Thyroid Tumor Capsular Invasion: the Bottom Line or Much Ado About Nothing?

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In this issue of *Endocrine Pathology*, Zhu et al. tackle the problem of the interpretive difficulties faced when assessing capsular invasion to distinguish minimally invasive thyroid follicular carcinoma from follicular adenoma [1]. Not unexpectedly, they show significant variability in this interpretive function.

Thyroid pathology has long been an area of controversy. With the recognition of the follicular variant of papillary carcinoma, nuclear morphology became the key diagnostic feature and there was controversy regarding the extent of nuclear atypia required to make a lesion malignant. More recently, with the move to invasion-based diagnosis at the expense of nuclear morphology, thyroid pathology has entered an era of unprecedented borderline diagnosis. The reason for this dramatic shift is that the diagnosis of invasion can be and often is extremely difficult. This point is well proven by this study of consensus among a group of Asian pathologists regarding tumor capsular invasion. The lack of agreement among pathologists is due to many factors, including what the individual was taught, what was the position of their mentor, and geographic differences in this type of interpretation. However, the problem is complex and can be solved if properly addressed.

A traditional aphorism holds that “Absence of evidence is not evidence of absence” and nowhere is this more important than in pathology. In the case of tumor capsular invasion, not seeing invasive tumor on a slide does not prove that there is no invasion in another section deeper in the block or in another place in the tumor capsule. The same is true for the

identification of angioinvasion; despite meticulous workup including complete submission of the tumor capsule, one cannot exclude the presence of angioinvasion in tissue that was not examined. An example of this is the prismatic 6.4 cm non-invasive encapsulated/well-demarcated follicular variant papillary thyroid carcinoma (diagnosed using rigid criteria and submitted entirely for microscopic examination) that gave rise to lung metastasis in a series of non-invasive follicular tumors with papillary-like nuclei (NIFT-P) [2]. These rare occurrences may sound anecdotal; however, the limitations that diagnosticians face daily must be kept in mind as we handle each specimen of individual patients. Despite increasing demand for the best risk stratification in thyroid oncology and the pressure to do more with fewer resources, pathologists continuously face this challenge. In fact, the only way to make an accurate diagnosis of a non-invasive neoplasm would be to examine every serial section of every piece of tumor capsule at the cost of exhausting the tissue. This would be considered absurd but may in fact become possible as we learn to apply novel imaging technologies that can see through full blocks of tissue [3]. In the interim, we must balance the risk by identifying areas of suspicion and recognizing that we have a responsibility to cut multiple deeper sections to ensure that we have not missed a focus of true invasion.

Thus, the careful assessment of a tumor capsule is indeed the “bottom line” that ultimately determines the diagnostic category of a follicular-patterned thyroid neoplasm. However, thyroid pathology is also plagued by a history of clinical abuse of therapies in an era that antedates the controlled clinical trials of today’s oncology. While there is no doubt that radioactive iodine (RAI) is an exceptional targeted therapy, biased studies and anecdotes led to its widespread use for any thyroid cancer, including papillary microcarcinomas and minimally invasive follicular thyroid carcinomas. Subsequent studies have suggested that this is overtreatment and, indeed, the pendulum has swung to less aggressive management, including active surveillance for papillary microcarcinomas [4]. Ironically, RAI is not very expensive; therefore, there is no financial incentive to carry out a large,

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randomized clinical trial to accurately determine the appropriate use of this agent that is cheap and easy to administer but not without adverse effects. Data from small studies suggest that such a trial would show no benefit in patients with low-risk thyroid cancers, including papillary microcarcinomas, and minimally invasive follicular and follicular-variant papillary carcinomas, particularly in young patients [5]. The rationale for total thyroidectomy in patients with unilateral disease is only to pave the way for RAI; therefore, surgical resection can be limited to lobectomy in most patients.

Thus, the issue of borderline neoplasms may indeed be “much ado about nothing.” The classification of a low-risk thyroid cancer as a minimally invasive follicular thyroid carcinoma, as “thyroid neoplasm of uncertain malignant potential” in the 2017 WHO classification [6] or as NIFT-P [7] should not alter the management of the patient. If the tumor is only minimally invasive without angioinvasion, these follicular-patterned neoplasms do not require more aggressive therapy but should be watched carefully after surgical resection.

By working with other members of the multidisciplinary care team, pathologists must educate surgeons and oncologists as well as patients to understand that not every thyroid carcinoma is biologically aggressive [8] and the requirement for adjuvant therapies should be individualized based on dynamic risk stratification. Despite the well-recognized limitations in our diagnostic assessment of follicular neoplasms, pathologists still need to develop a comprehensive and unified diagnostic approach for the assessment of invasive growth that will represent an important criterion of risk stratification in surgical pathology practice.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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