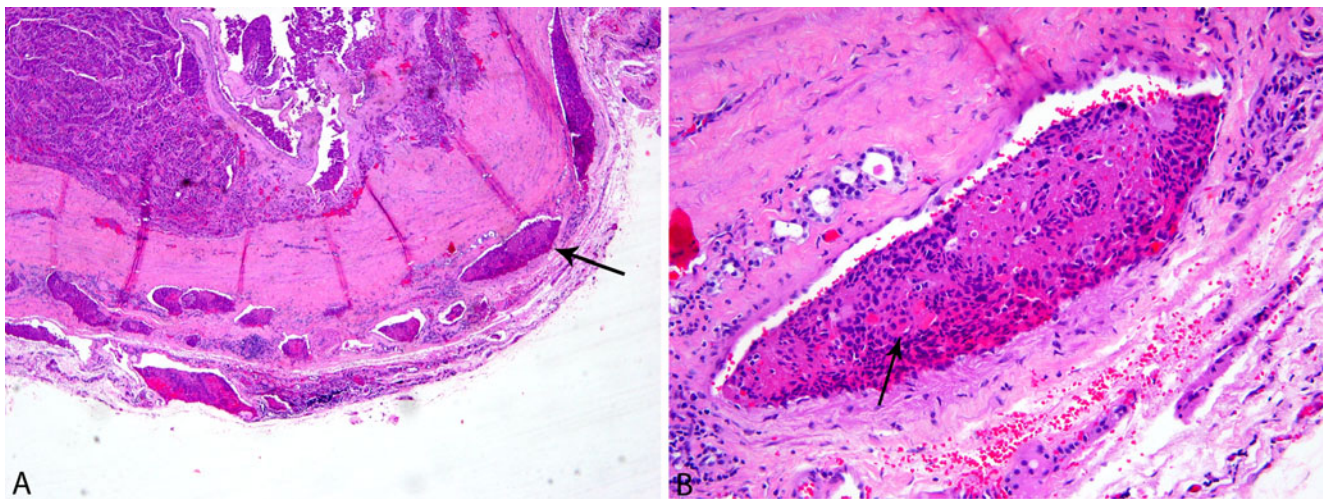


Fig. 4 Encapsulated follicular carcinoma (FC), oncocytic variant with multiple foci of microscopic vascular invasion (VI) and no gross invasion. In some classification schemes, these tumors are labeled as minimally invasive while others will use terms such as encapsulated angioinvasive FC or encapsulated FC with extensive angioinvasion to stress their potential for aggressive behavior. This 50-year-old patient developed bone metastases 10 years after thyroidectomy. **a** Low-

power view showing multiple microscopic foci of VI in tumor capsule (*arrow*) and immediately outside the capsule. **b** High-power view of a tumor thrombus (*arrow*) attached to vessel wall and covered by endothelial cells (reprinted from Ghossein R. Update to the College of American Pathologists Reporting on Thyroid Carcinomas. Head and Neck Pathol 3:86–93, 2009 [31], with kind permission of Springer Science and Business Media)

especially vascular invasion [24, 26–28]. We attempted to identify prognostic factors of recurrence in a series of 50 encapsulated follicular carcinomas, oncocytic variant (Hurthle cell) treated at Memorial Sloan-Kettering Cancer Center [27]. Forty-seven percent of these encapsulated Hurthle cell carcinomas with four or more foci of angioinvasion recurred (Figs. 4–5) [27]. Extensive capsular invasion, gender, and age did not confer a statistically higher recurrence rate. This correlation between extent of vascular invasion and adverse outcome was found in a small study of encapsulated non-Hürthle cell follicular carcinomas [28] and in larger studies analyzing follicular

carcinomas in general without emphasis on its oncocytic variant [24–29]. It is truly remarkable that the number of foci of vascular invasion we determined to place patients in high risk of disease recurrence (≥ 4 vessels) is very close to the number found by Lang et al. in 1986 (>4 foci) [24]. Based on the above data, we label tumors that have four or more foci of vascular invasion as “grossly encapsulated follicular carcinoma with extensive angioinvasion”. In another study, we showed that follicular oncocytic (Hürthle cell) carcinomas with a total of two foci of capsular/vascular invasion did not recur after a long follow-up and should therefore be called minimally invasive [26].

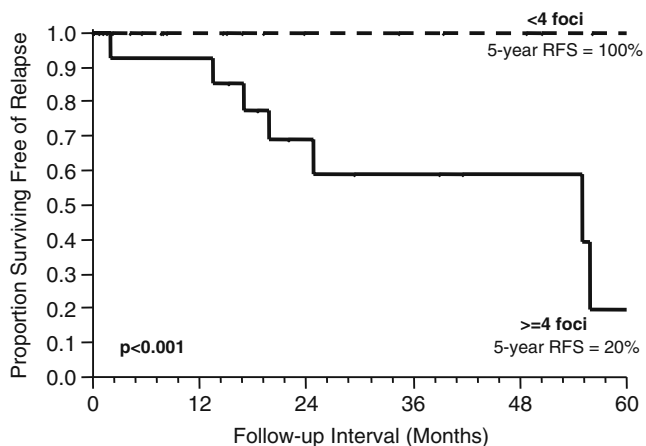


Fig. 5 Relapse-free survival (RFS) curve according to extent of vascular invasion in encapsulated Hurthle cell follicular carcinoma (reprinted with permission from Ghossein et al. [27])

Irrespective of one's philosophy in regard to the definition of minimally invasive follicular carcinoma, pathologists should report on the presence as well as the extent (focal, extensive) of capsular and lymph-vascular invasion. This approach has a dual advantage of collating the various terminologies suggested for these carcinomas, as well as and perhaps more importantly, providing a report that better assists the clinician in assessing recurrence risk and, therefore, in deciding on the extent of surgical intervention (e.g., completion thyroidectomy) and the use of postoperative RAI therapy.

Conclusion

Thyroid carcinomas of follicular cell origin are in need of continuous reclassification. The prognosis and therapy of many entities can be better delineated if a meticulous

microscopic examination is performed. An accurate assessment of the extent of invasion (especially vascular) is crucial. In addition, molecular data gathered in the last 20 years can help reassess these tumors at the histological level as in the case of the FVPTC.

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