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Original contributions

# Prognostic impact of extent of vascular invasion in low-grade encapsulated follicular cell–derived thyroid carcinomas: a clinicopathologic study of 276 cases☆

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**Summary** Continuous controversy surrounds the predictive value of the degree of vascular invasion (VI) in low-grade encapsulated follicular cell–derived thyroid carcinomas (LGEFCs). Some guidelines advocate conservative therapy in LGEFCs with focal VI. There is therefore a need to assess the survival rates of LGEFC patients with various degrees of VI to better stratify patients for subsequent therapy. Furthermore, the prognostic effect of VI within the different histotypes of LGEFCs is not well known. A total of 276 patients with LGEFCs were subjected to a meticulous histopathologic analysis. They were classified as encapsulated papillary thyroid carcinoma, encapsulated follicular carcinoma (EFC), and encapsulated Hurthle cell carcinoma (EHCC). Of the 276 patients, 24 had extensive VI (EVI) (≥4 foci) and 28 displayed focal (<4 foci) VI. EHCC and EFC showed a much higher rate of EVI than encapsulated papillary thyroid carcinoma. Median follow-up was 6 years. All 14 tumors with adverse behavior harbored distant metastases (DMs), of which 9 had DMs at presentation. All 3 patients without EVI who had aggressive carcinomas harbored DMs at presentation. EVI was an independent predictor of poor recurrence-free survival. Excluding cases with DMs at presentation, only patients with EVI had recurrence, and all relapsed cases were EHCC. EVI is an independent predictor of recurrence-free survival in LGEFCs. EHCC with EVI has a particularly high risk of recurrence. When DMs are not found at presentation, patients with focal VI are at a very low risk of recurrence even if not treated with radioactive iodine.


## 1. Introduction

Thyroid carcinoma is the cancer with the largest annual increase in the United States [1], accounting for 62980 newly diagnosed cancers per year [2]. Despite the increasing prevalence of thyroid cancers, a vast majority of them,

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namely, small organ-confined differentiated thyroid carcinomas, are considered low-risk lesions because they follow a highly indolent clinical course and rarely cause death. Several well-recognized organizations, including the American Thyroid Association [3] and the National Comprehensive Cancer Network (NCCN) [4], have published clinical management guidelines advocating for risk stratification using a variety of clinical and pathologic parameters. These societies recommend conservative treatment approaches that do not require completion thyroidectomy or radioactive iodine (RAI) therapy for indolent low-risk thyroid carcinoma.

The extent of vascular invasion (VI) was 1 criterion being adopted by the NCCN for risk assessment [3,4]. According to the NCCN guidelines, *minimal VI*, defined as a few microscopic foci of VI, in an intrathyroidal well-defined follicular or Hurthle cell carcinoma places a patient into a low-risk group in which RAI administration and completion thyroidectomy are not mandatory. On the other hand, patients with extensive (more than a few foci) VI (EVI) will be classified into a higher risk category, in which completion thyroidectomy and postsurgical RAI therapy are highly recommended [4]. Hence, it is crucial for pathologists to reliably evaluate and report the presence and extent of VI in low-grade thyroid carcinoma to direct risk stratification and subsequent clinical treatment decisions. However, the very definition of VI and the prognostic significance of its extent in thyroid carcinomas have been surrounded by controversies since its first description by Graham [5] in 1924. Although some authors argue that the mere existence of VI, even if just 1 focus, entails a substantial risk of distant metastasis (DM) (35% in 1 study) [6,7], others have shown that tumors with *focal VI* (defined as less than 4-5 foci) have a significantly better outcome compared with carcinomas with more foci of VI [8–11].

The confusion is compounded in part by a lack of consistency in applying the diagnostic criteria for VI across studies. Mete and Asa [6], for example, did not consider tumor protrusion into vascular space lined by endothelial cells as a diagnostic criterion for VI, whereas other authors did [8–10]. Additional larger-scale studies are therefore needed to clarify the prognostic value of focal and extensive VI in low-grade encapsulated follicular cell–derived thyroid carcinomas (LGEFCs). In this study, we aimed to identify the prognostic impact of extent of VI in patients with various histological types of LGEFCs with the hope that it will help better guide patient stratification and therapy.

## 2. Material and methods

### 2.1. Histologic definitions and inclusion criteria

The institutional database was searched for all cases with a diagnosis of thyroid carcinomas operated at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1980 and 2004. All cases from MSKCC with adequate material were examined microscopically under the supervision of a head and neck surgical pathologist with special interest in thyroid neoplasia (R. G.), who was blinded to the patients' outcome. Cases were included in the study if the tumor was an encapsulated papillary thyroid carcinoma (EPTC), encapsulated follicular carcinoma (EFC), or encapsulated Hurthle cell carcinoma (EHCC). Encapsulated carcinomas with high-grade features (ie, tumor necrosis or mitotic rate of 5 or more mitotic figures per 10 high-power fields [400×; field size, 0.24 $mm^2$]) were excluded. *Multicentric tumors* defined as containing more than 2 foci of carcinoma were also excluded. The study was approved by the institutional review board of MSKCC.

### 2.2. Pathology review

Tumor size was measured as the maximum diameter of the resected tumor specimen. Mitotic rate was determined by counting 10 high-power fields (400×) with an Olympus microscope (U-DO model, Center Valley, PA, United States) in the areas of greatest concentration of mitotic figures. *Capsular invasion* (CI) was defined as complete penetration of the capsule by tumor, and the number of these foci was recorded. The presence of VI was noted only when such foci were present within or beyond the capsule in accordance with criteria outlined by the Armed Forces Institute of Pathology fascicle [12]. Briefly, only when the invasive focus protruded into the lumen of the vessel in a polypoid manner covered by endothelial cells, or when it was attached to the vessel wall or associated with thrombus formation was considered true VI. Areas of VI that were closely adjacent to one another were counted as separate foci. The foci of CI and VI were subdivided into 2 categories: focal (<4 invasive foci) and extensive (≥4 foci). The presence or absence of extrathyroid tumor extension (ETE) into the perithyroid soft tissue stroma as well as the presence of extrathyroid VI was documented. ETE was subdivided into (1) none, (2) focal (presence of 1-2 microscopic foci of ETE measuring ≤1 mm each), and (3) extensive (presence of >2 microscopic foci of ETE [≤1 mm in size each] or any foci >1 mm in size). Microscopic resection margins were categorized as positive (tumor at the inked margin) or negative (no tumor at the inked margin). Finally, the number and metastatic status of the regional lymph nodes were also recorded.

### 2.3. Clinical review

The patients' medical records were reviewed for age at diagnosis, sex, type of surgery, and RAI therapy. In view of the fact that many cases from the1980s did not have adequate biochemical data, the patient disease status at recurrence or follow-up was based on a combination of clinical and imaging assessments. These evaluations include history taking, physical examination, RAI scanning, cross-sectional imaging and/or positron emission tomography scanning, or histological examination of the recurrent tumor. Thus,