Our approach to follicular-patterned lesions of the thyroid

Zubair W Baloch, Virginia A LiVolsi

Follicular-patterned lesions of the thyroid are common; these include hyperplastic/adenomatoid nodules, follicular adenoma, follicular carcinoma and follicular variants of papillary carcinoma. Most of these lesions can be diagnosed with ease; however, there is a controversial subgroup. In this review, we present our diagnostic approach based on our experience with the histological diagnosis of these tumours, which can help in appropriate clinical management.

According to the American Heritage Dictionary, “controversy” means a dispute, especially a public one, between sides holding opposing views. Thus, if one searches for controversy or controversial in thyroid pathology, the topic of “follicular-patterned lesions of the thyroid” meets the definition. This is evident by many articles, including original studies and reviews, that have been published on this single subject during the past decade. This lack of meeting of minds on how to diagnose follicular lesions of the thyroid has led to an increase in the number of cases sent to experts for a second opinion. We believe that to better understand this controversy and to apply any knowledge learnt to one’s own practice of pathology, we need to educate ourselves about the history of the follicular lesions of thyroid, and what it means to clinicians.

In this review, we provide and explain the basis of our diagnostic approach to these lesions. Although these maybe perceived as biases by some, they are based on published data and our experiences.

THE MEANING OF “FOLLICULAR”

This term is often used to either designate thyroid parenchymal cells, which produce thyroid hormone and show expression of thyroglobulin or the growth pattern of a thyroid lesion—that is, follicle forming or follicular patterning (regarded as the functional unit of the thyroid in normal histology). Follicular-patterned lesions are further subclassified based on the size of the follicles (microfollicular or macrofollicular) and type of encapsulation (totally or partially encapsulated or unencapsulated).

THE LOW-POWER PATHOLOGY APPROACH

In general, most follicular lesions of the thyroid can be classified into benign and malignant categories on the basis of encapsulation, lack or presence of invasion and nuclear features of papillary thyroid carcinoma (PTC). These are classified as follows.

The so-called “adenomatoid nodules and adenomas”

Thyroid nodules are common and can occur in up to 60% of the US population, and most are part of a multinodular gland. These can show complete or partial encapsulation. Historically, multiple thyroid nodules in a goitrous thyroid were classified as hyperplastic nodules. Adenomas are defined as solitary, and lack any evidence of capsular or vascular invasion. They are classified based on their growth pattern as macrofollicular, simple, microfollicular, fetal, embryonic and trabecular. These patterns do not need to be mentioned in the surgical pathology report, as they have no clinical relevance. Papillary formation can occur locally in follicular adenomas; these papillae are usually oriented towards the centre of the lesion, show oedematous “cores” and small follicles within the cores, and lack the nuclear morphology of papillary carcinoma. Rarely, calcification can occur in these lesions, which can be mistaken for psammoma bodies, especially in fine needle aspirate (FNA) specimens.

Differentiation between hyperplastic nodules and follicular adenoma on the basis of the above-mentioned features can be difficult; thus, in some cases, a hyperplastic nodule in a multinodular gland can show complete encapsulation and distinct growth pattern compared with the surrounding thyroid. Therefore, multiple encapsulated nodules are usually termed “adenomatoid hyperplasia.” It has been shown that up to 70% of the hyperplastic nodules are clonal proliferations, and can express various markers of malignant follicular-derived thyroid tumours such as peroxisome proliferator-activated receptor (PPAR)γ and RET. This may also explain why malignant transformation in follicular-patterned lesions of the thyroid involves a sequence of molecular events originating in adenomatoid hyperplasia and leading to carcinoma.

No molecular study to date has been able to distinguish between adenomatoid nodules, follicular adenoma and carcinoma with 100% sensitivity and specificity. Some forms of follicular adenomas have been identified as distinct pathological entities. These include hyalinising trabecular adenoma/neoplasm and atypical adenoma. Hyalinising trabecular adenoma/neoplasm is a distinct entity, which some believe,
is a form of encapsulated PTC, based on immunohistochemical and molecular characterisation. However, recent studies have shown that BRAF mutations, which are specific to papillary carcinoma, do not occur in these lesions. The term “atypical follicular adenoma” is restricted to a group of encapsulated follicular lesions, which show spontaneous necrosis, infarction, numerous mitoses or unusual cellularity (excluding the unusual cells noted above), and which lack any evidence of capsular or vascular invasion. Follow-up studies have shown that these tumours behave in a benign fashion.

The question arises as to why we need to make a distinction between hyperplastic/adenomatoid nodules and adenoma when both are so biologically similar. Until molecular evidence can effectively differentiate between benign and malignant follicular-patterned lesions, we believe that an encapsulated thyroid nodule with a distinct growth pattern compared with the surrounding thyroid can be classified as a follicular adenoma.

**Follicular carcinoma**

Follicular carcinoma is a rare (approximately 5% of all thyroid malignancies) form of thyroid cancer in the USA. It is reported to be more prevalent (25–40%) in iodine-deficient regions (it must be remembered that many of the studies of this question are based on PTC criteria used before the definition of the follicular variant was used, hence these data need to be re-examined). It is more common in women and shows a wide age distribution (peaking in the fifth and sixth decades).

Clinically, follicular carcinoma presents as a solitary mass (usually measuring >2 cm) in the thyroid; incidental follicular carcinoma is rare. The sole criterion for the diagnosis of follicular carcinoma is demonstration of capsular or vascular invasion. Therefore, histological examination of the tumour capsule interface is more prudent than examination of central portion of the tumour. Follicular carcinoma does not invade lymphatics; true embolic lymph node metastases are exceedingly rare. Follicular carcinoma disseminates haematogenously and characteristically metastasises to bone, lung, brain and liver.

The treatment of follicular carcinoma remains controversial. Some consider total thyroidectomy the appropriate treatment for encapsulated follicular cancers for effective radioactive iodine treatment, whereas others believe complete thyroidectomy may represent “overtreatment”, as the disease-free interval after lobectomy or cure of these encapsulated lesions is so great. Total thyroidectomy is the treatment of choice in patients who initially present with metastases. Lymph node dissection is not warranted as these tumours do not spread to nodes; however, abnormal-appearing or enlarged nodes should be sampled.

**Pathology**

To date, several articles on the pathological diagnosis of follicular carcinoma have been published; many of these lack reproducibility and long-term clinical follow-up to substantiate the diagnostic approach. This is further complicated by the present clinical staging systems, which do not consider the age and sex of patients, as most of these are based on patients with PTC.

Traditionally, follicular carcinoma is classified as so-called widely invasive and minimally invasive. Widely invasive follicular carcinoma is clinically and surgically recognisable as a cancer; the role of the pathologist in its diagnosis is to confirm that it is of follicular origin. These lesions grossly spread throughout the thyroid and invade the perithyroidal tissues. Such tumours are often fairly cellular, usually microfollicular, or solid or trabecular in pattern and are often classified as poorly differentiated/insular carcinoma. The mortality is high; >50% of patients die of disease.

Minimally invasive follicular carcinoma resembles a follicular adenoma; grossly, the lesion is well defined. Most measure >4 cm. Usually, these tumours have thickened capsules compared with the benign counterpart—that is, follicular adenoma. The pathological diagnosis of minimally invasive follicular carcinoma is made when there is capsular invasion; however, some authors have suggested this terminology also for tumours with invasion of the capsular vessels.

Capsular invasion is usually seen as nests of tumour cells penetrating into the tumour capsule (fig 1). In most cases, there are multiple foci of capsular invasion; rarely, one may encounter only a single focus of capsular invasion in a well-sampled tumour. Capsular invasion remains a controversial topic in the diagnosis of follicular carcinoma. Some experts believe that capsular invasion alone—that is, without vascular invasion—does not warrant a diagnosis of carcinoma. Lang and Franssila et al consider nests of tumour in the capsule to possibly represent trapping and distortion by fibrosis rather than invasion. These authors require penetration of the capsule to diagnose a follicular tumour as carcinoma, preferring not to overdiagnose such lesions. Iida et al noted that distinguish-
total capsular invasion without vascular invasion as, rarely some of these tumours can develop recurrent or metastatic disease.

Some authors have proposed that encapsulated follicular tumours with capsular “invasion” should be designated as atypical adenomas to indicate a benign clinical course after thyroid lobectomy. However, these reported cases/series lack long-term follow-up.22,79 Encapsulated follicular carcinomas notoriously can present as metastases many years after initial resection.

It is important to recognise that the debate about the capsular invasion criterion is similar to looking through crystal ball for predicting prognosis and hence guiding the management. Most pathologists have seen cases of follicular carcinoma presenting initially in metastatic sites; when the primary thyroid tumour is resected, extensive sampling may disclose only capsular invasion.23 To extrapolate from these cases to all follicular tumours confined to the thyroid at diagnosis may not be justified. It is possible that the small group of patients presenting with metastases and primary lesions showing only capsular invasion harbour tumours of a different biological nature or that unknown host factors are operating in these individuals.

Our approach is that capsular invasion alone presenting as a single or multiple foci in an encapsulated follicular-patterned lesion is a definite criterion of malignancy, and the tumour does not have to invade through the entire thickness of the capsule to be classified as carcinoma. In our experience, deeper sectioning of these foci in most cases will show the tumour traversing the entire thickness of the capsule. The invading tumour nests should show a connection with the main tumour mass, as free-floating nests of cells in the tumour capsule may represent entrapment due to preoperative FNA or tumour degeneration. Small nodules outside the tumour capsule, which appear similar in morphology to the main tumour mass, should also not be considered as foci of invasion if they fail to show any connection to the tumour. In our practice, we classify encapsulated follicular tumours with only capsular invasion (and if they lack nuclear features of papillary carcinoma) as minimally invasive follicular carcinoma. We strongly believe that these tumours have a low risk of recurrence or metastases.

Vascular invasion is defined as the presence of a tumour embolus in the capsular vessels adherent to the vessel wall and the endothelial cells lining its free surface44–46 (fig 2). The criterion for vascular invasion applies solely and strictly to vessels in or beyond the capsule, as tumour plugs within capillaries in the substance of the tumour have no apparent diagnostic or prognostic importance.

The histological criteria for diagnosis of vascular invasion are defined as follows:

1. The invasive tumour should form a plug or polyp in a subendothelial location; a few cells or nests slightly impinging into a lumen are insufficient evidence for invasion (fig 2).
2. The tumour thrombus is usually covered by endothelium. Tumour cells or small nests strewn freely in a vessel lumen probably represent artefacts.
3. The endothelium-covered tumour thrombus does not have to be attached to the vessel wall to be accepted as invasion.

Our approach is that when vascular invasion is found in an encapsulated follicular-patterned lesion without the nuclear features of papillary carcinoma, we use the diagnostic term “grossly encapsulated angioinvasive follicular carcinoma”, as this group has a considerable propensity for clinically malignant behaviour.

Do follicular adenoma and carcinoma represent two extremes of a spectrum? It has been shown that most of the so-called markers of malignancy (in both immunohistochemical and molecular studies) are also expressed in patients diagnosed with hyperplastic adenomatoid nodules and follicular adenoma.20–22 Comparative genomic hybridisation studies have shown that follicular adenomas show genetic aberrations similar to follicular carcinoma. These findings are further supported by cytogenetic karyotyping and allelotyping studies. Among the numerous chromosomal changes described in follicular adenoma and carcinoma, chromosomal loss at 3p25 is most commonly found in both tumours.76–78 Kroll et al34 described a change involving t(2;3)(q13;25) as a fusion of PAX8 (2q13) with PPARG (3p25). Initial studies showed this PAX8–PPARG rearrangement may be specific for follicular carcinoma, as for RET gene rearrangements in PTC. However, later studies showed that this rearrangement was also seen in cases of follicular adenoma.35 Similarly, RAS gene mutations have been described in both follicular adenoma and carcinoma.35 Recently, Barden et al36 analysed gene expression profiles of follicular adenomas and carcinomas by oligonucleotide array analysis. They found 105 genes differently expressed between adenomas and carcinomas. Of these, six genes showed a relevant differential expression between adenomas and carcinoma. Interestingly, only two cases of minimally invasive follicular carcinoma were included in this study, which showed expression profiles similar to follicular adenomas; all other cases of follicular carcinomas were angioinvasive, including one Hürthle cell carcinoma (considered by many to be biologically different from follicular carcinoma).

The aforementioned studies are provocative and challenge the diagnostic approach and management of follicular lesions of the thyroid. Hence, most cases of minimally invasive carcinoma will behave in a benign fashion, and their treatment should be conservative—that is, lobectomy or partial thyroidectomy (if the tumour capsule is well-sampled and angioinvasion is ruled out).

FOLLICULAR VARIANT OF PAPILLARY THYROID CARCINOMA

This is the second most common variant of papillary carcinoma of thyroid after the classic variety. Follicle formation and nuclear features of papillary carcinoma—that is, nuclear elongation, chromatin clearing, intranuclear grooves and inclusions, eccentric nuclei and irregular nuclear envelope characterise this tumour77 (figs 3 and 4). Follicular variant of papillary thyroid carcinoma (FVPTC) clinically behaves similarly to classic PTC. This tumour can clinically present either as a single nodule or arise against a background of multinodular goitre. Using light microscopy, some tumours are shown to be completely encapsulated (fig 3), whereas others may show partial to total lack of capsule.77,78

In most instances, the diagnosis of FVPTC is not difficult; this mainly applies to cases that show classic nuclear morphology of papillary carcinoma diffusely distributed throughout the tumour. However, there are cases that show multifocal rather than diffuse distribution of nuclear features of papillary carcinoma. The diagnosis of such lesions as carcinoma is controversial.77,80 Some authors have suggested that these cases should not be placed into a definite benign or malignant category and should be termed as “well-differentiated tumour of uncertain malignant potential”, thus preventing more surgery and treatment.81 However, recent studies have looked into RET/PTC distribution in cases of FVPTC, which show multiple rather than diffuse foci diagnostic of PTC, and have shown that RET/PTC is expressed in the areas of PTC; this
confirms the morphological impression that these are indeed multiple foci of PTC.

When faced with a follicular-patterned encapsulated nodule with multiple foci showing cytological features characteristic of PTC, how should such cases be diagnosed? We believe that we can approach such cases in two ways: count all the foci diagnostic of PTC and report them as multiple foci of micro-PTC arising in a benign nodule, giving their size measurements of each focus, or diagnose the entire nodule as FVPTC. We believe that the first method of diagnosing these lesions will create confusion—that is, whether to perform completion thyroidectomy or not—as some clinicians/surgeons do recommend total thyroidectomy for patients with multiple foci of papillary carcinoma.

In our practice, we take the second approach; if an encapsulated follicular-patterned lesion shows multiple foci of PTC intermixed with areas lacking nuclear features of PTC, then, for treatment and staging purposes, we diagnose the entire lesion as FVPTC. In addition, we have studied cases that have been diagnosed as follicular adenoma or tumours of uncertain malignant potential on the basis of minimal nuclear features of PTC and that have later developed lymph node and bone metastases.

Is FVPTC a hybrid of follicular carcinoma and papillary carcinoma? Although FVPTC is a variant of papillary carcinoma (on the basis of cytology and clinical behaviour), it does share some morphological and clinical features with follicular carcinoma. These include follicular growth pattern, encapsulation, capsular and vascular invasion (fig 4), and distant metastases to lung and bone. This association of FVPTC with follicular carcinoma is further substantiated by genetic studies. Gene expression profiling studies have shown that some cases of FVPTC show profiles similar to follicular carcinoma. Comparative genomic hybridisation analyses have shown that the presence and pattern of chromosomal aberration in FVPTC are markedly different from those in classic PTC, being more comparable to follicular adenoma and follicular carcinoma. RAS gene mutations, an abnormality seen in follicular adenoma and carcinoma, are exclusively seen in FVPTC and not in classic PTC; similarly, RET gene translocations and BRAF mutations, which are common in classic PTC, are rare in cases of FVPTC. Therefore, in view of morphological features, clinical behaviour and genetic analysis, it is not unreasonable to hypothesise that cases of FVPTC may represent a hybrid of papillary carcinoma and follicular adenoma or carcinoma.

What does this hybrid theory mean? If confirmed, this reclassification would have important prognostic and therapeutic implications. Encapsulated FVPTC without any capsular and vascular invasion (if the tumour is well sampled) will behave like follicular adenomas and those with capsular and vascular invasion as follicular carcinomas.

**Follicular tumours of uncertain malignant potential**

In the practice of pathology, it is not uncommon to come across lesions that cannot be categorised as definitely benign or malignant. Such lesions represent a “grey zone” and are usually termed tumours of uncertain or borderline malignant potential. This terminology is well recognised in gynaecological pathology and is applied to epithelial tumours of the ovary and smooth muscle tumours of the uterus. Gynaecologists and oncologists are familiar with these diagnoses and know how to manage their patients on the basis of extensive experience in clinical trials and patient follow-up.

Williams et al proposed the term “follicular tumour of uncertain malignant potential” 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...
questionable/minimal capsular invasion. The main reason behind this proposal is to avoid extensive treatment (total thyroidectomy followed by radioactive iodine) of thyroid tumours, which clinically behave in a benign fashion and carry excellent prognosis. This proposal seems to be of value in the context of controversial follicular lesions of thyroid. However, we should not forget that currently there are no clinical follow-up data to justify the use of the term “follicular tumors of uncertain malignant potential” and hence, this diagnosis will generate confusion among clinicians regarding the management of patients. To date, we have not used this terminology in our practice, and we diagnose patients on the basis of diagnostic criteria discussed above.

Intraoperative consultation in follicular-patterned lesions of the thyroid

Intraoperative consultation is not helpful in the diagnosis of follicular or Hurthle cell carcinomas because the diagnosis of these lesions is dependent on the demonstration of capsular and vascular invasion. Most sections from the tumours are needed because focal invasion can be missed on a single frozen section as practical issues preclude freezing multiple areas of the nodule. Hence, invasion is not often identified on frozen sections.

The major problems in frozen section analysis of thyroid nodules include: freezing artefacts that can mimic nuclear features of papillary carcinoma; sampling errors; and, as most of these lesions had undergone preoperative FNA, post-FNA changes in the tumour capsule that can be mistaken for capsular or vascular invasion and reactive/ reparative nuclear changes that can be mistaken for papillary carcinoma.

In our experience, intraoperative consultation of thyroid lesions is most beneficial in cases diagnosed as suspicious for papillary carcinoma on FNA. The diagnosis of FVPTC depends on nuclear features and not invasion; in these cases, when intraoperative cytology is combined with frozen sections, ≥35% of such lesions can be diagnosed as papillary carcinoma. This then leads to definitive surgery as the primary procedure rather than a two-staged surgical procedure.

CONCLUSIONS

The topic of follicular-patterned lesions of thyroid is exciting, because we are in the process of learning more about these lesions and are finally asking the right biological questions. The answers may seem puzzling because the whole notion of benign versus malignant is not as clear-cut as initially thought. As discussed earlier, some cases of FVPTC and follicular carcinoma share genetic profiles with benign lesions such as follicular adenoma and hyperplastic/adenomatoid nodule. Therefore, are we ready to reclassify the follicular lesions of the thyroid on the basis of these recent molecular data? We believe that these studies need to be reproduced by multiple investigators in larger cohorts of cases with clinical data to propose a new classification of follicular-patterned lesions of the thyroid and change/modify the existing paradigm of clinical management. Until then, we will continue to classify these lesions according to the scheme discussed earlier.

Authors’ affiliations

Z W Baloch, V A LiVolsi, Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania, USA

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REFERENCES


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