Thyroid gland follicular carcinoma.

by Lester D. R. Thompson, MD

Thyroid gland follicular carcinoma is a malignant epithelial neoplasm of follicular cell differentiation that exhibits capsular and/or lymphovascular invasion while lacking the nuclear features of thyroid papillary carcinoma. While rarely inherited, follicular carcinoma will develop in about 20% of patients with Cowden syndrome, related specifically to PTEN germline mutations. Previous radiation exposure and iodine deficiency are known environmental etiologic factors.

Follicular adenoma may be a precursor lesion, as affected patients are on average 8 to 10 years older than patients with adenoma. Also, while both lesions have RAS, PTEN, and PIK3CA mutations, the frequency of mutations is much greater in carcinoma. The follicular variant of papillary carcinoma accounts for about 10% of all primary thyroid gland malignancies. Increased recognition of this variant has resulted in a downward trend in the overall incidence of follicular carcinoma. Women are affected more often than men (2 to 2.5:1), and its incidence peaks at 40 to 50 years of age, although the oncocytic type develops in patients who are about a decade older.

Most patients present with an asymptomatic, solitary, painless, and enlarging, often palpable, thyroid gland mass. Ultrasonography is useful in documenting the size and extent of the tumor and in following a tumor serially over time. Ultrasonography often highlights the solid nature of the mass, and it can be used for guidance during fine-needle aspiration.

The recommended treatment is lobectomy or total thyroidectomy, with or without radioablation. The choice depends on the size and stage of the tumor, extent of lymphovascular invasion, and patient's age. As many as 25% of all follicular carcinomas and 75% of the oncocytic type do not take up radioactive iodine.

Twenty-year survival rates are approximately 97% for patients with a minimally invasive tumor and 50% for those with a widely invasive tumor. Tumors that contain RAS mutations have been associated with tumor dedifferentiation, distant metastases, and a poorer survival rate.

Follicular carcinomas are usually solitary, solid masses with a thicker, more irregular capsule than follicular adenomas. Degenerative changes are rare, although oncocytic tumors tend to show these changes more often. In general, 2 or 3 sections per block of the parenchyma-capsule-tumor interface with a minimum of 10 blocks yields the best tumor evaluation. It bears stating that the histologic features of papillary carcinoma are absent. The tumor is surrounded by a variable, thick, fibrous connective tissue capsule that contains smooth-muscle-walled vessels (figure 1). Either capsular (figure 2) or lymphovascular (figures 3 and 4) invasion is sufficient for the diagnosis of follicular carcinoma.

Figure 1. In this follicular carcinoma, invasion by neoplastic cells is seen beyond the contour of the tumor and through its capsule.

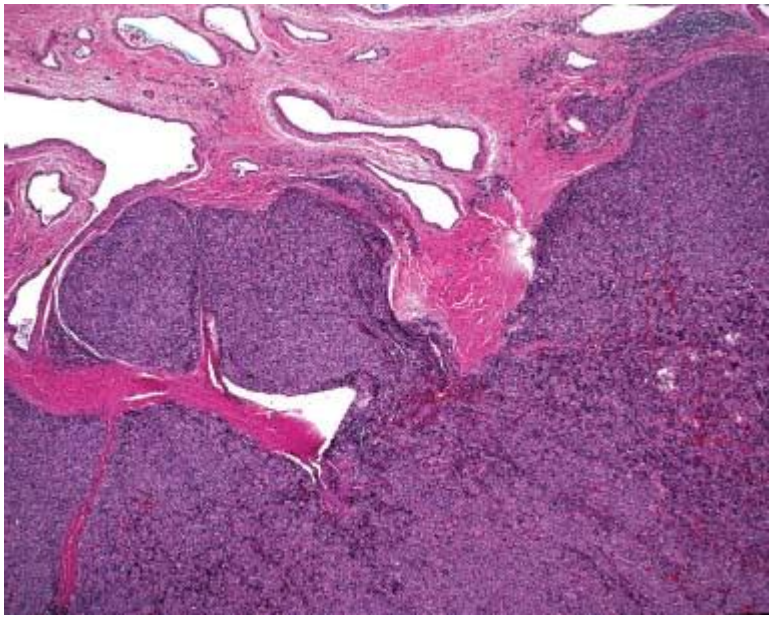


Figure 2. A broad tongue of tumor is seen extending into the adjacent parenchyma, which confirms capsular invasion.

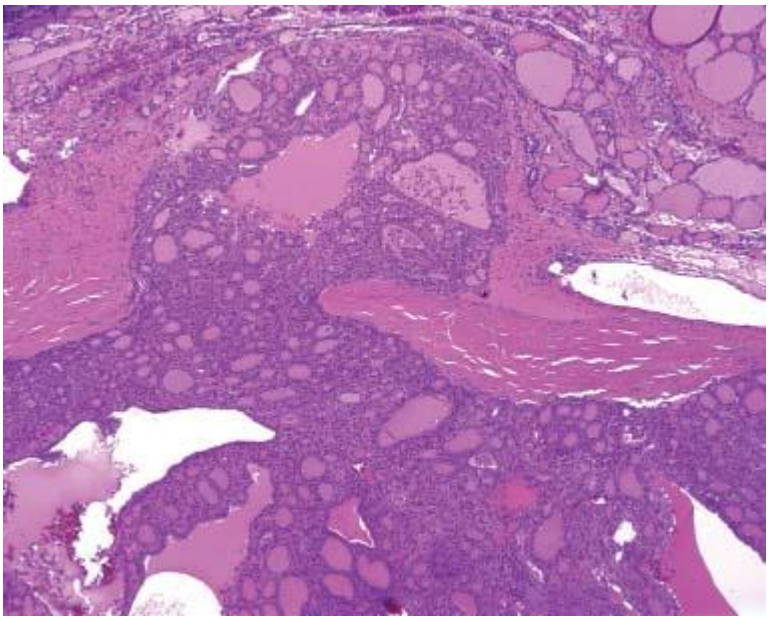


Figure 3. A: Tumor cells are present within the lymphovascular space. B: CD34 highlights the vessels, which contain neoplastic cells.

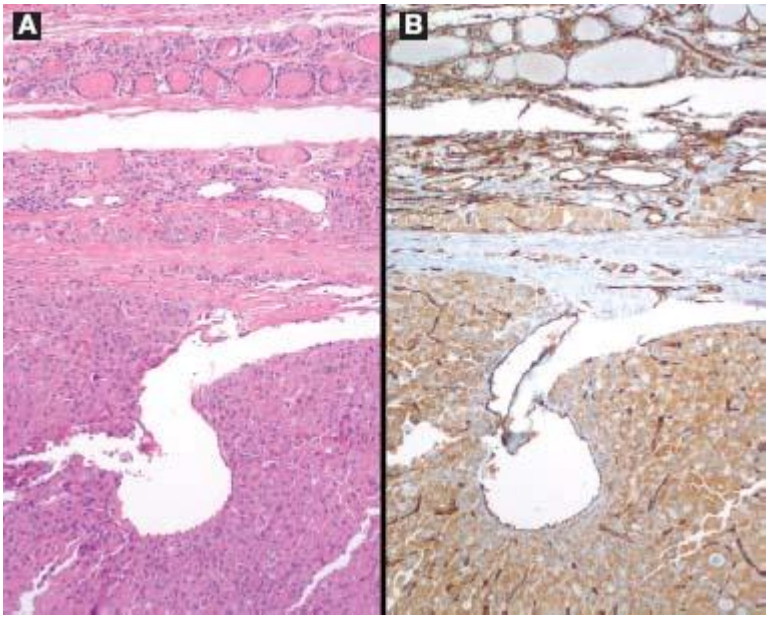
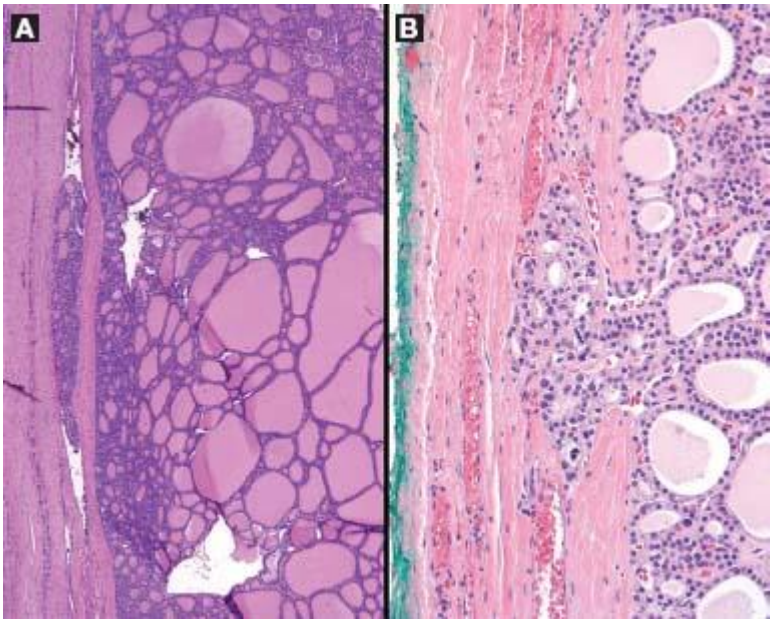


Figure 4. A: Tumor cells fill a vessel. Note that the vessel is within the capsule (not within the tumor). B: Tumor cells are seen expanding into and filling this vessel. Other vessels are seen immediately adjacent to it; they may represent part of the same vessel, although the vessel is tangentially sectioned.



Definitions of invasion abound, but suffice it to say that invasion must be present to place the lesion in a carcinoma category. Vascular invasion occurs when tumor cells within vessels are (1) within or beyond the capsule, (2) identified by direct extension into the vessel, (3) lined by endothelial cells, (4) associated with thrombus, (5) not freely floating within the vascular space, and (6) having a morphology that is identical to the cells within the tumor (figures 3 and 4). In some cases, confirming the presence of a vessel with CD34 or podoplanin (figure 3) may help determine the presence of vascular invasion.

The neoplastic cells are usually arranged as well-formed follicles (microfollicles) in a solid, cystic, trabecular, and/or insular pattern; one of these patterns usually predominates. Colloid should be identified or confirmed by thyroglobulin immunohistochemistry staining. The tumor cells are enlarged with variable cytoplasm that surrounds round and regular nuclei that feature a smooth contour and coarse to heavy nuclear chromatin. A finding of pleomorphism does not alter the diagnosis, but if there is tumor necrosis and more than 4 mitoses/10 hpf, then a poorly differentiated carcinoma should be considered.

Extrathyroidal extension is associated with a worse prognosis. Variants include microscopic (<1 cm), widely invasive, oncocytic (Hürthle cell, Ashkenazy cell, oxyphilic cell) (figure 3), insular, trabecular, solid, signet-ring, and clear-cell types, among others. While cytology is performed preoperatively in nearly all thyroid gland nodules, making a definitive distinction between follicular adenoma and carcinoma cannot be reliably or predictably achieved by fine-needle aspiration analysis, even with adjunct molecular evaluation.

Molecular findings have shown rearrangements of the peroxisome proliferator-activated receptor gamma (PPARγ) gene in as many as 50% of follicular carcinomas, which results in a fusion between the PAX8 gene on 2q13 and the PPARγ gene on 3p25. When the PPARγ gene is identified, there is almost never a concurrent RAS mutation, although point (activating) mutations in RAS are seen in as many as 50% of follicular carcinomas while PTEN or PIC3CA mutations are seen in as many as 10% of tumors.

Follicular carcinoma must be distinguished from follicular adenoma, adenomatoid nodules, the follicular variant of thyroid papillary carcinoma, medullary carcinoma, and other clear-cell tumors (parathyroid adenoma/carcinoma) or metastatic renal cell carcinoma.

Suggested reading

1. Ko HM, Jhu IK, Yang SH ,et al. Clinicopathologic analysis of fine needle aspiration cytology of the thyroid. A review of 1,613 cases and correlation with histopathologic diagnoses. Acta Cytol 2003; 47 (5): 727 - 32.
2. Nikiforov YE. Thyroid carcinoma: Molecular pathways and therapeutic targets. Mod Pathol 2008; 21 (Suppl 2): S37 - 43.
3. Thompson LD, Wieneke JA, Paal E ,et al. A clinicopathologic study of minimally invasive follicular carcinoma of the thyroid gland with a review of the English literature. Cancer 2001; 91 (3): 505 - 24.

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