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Diagnosis of Follicular Variant of Papillary Thyroid Cancer: Is Frozen Section a Guide for the Surgeon?

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Abstract

Introduction: Fine needle aspiration cytology (FNAC) is a useful tool in the diagnosis of papillary thyroid cancer (PTC). However, it is difficult to diagnose the follicular variant of PTC (FVPTC) preoperatively via FNAC or frozen section (FS) examination. In this retrospective study, we measured the sensitivities of, and extent of agreement between, these two diagnostic tools in patients ultimately diagnosed with FVPTC.

Materials and Methods: Between November 2013 and December 2014, a total of 100 patients were diagnosed with FVPTC and operated upon in the Thyroid Clinic of Acibadem Hospital. All patients were operated upon by the same surgeon, and all FNAC and FS data were evaluated by the same cytopathologist and histopathologist, respectively. The sensitivities of FNAC and FS were determined, and the Kappa test was used to calculate the extent of agreement between the two tools.

Results: A total of 78 patients underwent bilateral total thyroidectomy and 22 completion thyroidectomy following diagnostic lobectomy. The FNAC results were benign (25%), atypical cells/follicular lesions of unknown significance (AFCUS) (14%), follicular neoplasia (31%), suspicious for PTC (18%), and PTC (12%). The FS results were benign (27%), follicular neoplasia (46%), suspicious for PTC (13%), and PTC (14%). Surgery was scheduled for patients with nodules larger than 3 cm that were benign on FNAC, those who had nodules of any size and were repeatedly of FNAC AFCUS status, and those who had nodules of any size and FNAC indications of follicular neoplasia, suspicion of PTC, or PTC. The sensitivity of FNAC used to diagnose FVPTC was 32.4% and that of FS 34.1%. Moderate agreement was evident between the two diagnostic tools, with a Kappa value of 0.423 (95% confidence interval, 0.078-0.747). Patients for whom the FS data raised a suspicion of PTC or indicated the presence of PTC underwent bilateral total thyroidectomy as the initial surgery. The initial surgical strategy was changed in 17% of patients after FS analysis indicated a suspicion of PTC or PTC.

Conclusion: Although the utility of FS data is debatable in patients who undergo surgery for treatment of thyroid nodules, we found that the FS results may change the initial surgical strategy and reduce the need for completion thyroidectomy.

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Introduction

Thyroid carcinoma is the most common endocrine malignancy, and papillary thyroid carcinoma (PTC) constitutes up to 90% of cases [1]. The recentrise in disease prevalence is probably attributed to the increased resolution of ultrasound probes, which now detect smaller lesions, including microcarcinomas [2] Many PTC variants have been defined; the classical and follicular variants are the most common [3]. Follicular variant papillary thyroid carcinoma (FVPTC) is a well-defined histopathological form of PTC accounting for 24-33% of all PTCs. FVPTC exhibits the nuclear features of classical variant papillary carcinoma (CVPTC) and a follicular growth pattern. The follicular arrangement of tumor cells can cause CVPTC to be misdiagnosed as other follicular lesions, including adenomatous nodules, follicular adenoma, and follicular carcinoma [4] Sonographically, the tumor margins are well defined, the tumor is not round, and microcalcification is absent. These features are typical of benign tumors, causing malignant lesions to be overlooked [5] The clinical behavior of FVPTC is intermediate between that of papillary and follicular neoplasia, but the incidences of lymph node metastasis and extra thyroidal extension are lower, although

Table 1: Bethesda classification system.

I	Non-diagnostic/unsatisfactory
II	Benign
III	Atypical cells/follicular lesion of unknown significance
IV	Follicular neoplasm
V	Suspicious for malignancy
VI	Malignant

Table 2: Pre- and per-operative pathological diagnosis of patients with follicular variant of PTC.

FNAC (n: 65)	Frozen section biopsy (n : 65)	Final histopathological result (n: 65)
Benign (n: 16)	Benign (n: 8) Follicular lesion (n: 7) Suspicious for PTC (n: 1)	Follicular variant of PTC
Atypia/FLUS (n: 9)	Benign (n: 2) Follicular lesion (n: 6) Suspicious for PTC (n: 1)	Follicular variant of PTC
Follicular neoplasm or suspicious for follicular neoplasm (n: 20)	Benign (n: 4) Follicular lesion (n: 12) Suspicious for PTC (n: 2) PTC (n: 2)	Follicular variant of PTC
Suspicious for PTC (n: 12)	Follicular lesion (n: 3) Suspicious for PTC (n: 4) PTC (n: 5)	Follicular variant of PTC
PTC (n: 8)	Follicular lesion (n: 2) Suspicious for PTC (n: 1) PTC (n: 5)	Follicular variant of PTC

distant metastases have been reported. The disease is less aggressive and associated with outcomes similar to or better than those of CVPTC. The biological behavior of non-invasive FVPTC resembles that of follicular adenoma [6].

Ultrasonography (USG)-guided fine needle aspiration cytology (FNAC) is accepted to be the gold standard for diagnosis of thyroid nodules, with a sensitivity of 83-98% [7]. The thyroid is the most frequently biopsied organ; USG-guided FNAC affords excellent diagnostic accuracy [8]. FNAC candidates include male patients with thyroid nodules greater than 1 cm in diameter, patients with family histories of thyroid malignancy, patients who have received neck external beam therapy, patients with evidence of hard and fixed nodules on palpation, and patients with non-palpable nodules but malignant sonographic findings [9]. Because FVPTC does not adequately exhibit the cytological features of PTC, it is detected less sensitively by FNAC (25-42%), and false-negatives have been reported. In addition, the patchy distribution of FVPTC within a nodule may lead to FNAC false-negativity if the nodule is sampled inaccurately [10]. A core needle biopsy is not routinely recommended, because the gland is highly vascular.

The sensitivity of FS analysis in detecting FVPTC ranges from 29to 73% and is believed to be lower than that for the nonfollicular variant. Some studies have suggested that both FNAC and FS analysis afford high-level diagnostic sensitivities and specificities; others found that FS examination was better than was FNAC for distinguishing between benign and malign thyroid nodules [11].

These difficulties in FVPTC diagnosis pose treatment problems. The preferred treatment for PTCs larger than 1 cm in diameter is bilateral total thyroidectomy [12]. If an FVPTC is encapsulated, the tumor behavior is believed to be similar to that of a follicular neoplasia. The diffuse form of FVPTC metastasizes to regional lymph nodes, as does CVPTC. This may explain the lower incidence of lymph no demetastasis and the relatively higher incidences of lung and bone metastases of FVPTC compared with CVPTC [13]. Misdiagnosis of FVPTC as a benign follicular lesion will mostly likely lead to plans for a lobectomy, which will in turn trigger the need for completion thyroidectomy, increasing patient morbidity and cost [14].

The aim of the present study was to assess the efficacy of FNAC and FS analysis in the diagnosis of FVPTC.

Materials and Methods

This retrospective study was approved by the institutional review board of Acibadem Maslak Hospital. We retrospectively reviewed 100 consecutive cases of cytologically confirmed FVPTC who underwent operations between November 2013 and December 2014. FNAC of all suspect nodules was performed under USG guidance. On-site cytopathological examinations were performed to ensure appropriate lesion sampling. All patients were operated upon by the same surgeon, and all FNAC and FS specimens were examined by the same cytopathologist and histopathologist, respectively.

Statistical analysis

The sensitivities of FNAC and FS were determined, and the Kappa test was used to determine the extent of agreement between the two tools.

Results

A total of 78 female and 22 male patients were included. The median patient age was 42 years (range, 18-78years). The median age of the female patients was 40.5 years and that of the male patients50 years. A total of 78 patients underwent bilateral total thyroidectomy and 22 completion thyroidectomy following diagnostic lobectomy. The mean tumor diameter was 15.03 mm. The tumors were located in the right lobe in 39 patients, the left lobe in 37, and bilateral tumors were seen in 23. One tumor was located in the isthmus. The tumors of 37 patients were multicentric. Sixty-five patients underwent FNAC; the results (using the Bethesda classification (Table 1) were as follows: 16 patients of class 2 (25%), 9 of class 3(14%), 20 of class 4 (31%), 12 of class 5 (18%), and 8of class 6 (12%). FS examination showed

that 27 patients had benign nodules, and14 had malignant nodules. Thirteen patients were found to be suspicious for malignancy, and 46nodules were reported to be follicular neoplasias (Table 2). Tumor capsules were evident in 52 specimens, and 23 exhibited tumor capsule invasion.

Surgery was performed on patients with nodules larger than 3 cm that were benign on FNAC, patients who had nodules of any size and were repeatedly of FNAC AFCUS status, and patients who had nodules of any size and FNAC indications of follicular neoplasia, suspicion of PTC, or PTC. The sensitivity of FNAC for FVPTC detection was 32.4% and that of FS analysis 34.1%. Moderate agreement was evident between the two tools, with a Kappa value of 0.423 (95% CI 0.078-0.747). Patients for whom the FS data raised a suspicion of PTC or identified PTC underwent bilateral total thyroidectomy as the initial surgery. The initial surgical strategy was changed in 17% of patients for whom FS examination raised a suspicion of PTC or identified PTC. We performed completion thyroidectomy in all T2 patients, because we routinely recommend radioactive iodine ablation to all such patients.

No patient underwent central neck dissection, but three had metastatic lymph nodes. Fifteen patients required immunohistochemical evaluation of their tumor tissues to yield the final pathological diagnoses. After surgery, radioactive iodine was given to 38 patients. Only one patient suffered bone metastasis.

Discussion

The prognosis of PTC is favorable [15]. Although diffuse FVPTC can trigger distant metastases, non-invasive FVPTC has a very low metastatic potential and recurrence rate; the 10-year survival rate is>90% [16]. Treatment is based on the histopathological findings. FNAC and FS examination are both routinely used to manage thyroid nodules [17]. PTC should be diagnosed either preoperatively or perioperatively. A lobectomy (only) may be necessary if the nodule is benign, whereas PTC may require bilateral lobectomy. A misdiagnosis may lead to completion thyroidectomy, increasing the cost and patient morbidity [14].

The sensitivity of FNAC is high when used to detect PTC, but diagnosis of the follicular variant may pose difficulties to the cytopathologist. The nuclear features are not as prominent as those of CVPTC, and the tumor has a patchy distribution within the nodule, which causes inappropriately obtained samples to yield false-negative findings. FVPTC can be confused with other follicular lesions including follicular adenoma [18]. A core biopsy is not routinely recommended, because the gland is highly vascular.

FS analysis may aid in determining the correct diagnosis of misdiagnosed FVPTC during surgery. Although the use of FS data remains controversial, the technique may be of preoperative utility in patients for whom the FNAC findings raise suspicions. In our present study, 3 of 29 patients (10%) who had nodules preoperatively diagnosed as follicular lesions/AFCUS/follicular neoplasms were found to be suspicious for PTC intraoperatively. Two of these 29 patients (7%) were diagnosed with PTC upon examination of the FS data. In addition, FS analysis resulted in changing the diagnosis from PTC to a follicular lesion in 5 of 20 patients (25%) who had preoperative FNAC diagnoses of suspicious for PTC or definite PTC. The sensitivities of FNAC and FS analysis for the diagnosis of FVPTC were 32.4% and 34.1%, respectively. FS data caused us to change our operative technique to bilateral total thyroidectomy in 17% of all patients, thus eliminating the need for later completion surgery. FS evaluation seems to be logical when the risk of complications, costs, and stress associated with completion thyroidectomy are considered. We recommend that FS examinations be continued until more sensitive molecular techniques supplant FNAC.

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