Human Pathology (2015) **46**, 657–664

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Invasion rather than nuclear features correlates with outcome in encapsulated follicular tumors: further evidence for the reclassification of the encapsulated papillary thyroid carcinoma follicular variant☆

Ian Ganly MD, PhD[a], Laura Wang MD[a], R. Michael Tuttle MD[b], Nora Katabi MD[c], Gustavo A. Ceballos MD[d], H. Ruben Harach MD, PhD[e], Ronald Ghossein MD[c,*]

[a]*Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY 10065*
[b]*Department of Medicine, Endocrinology Service, Memorial Sloan-Kettering Cancer Center, New York, NY 10065*
[c]*Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY 10065*
[d]*Department of Surgery, "Dr. A. Oñativia" Hospital, Salta, Argentina*
[e]*Pathology Unit, "Dr. A. Oñativia" Hospital, Salta, Argentina*

Received 3 November 2014; revised 19 December 2014; accepted 21 January 2015

Keywords:
Follicular variant;
Papillary;
Thyroid;
Carcinomas;
Encapsulated

Summary The prognosis of the encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) and its relationship to encapsulated follicular carcinoma (EFC) and follicular adenoma (FA) is subject to controversy. All EFVPTCs, EFCs, and FAs identified at a single institution between 1981 and 2003 were analyzed microscopically. A cohort of FAs from a different hospital was also examined. EFVPTCs were subdivided into noninvasive EFVPTC (NIEFVPTC) and invasive EFVPTC (IEFVPTC) displaying capsular/vascular invasion. There were 83 EFVPTCs (57 noninvasive, 26 invasive), 14 EFCs, and 52 FAs. Similar to FA, over a median follow-up of 9.5 years, none of the NIEFVPTCs manifested lymph node metastasis (LNM) or recurred. Furthermore, with a median follow-up of 10.5 years, none of 39 NIEFVPTCs without radioactive iodine therapy recurred. Four (15%) of 26 IEFVPTCs and none of 14 EFCs harbored distant metastasis ($P = .29$). There was no difference in LNM rate and degree of vascular or capsular invasion between IEFVPTC and EFC ($P > .1$). All 4 IEFVPTCs with adverse behavior presented with distant metastasis and no LNM. Sixteen percent of IEFVPTCs had poor outcome, whereas there was none in the NIEFVPTCs ($P = .007$). In conclusion, NIEFVPTC seems to behave similarly to FA, whereas IEFVPTC can metastasize and spread like EFC. Thus, invasion rather than nuclear features drives outcome in encapsulated follicular tumors. Non-IEFVPTC could be treated in a conservative manner sparing patients unnecessary total thyroidectomy and radioactive iodine therapy. The position of the EFVPTC in the classification of thyroid neoplasia should be reconsidered.

☆ Author disclosure statement: No competing financial interests exist.

* Corresponding author. Department of Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065.
E-mail address: ghosseir@mskc.org (R. Ghossein).

http://dx.doi.org/10.1016/j.humpath.2015.01.010
0046-8177/

1. Introduction

Despite past and recent efforts, there are many problems and controversies in the classification of follicular cell–derived thyroid carcinomas. The most controversial class of carcinomas is the follicular variant of papillary thyroid carcinomas (FVPTC). This tumor is a common subset of papillary thyroid carcinoma (PTC) found in 9% to 22.5% of PTC patients [1–4]. This variant has less than 1% papillary formations and is composed predominantly of follicles lined by cells having the nuclear features of the PTC family of tumors [5]. Thus, FVPTC shares with follicular adenomas (FAs) and follicular thyroid carcinoma (FTC) the presence of follicles.

When FVPTC is nonencapsulated and infiltrates the surrounding thyroid parenchyma, the diagnosis of carcinoma usually poses no problem. For the encapsulated tumor without invasion of surrounding thyroid tissue, the diagnosis of malignancy relies solely on the presence of the nuclear features of PTC (eg, irregular nuclear membrane, clearing, and grooves), which can often be borderline. Therefore, the diagnosis of noninvasive, encapsulated FVPTC (EFVPTC) versus FA is subject to considerable interobserver variability [6,7].

We and others have shown that noninvasive EFVPTCs do not recur even when treated with lobectomy alone [8–10]. Furthermore, many studies have found that the molecular profile of FVPTC as a whole is much closer to FA and FTC than to classical PTC [11–13]. This is especially true for the encapsulated/well-circumscribed FVPTC that harbors a relatively high rate of *RAS* mutations and no *BRAF*V600E mutations [14,15].

Despite all this evidence, the noninvasive EFVPTC is still classified as a variant of PTC. More importantly, most clinicians and all professional societies recommend for this noninvasive variant a therapy similar to the one designed for garden-variety intrathyroidal PTC of similar size [16]. For example, based on the American Thyroid Association guidelines, a 4.1-cm FA is treated with lobectomy alone, whereas a similar sized noninvasive EFVPTC is subjected to total thyroidectomy and radioactive iodine (RAI) remnant ablation [16]. This rationale is based on the fact that PTC nuclear features (the only differential histologic finding between encapsulated noninvasive FVPTC and FA) are thought to be by themselves an indicator of carcinoma in encapsulated follicular-patterned lesions conveying the message of worse outcome than FA.

Our hypothesis is that the presence of PTC nuclei has little effect on outcome in encapsulated follicular tumors. If this is proven, then patients with encapsulated noninvasive FVPTC should have initial therapy similar to FA and spared unnecessary aggressive up-front therapy. In order to explore the prognostic value of PTC nuclei in encapsulated follicular patterned tumors, we compared the survival of a series of FA, FTC, invasive EFVPTC, and noninvasive EFVPTC.

2. Materials and methods

2.1. Histologic definitions and inclusion criteria

The institutional database was searched for all cases with a diagnosis of thyroid carcinomas treated at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1981 and 2003. All cases from MSKCC with adequate material were examined microscopically under the supervision of a head and neck pathologist with special interest in thyroid neoplasia (R. G.). A median (range) of 19 (1-48) slides per specimen were examined microscopically in the MSKCC series. A median (range) of 13 (3-48) slides were reviewed in the noninvasive EFVPTC group.

Tumors were classified as *EFVPTC* if completely surrounded by a fibrous capsule, composed predominantly of follicles with less than 1% papillary formations and containing tumor cells with the nuclear features of PTC (ie, irregular enlarged clear nuclei with grooves, pseudoinclusions, and overlapping; Table 1). The pathologists on the study had agreed before the analysis on a common set of nuclear criteria for the diagnosis of EFVPTC. Tumors with a very thin capsule or well circumscribed as well as those with multifocal nuclear features of PTC were also included under the rubric of EFVPTC. Papillary carcinomas fulfilling the cytoarchitectural criteria for all other variants of PTC including the solid, tall, or columnar cell variant of papillary carcinomas were not classified as FVPTC [17,18]. EFVPTC less than 1 cm and those associated with other foci of PTC were excluded from the analysis.

*FA*s were defined as encapsulated tumors composed of follicles or nests of tumor cells lacking an oncocytic cytoplasm and the nuclear features of PTC. *Encapsulated FTCs* were defined as tumor having the cytoarchitectural features of FA but harboring capsular and/or vascular invasion. Carcinomas with high mitotic rate ($\geq$5 mitosis per 10 high-power fields; ×400) and any neoplasm with tumor necrosis were excluded from the analysis.

Using the above histologic definitions, an additional cohort of FA from Salta, Argentina, were included in the study and reviewed by a pathologist with special interest in thyroid pathology (H. R. H.). Six to 10 sections per tumor were submitted for histology in the Argentinian series.

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, Olympus, Waltham, MA) in the areas of greatest concentrations of mitotic figures. *Capsular invasion* was defined as complete penetration of the capsule by tumor, and the number of these foci was recorded. The presence of vascular invasion was noted only when such foci were present within or beyond the capsule in accordance with