Follicular Variant of Papillary Thyroid Carcinoma

A Long-term Follow-up

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Hypothesis: The clinical behavior of the follicular variant of papillary thyroid carcinoma (FVPTC) is similar to pure papillary thyroid carcinoma (PPTC) and completely different from follicular thyroid carcinoma (FTC).

Design: Retrospective analysis of prospectively documented data.

Setting: Referral center of a university hospital.

Patients: Two hundred thirty-seven consecutive patients with follicular cell–derived thyroid carcinomas were operated on in our institution during a 15-year period, from January 1, 1980, to December 31, 1994. Of the 154 PTC patients, 37 (24%) had FVPTC. The mean follow-up was 128.2 months (10.7 years).

Main Outcome Measures: Demographic features, tumor characteristics, local and distant spread, persistence or recurrence of disease, and carcinoma-related mortality were compared between the groups with FVPTC, PPTC, and non–Hurthle cell FTC (NHFTC).

Results: The frequency of multicentricity was significantly higher in the FVPTC group than in the PPTC group (P=.03) or in the NHFTC group (P=.01) (12 [32%] of 37 patients vs 17 [15%] of 117 patients vs 6 [10%] of 58 patients, respectively). The incidence of cervical lymph node metastases was lower in the FVPTC group than in the PPTC group (P=.30) and higher than in NHFTC group (P=.004) (12 [32%] of 37 patients vs 53 [45%] of 117 patients vs 6 [10%] of 58 patients, respectively). At diagnosis, no patient with FVPTC showed distant metastases, compared with 5 patients (4%) with PPTC (P=.34) and 19 (33%) with NHFTC (P<.001). There was no carcinoma-related death in the FVPTC group. The strikingly poorer prognosis for the NHFTC group was statistically significant (P<.001), whereas the difference in carcinoma-specific survival between the PPTC and the FVPTC groups did show a trend toward better survival in the FVPTC group.

Conclusion: The clinical behavior of the FVPTC group did not differ significantly from that of the PPTC group, whereas compared with the NHFTC group, the FVPTC group showed statistically significant differences for most of the analyzed variables.

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**B**ased on the predominant histological pattern, well-differentiated thyroid carcinomas are classified as papillary thyroid carcinoma (PTC) or follicular thyroid carcinoma (FTC). Many variants of PTC have been described, such as follicular, tall cell, columnar cell, diffuse sclerosing, encapsulated, and oncocytic. The follicular variant of PTC (FVPTC) is the most common variant, and constitutes 9% to 22.5% of cases. It was first described by Crile and Hazard, using the term alveolar variant of papillary carcinoma, and reaffirmed by Lindsay as follicular variant of papillary carcinoma. It is defined as a neoplasm with the nuclear features of PTC and a predominantly follicular growth pattern.

In clinical terms, the behavior of FVPTC is generally regarded as being similar to that of pure PTC (PPTC). Some reports have suggested differences in the frequency of lymph node involvement, distant (especially pulmonary) metastases, and prognosis. Most publications report only a few cases or a relatively short follow-up.

This study compares the clinical behavior, demographic features, tumor characteristics, local and distant spread, persistence and/or recurrence of disease, and carcinoma-specific mortality of FVPTC with those of PPTC and non–Hurthle cell FTC (NHFTC).

**METHODS**

Two hundred fifty-six patients with a well-differentiated thyroid carcinoma, operated on between January 1, 1980, and December 31, 1994, were prospectively documented and retrospectively analyzed. Nineteen patients (7%)
who initially underwent an operation at another hospital were subsequently referred to our center for local recurrence. These patients were not considered for further analysis. Of the 237 patients primarily operated on at our institution, 154 (65%) revealed PTC and 83 (35%) revealed FTC. Of the FTC patients, 25 (30%) had a Hurthle cell carcinoma and were excluded from further analysis because of the well-known worse prognosis of this type of cancer.

The diagnosis of FVPTC was made when the nuclear characteristics of PTC, such as ground glass nuclei, nuclear grooves, overlapping nuclei, and/or nuclear inclusions, were associated with an exclusively (or a nearly exclusively) follicular growth pattern.

Following the standard criteria approved by the World Health Organization,13 the slides of all patients analyzed were reclassified by one of us (K.K.), with the result that 37 (24%) of the 154 patients with PTC were classified as having FVPTC.

Whenever the diagnosis was made intraoperatively, the combination of total thyroidectomy, bilateral central lymph node dissection (extirpation of the lymphatic tissue along the recurrent laryngeal nerve), and extirpation of the central jugular lymph nodes was the preferred form of treatment. Whenever positive lymph nodes were detected in the central jugular compartment on frozen sections, a complete lateral neck dissection was performed, attempting to save the jugular vein. If the diagnosis was only made postoperatively, the decision of whether to perform a completion thyroidectomy depended on the patient’s age, the tumor characteristics, and the patient’s choice.

Postoperative treatment consisted of radioiodine ablation (80-100 mCi [2.96 × 10^12 – 3.70 × 10^12 mBq]) and T4 tumor suppression. Patients were seen in a special outpatient department in which a standardized follow-up protocol was used (namely, 3, 6, and 12 months after surgery; every 6 months until the third year; every year until the 10th year; and every 2 years from the 10th year onward). Clinical investigations and cervical ultrasonography were performed, chest x-ray films were obtained, and thyroglobulin levels were measured. Radioiodine scans were performed at regular intervals during the first 3 years.

The mean ± SD follow-up was 128.2 ± 4.0 months (mean, 10.7 years; median, 120.8 months). Of the 212 patients, 192 (91%) were monitored for a minimum of 5 years or until death and 120 (57%) were monitored for at least 10 years or until death.

Data were analyzed and differences were compared using a 2-tailed Fisher exact test, which states that P values calculated for the differences between FVPTC and PPTC are known as P₁, and those used for comparisons between FVPTC and NHFTC, as P₂. Carcinoma-specific survival was estimated according to the Kaplan-Meier method, and the log-rank test was used to assess differences in survival between the various groups. Differences were considered significant at P < .05.

RESULTS

There were 59 men (28%) and 153 women (72%), leading to a male-to-female ratio of 1:2.6. The percentage of male patients was lower in the FVPTC group than in the PPTC group and in the NHFTC group. The age at diagnosis was significantly lower in the FVPTC group when compared with the NHFTC group, whereas there was no statistically significant difference compared with the PPTC group. Results are summarized in the Table.

TREATMENT

The most frequent surgical procedure was primary total or near total thyroidectomy (Table). A primary total thyroidectomy was performed in 16 patients (43%) with FVPTC, 11 patients underwent a completion thyroidectomy, and 1 underwent a near total thyroidectomy. Nine patients underwent less than a near total thyroidectomy. Two of these patients underwent a unilateral subtotal resection; 4, a unilateral lobectomy; 1, a bilateral subtotal resection; and 2, a unilateral lobectomy and a contralateral subtotal resection (Dunhill procedure). Of the 117 patients with PPTC, 71 (61%) underwent a primary total thyroidectomy. In 28 patients with PPTC, a completion thyroidectomy was performed; 2 patients underwent a near total thyroidectomy, and 16 underwent less than a near total thyroidectomy. These procedures consisted of 1 unilateral subtotal resection, 4 unilateral lobectomies, 5 bilateral resections, and 6 Dunhill procedures. Of the 58 patients with NHFTC, 56 (97%) underwent at least a near total thyroidectomy (primary total thyroidectomy, 26 [45%]; completion thyroidectomy, 29 [50%]; and near total thyroidectomy, 1 [2%]). One patient with a widely invasive NHFTC underwent palliative resection, and another patient, a less than near total thyroidectomy. All patients who underwent at least a near total thyroidectomy underwent postoperative radioiodine ablation.

TUMOR CHARACTERISTICS

Fourteen FVPTC patients and 42 PPTC patients had a pT1 classification, vs only 4 NHFTC patients (Table). On the other hand, the frequency of the pT3 classification was lower in the FVPTC and PPTC patients vs the NHFTC patients. The distribution of the various tumor classifications was significantly different between the FVPTC and the NHFTC group. There was no significant difference compared with the PPTC group.

The incidence of tumor extension beyond the thyroid capsule (pT4 classification) did not differ between the 3 histological groups.

The mean ± SD tumor diameter of the FVPTC group was 17.9 ± 17.6 mm (median, 12 mm), compared with 24.2 ± 21.0 mm in the PPTC group (median, 20 mm) and 39.1 ± 22.7 mm in the NHFTC group (median, 39 mm). The primary lesions of FVPTC were smaller than those of PPTC (not significantly, P₁ = .12) and NHFTC (significantly, P₂ < .001).

Of the FVPTC group, 32% showed multifocal tumor growth, compared with 15% of the PPTC group and 10% of the NHFTC group. Bilateral tumors were found in 7 patients (19%) with FVPTC, 12 (10%) with PPTC, and 3 (5%) with NHFTC; unilateral multifocal tumors were found in 5 patients (14%) with FVPTC, 5 (4%) with
Characteristics of the 3 Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FVPTC Group (n = 37)</th>
<th>PPTC Group (n = 117)</th>
<th>NHFTC Group (n = 58)</th>
<th>P₁</th>
<th>P₂</th>
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<td>III</td>
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Abbreviations: FVPTC, follicular variant of papillary thyroid carcinoma; NHFTC, non–Hurthle cell follicular thyroid carcinoma; NTTH, near TTH; P₁, P value (using the Fisher exact test) comparing the FVPTC group with the PPTC group; P₂, P value (using the Fisher exact test) comparing the FVPTC group with the NHFTC group; PPTC, pure papillary thyroid carcinoma; TH, thyroidectomy; TTH, total TH.

*Data are given as number (percentage) of each group unless otherwise indicated. Percentages may not total 100 because of rounding.
†Percentages are based on those who underwent a completion TH.

Figure 1. A, A unifocal tumor. B, A unilateral multifocal tumor. C, A bilateral multifocal tumor.

PPTC, and 3 (5%) with NHFTC (Figure 1). Unifocal tumors were found in 25 patients (68%) with FVPTC, 100 (85%) with PPTC, and 52 (90%) with NHFTC. Multicentricity was seen significantly more often in the FVPTC group than in the PPTC or the NHFTC group. In the pT1 stages, 4 (29%) of 14 patients with FVPTC and 4 (10%) of 42 patients with PPTC showed multicentricity. This difference did not reach statistical significance (P₁ = .08).

During a completion thyroidectomy, which was performed in 11 FVPTC patients, a residual tumor was found in 5 patients (45%) (Table). In 3 of these patients, the residual tumor was located in the contralateral thyroid lobe, and in 1, a bilateral residual tumor was detected. In 1 patient, an additional residual tumor was seen in the ipsilateral lymph nodes, whereas another patient showed no residual tumor in the thyroid, but rather residual lymph node involvement. Residual tumors, in those undergoing a completion thyroidectomy, were found in 5 patients in the PPTC group and in 1 patient in the NHFTC group. The differences in frequency of residual tumor after completion thyroidectomy are statistically significant comparing the FVPTC group with the NHFTC group (P₂ = .003), whereas no significance was found comparing the FVPTC group with the PPTC group (P₁ = .12) (Table).

NODAL AND DISTANT METASTASES

Twelve patients with FVPTC revealed local extension to cervical lymph nodes, as did 53 with PPTC and 6 with NHFTC (Table). Cervical lymph node involvement was significantly less common in the NHFTC group (P₂ = .004). The frequency of lymph node metastases was also markedly lower in the FVPTC group compared with the PPTC.
group, but this difference was not statistically significant ($P=.30$).

At diagnosis or within the first 3 months after the primary operation, there was no evidence of distant metastases in any FVPTC patients, whereas distant metastases were observed in 5 PPTC patients and in 19 NHFTC patients, revealing a significantly higher incidence in the latter group. The fact that none of the FVPTC patients presented with distant metastases was of no statistical significance when compared with the PPTC patients.

**STAGING**

Tumors were also classified according to the Union Internationale Contre le Cancer–American Joint Committee on Cancer (TNM) staging system. Most patients with FVPTC and PPTC were classified as having a stage I tumor (Table). There was no FVPTC patient and just 1 PPTC patient classified as having a stage IV tumor, whereas 18 NHFTC patients had a stage IV tumor. The distribution of patients in different stages was similar in the FVPTC and the PPTC groups, and was significantly different from that in the NHFTC group.

**PROGNOSIS**

At the conclusion of this study, there was not a single recorded case of mortality arising from carcinoma-related causes in patients with FVPTC. For 5-, 10-, and 15-year follow-up, the respective numbers of patients at risk were 32, 9, and 1. Carcinoma-specific mortality was 5% ($n=6$) in PPTC and 26% ($n=15$) in NHFTC patients. The 5-, 10-, and 15-year carcinoma-specific survival rates were 97.4% ($n=103$), 93.1% ($n=53$), and 90.9% ($n=20$) for PPTC and 83.6% ($n=42$), 72.6% ($n=17$), and 63.5% ($n=4$) for NHFTC, respectively (data in parentheses are patients at risk) (Figure 2). This strikingly poorer prognosis for the NHFTC group was statistically significant ($P<.001$); the difference in carcinoma-specific survival between the PPTC and the FVPTC group did show a trend toward better survival in the FVPTC group, although it had no statistical significance ($P=.18$).

Three patients with FVPTC (8%) developed recurrence of the disease during the follow-up period, which consisted of local recurrence in 1 patient and distant metastases in 2 patients. The patient with the local recurrence presented with a multifocal microcarcinoma (pT1b) and bilateral lymph node metastases (pN1b) during the primary operation. She developed recurrence 67 months after initial treatment and died of a mesenteric artery embolism 3 months after the diagnosis of the recurrence. The second patient with recurrence of the disease developed distant metastases to the lungs and bones 29 months after the first surgical intervention. The initial tumor classification was pT3a pN0. The treatment of the recurrence consisted of radioiodine ablation. The patient is still alive, with persisting metastases 86 months after primary treatment and 57 months after the diagnosis of disease recurrence. The third patient with recurrence developed distant metastases to the lungs 32 months after the initial operation, during which it was observed that the tumor was multifocal and had invaded the adjacent tissue (pT4b classification) and extended to ipsilateral and contralateral lymph nodes (pT1b classification). The recurrence could, however, be successfully treated with radioiodine therapy. The patient is still alive, without any evidence of the disease (thyroglobulin levels are not detectable, and the findings from the chest x-ray film are normal) 104 months following the initial operation and 72 months after the diagnosis of distant metastases.

Three patients with PPTC (3%) and 18 with NHFTC (31%) showed signs of persistent disease (persistent metastases in 3 PPTC patients and in 16 NHFTC patients and a persistent local tumor in 2 NHFTC patients). Twelve PPTC patients (10%) and 5 NHFTC patients (9%) developed recurrence of the disease during the follow-up period. Six of the 12 PPTC patients and 4 of the 5 NHFTC patients with recurrence of disease died of carcinoma-related causes.

**COMMENT**

The follicular variant is the most common histological subtype of PTC. Nevertheless, most publications only report a few cases or a relatively short follow-up period. Our study presents 37 patients with FVPTC (37 of 154 patients [24%]) and a follow-up of more than 9 years—to our knowledge, a period not previously reached. The percentage of FVPTC reported in the literature is as high as 9% to 13%. This proportion was much higher in our patient cohort, reaching 24%, although a recently published article by Ortiz Sebastian et al reported an incidence of FVPTC that is close to ours (22.5%).

The preponderance of differentiated thyroid carcinoma in female patients was obvious, but it was much higher in the FVPTC group (31/37 [84%]) than in the PPTC group (85/117 [73%]) and the NHFTC group (37/58 [64%]). In addition, FVPTC and PPTC patients were significantly younger than NHFTC patients. This finding is in contrast to that of Tielen et al.

The primary lesions of FVPTC tend to be smaller than those of PPTC and NHFTC; the median tumor diameter of FVPTC was 12 mm, 8 mm less than that of PPTC and 27 mm less than that of NHFTC. This is in accord with other findings.
An interesting feature was the significantly higher proportion of multifocal tumor growth in FVPTC compared with PPTC or NHFTC. In a similar study by Tielens et al., this higher frequency of multicentricity in FVPTC patients could not be observed. Nevertheless, analyzing pT1 stages only, this difference did not reach statistical significance, probably because of the few patients in the subgroups (statistical type II error). In 5 of 11 patients with FVPTC undergoing a completion thyroidectomy, a residual tumor in the ipsilateral and/or contralateral thyroid lobe and/or residual involvement of cervical lymph nodes could be detected. There was no evidence of this high proportion of residual tumor (45%) in PPTC patients, in whom it was histologically detected in only 18% of completion thyroidectomies. By basing ourselves on Tielens et al., we observed a less frequent involvement of cervical lymph nodes in the FVPTC than in the PPTC group, a finding that is in contrast to other reports. On the other hand, at diagnosis, we did not find any distant metastases in patients with FVPTC. Nevertheless, 2 patients developed lung metastases during follow-up. According to our findings, distant spread of the disease does not occur more frequently in FVPTC than in PPTC patients, as proposed in previous publications. In this respect, it is worth noting that the diffuse follicular variant, as described by Sobrinho-Simões et al. and Mizukami et al., has to be a totally different entity because of its highly aggressive and invasive growth pattern, its early distant spread, and its strikingly poor prognosis.

The frequency of local and/or distant recurrence was similar in FVPTC, PPTC, and NHFTC patients. As described by others, the carcinosmaspecific survival of FVPTC patients was similar to that of PPTC patients, but was much better than that of NHFTC patients. Since, in our study, no patient with FVPTC died of cancer, a trend toward better survival was evident if compared with those with PPTC, although this factor did not have statistical significance. This could, however, have been because of the low number of patients. The diffuse follicular variant, as described by Sobrinho-Simões et al. and Mizukami et al., is characterized by a strikingly poor prognosis and seems to be a totally different entity; therefore, it cannot be compared with the commonly described FVPTC.

In conclusion, the clinical behavior of the FVPTC and the PPTC groups did not differ significantly, whereas the NHFTC group showed statistically significant differences for most analyzed variables.

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