



New Insights on the Importance of the Extent of Vascular Invasion in Encapsulated Angio-invasive Follicular Thyroid Carcinoma

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The significance of the extent of vascular invasion (VI) in thyroid cancer has been thoroughly investigated and debated in the literature, and yet there is always more to discover, as described in the article “Encapsulated Angio-invasive Follicular Thyroid Carcinoma: Prognostic Impact of the Extent of Vascular Invasion” by Yamazaki et al.¹ In this study, Yamazaki et al. have revisited the significance of the number of foci of VI on recurrence and survival in patients with thyroid cancer. Notably, only patients with encapsulated angio-invasive follicular thyroid carcinoma (FTC) were included in this study with a relatively large final cohort of 264 patients. Following receiver operating characteristic (ROC) curve analysis, a new optimal cut-off—VI foci of 2—was identified for both cause-specific survival (CSS) [area under the curve (AUC) = 0.60 (sensitivity, 1.00; specificity, 0.40)] and disease-free survival (DFS) [AUC = 0.67 (sensitivity, 0.90; specificity, 0.45)]. Moreover, patients with 1 focus of VI had statistically significant superior CSS and DFS rates compared with patients who had 2 or more foci of VI. The 10-year CSS rates were 100% and 94.5%, respectively, with a *p* value of 0.042. The 10-year DFS rates showed even more striking differences (94.9% and 77.9%; *p* < 0.001). Surprisingly, when comparing the usual classification of 1–3 foci versus 4 or more foci, there was no statistically significant difference for CSS (*p* = 0.597) or DFS (*p* = 0.311). Age

≥ 55 years along with 2 or more foci of VI were reported as significant negative prognostic factors for DFS in a multivariate analysis.

The extent of VI has been a controversial topic in thyroid cancer since it was first described by Graham in 1924.² The very definition of VI in thyroid cancer has evolved and changed without ever reaching an absolute consensus regarding the criteria to characterize VI. The impact of the mere presence of VI on survival outcomes has been also debated. Sugino et al. showed that VI did not increase the risk for distant metastases.³ In contrast, Mete and Asa⁴ highlighted the presence of VI as a valuable predictor of developing distant metastasis, especially in well-differentiated thyroid cancer, and this has been corroborated by several other studies.^{5–10} The relevance of the number of foci of VI also has been questioned. Wreesmann et al.⁷ did not find a significant difference comparing < 4 and ≥ 4 foci of VI in well-differentiated papillary thyroid carcinomas (PTCs), granted that PTCs were included. However, in a cohort of 276 patients with low-grade, encapsulated, follicular, cell-derived, thyroid carcinomas, Xu et al.¹¹ reported that extensive VI (≥ 4 foci) was an independent prognostic predictor of recurrence. Ghossein et al.⁵ also demonstrated that ≥ 4 foci of VI was the most important predictor of recurrence in patients with encapsulated Hürthle cell carcinoma (HCC). Recurrence-free survival rates were significantly higher for patients with < 4 foci compared with ≥ 4 foci (100% vs. 20%, respectively; *p* < 0.001).⁵

Notably, the existing literature on this matter diverges not only on the results but also the inclusion criteria and the classification of tumors. As noted by Yamazaki et al.¹ most of the previous studies included different histological types of thyroid carcinomas to evaluate VI. Furthermore, over the years the nomenclature and criteria to classify tumors also have changed, making it difficult to compare prior

studies. For instance, FTC encompassed HCC tumors until 2017 when HCC was finally classified as an independent entity. Using the extent of VI, FTC was traditionally classified into minimally invasive and widely invasive.^{12–14} In 2014, the Armed Forces Institute of Pathology subdivided minimally invasive tumors into 3 subcategories: tumors with only capsular invasion; tumors with limited VI (< 4 foci); and tumors with extensive vascular VI (> 4 foci). Lastly, in 2017, the World Health Organization Classification of Endocrine Tumors¹⁵ grouped FTC into 3 categories: minimally invasive (capsular invasion only); encapsulated angio-invasive (presence of angioinvasion, regardless of the number of foci); and widely invasive. These modifications underline how much has changed in the classification of these tumors throughout the years.

Another limitation of the aforementioned studies is the very nature of FTCs and HCCs, rare types of thyroid cancers. The cohorts are limited to few patients as are the events of interest, such as death or recurrence, thereby impacting the study power and generalizability. However, Yamazaki et al.¹ presents one of the largest series studied in the literature on this topic including only encapsulated angio-invasive FTC. Another highlight of this study is the comprehensive pathological review that provides detailed information and allows reproducibility.

The study by Yamazaki et al.¹ not only emphasizes the importance of VI on survival outcomes in patients with encapsulated angio-invasive FTC but also brings awareness that patients with 2 or more foci, especially patients older than aged 55 years, might present poorer clinical outcomes. This study will pave the way for new studies that could validate these findings in different target populations, leading to possible impactful changes in the current practice regarding extent of surgery, adjuvant treatments, and follow-up of these patients. Lastly, and maybe most importantly, it reminds us to always question the established cutoffs and truths in order to advance science and patient care.

DECLARATIONS

DISCLOSURES The authors declare no conflicts of interest.

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