Risk of Malignancy in Patients With Follicular Neoplasm

Predictive Value of Clinical and Ultrasonographic Features

Nese Ersoz Gulcelik, MD; Mehmet Ali Gulcelik, MD; Bekir Kuru, MD

Objective: To identify clinical and ultrasonographic features that may help in predicting malignant tumors in patients with a diagnosis of follicular neoplasm on findings from fine-needle aspiration cytology (FNAC) because FNAC diagnosis of follicular neoplasm does not differentiate a benign tumor from a malignant tumor.

Design: Prospective study of 98 patients having a diagnosis of follicular neoplasm on FNAC.

Setting: Tertiary cancer referral center.

Patients: Ninety-eight patients with thyroid nodules diagnosed by FNAC as being a follicular neoplasm.

Interventions: Ultrasonography was performed in each patient, and microcalcifications, echo structure, and echogenicity of the nodules were assessed. All patients underwent surgery.

Main Outcome Measures: Sensitivity, specificity, positive predictive value, and negative predictive value of ultrasonographic features.

Results: Thyroid cancer was diagnosed in 26 patients (27%). Ultrasonographic features (eg, a solid echo structure, microcalcifications, and a hypoechoic pattern) were predictive for malignant neoplasms. The variable associated with the highest sensitivity was the presence of a solid nodule (88.5%), and the variable associated with the highest specificity was the presence of microcalcifications (94.4%). The combination of the 3 ultrasonographic features (solid echo, hypoechoic pattern, and microcalcifications) resulted in a sensitivity of 95.0% and a specificity of 98.6%. Older age, male sex, solitary nodule, and larger nodule size were not predictive for malignant neoplasms in patients with follicular neoplasm cytologic findings.

Conclusions: We confirmed that the best compromise between the risk of missing carcinomas and the need for reducing unnecessary surgical procedures would consist of submitting to surgery those nodules presenting a solid echo structure, microcalcifications, or a hypoechoic pattern. Low-risk patients may be observed closely if they are willing to accept a small risk of cancer and if they appreciate the need for a close clinical follow-up.


The first step for the treatment of thyroid nodules is fine-needle aspiration biopsy (FNAB), which is a reliable and simple diagnostic procedure. Clinicians decide whether to perform surgery or to follow thyroid nodules according to the findings from fine-needle aspiration cytology (FNAC). The routine application of this method reduced unnecessary surgery for patients with thyroid nodules. However, FNAC is of limited value in the presence of indeterminate cytologic findings. To avoid misdiagnosing thyroid carcinoma, surgery is recommended for these patients. The risk of malignancy in indeterminate nodules is 12% to 30%. This means that up to 70% of these patients are undergoing surgery for a benign disease. This potentially places a large economic burden on the health care system. Besides the increased costs, these patients face the risk of complications. Of note, frozen section is essentially worthless for most of these patients.

To predict malignancy in indeterminate nodules, ultrasonographic and pathologic features were investigated previously. Age, male sex, nodule size, solitary nodule, solid nodule, a hypoechoic pattern, and the presence of microcalcifications were the main risk factors that were analyzed previously for the value in defining the patients at risk for malignant neoplasms. However, there is no consensus on the value of these parameters in predicting malignancy in thyroid nodules diagnosed as follicular neo-
plasm. We evaluated clinical and ultrasonographic features to predict malignant neoplasms in patients identified as having follicular neoplasm by FNAC.

**METHODS**

From January 1, 2002, through November 1, 2007, 1173 patients were referred to our outpatient department because of palpable nodular thyroid disease. Beginning January 1, 2002, all patients who were being treated for thyroid disease were recruited in a prospective manner according to a protocol that documented the clinical and ultrasonographic features of the patients with thyroid nodules. All patients underwent FNAB, which was performed on a solitary nodule or a dominant nodule in a multinodular goiter.

Ninety eight of these patients—who were the subjects of the present study—were diagnosed as having follicular neoplasm on FNAC findings. Patients with previous thyroidectomy and with thyrotoxicosis were not eligible. All patients were queried for symptoms and had a physical examination. According to protocol, we documented the clinical and ultrasonographic features of these patients. All patients underwent surgery. Free triiodothyronine, free tetraiodothyronine, and thyrotropin values were assessed using Cobas Immunassay Systems (Roche Diagnostics GmbH, Mannheim, Germany).

Ultrasonography of the thyroid was performed using high-frequency 7.5- to 15-MHz linear transducers (model EUB-6500; Hitachi Medical Systems Holding AG, Zug, Switzerland). Ultrasonographic findings were assessed for nodular status (solitary or multinodular), nodule size, presence of microcalcifications, structure (cystic, solid, or mixed), and echogenicity (isoechoic, hypoechoic, hyperechoic, or mixed).

Fine-needle aspiration biopsies were performed using a 20- to 22-gauge needle attached to a 10- or 20-mL syringe and each nodule was aspirated at least 2 times; usually 4 smears were used. Diagnostic cytopathological examination of FNAB specimens was performed and reported by 2 experienced cytopathologists; the specimen was labeled as diagnostic if it contained a minimum of 6 groupings of thyroid epithelial cells, consisting of at least 10 cells per group. A cytological diagnosis of follicular neoplasm was defined by abundant follicular cells arranged in microfollicular aggregates in a background of scanty or absent colloid. A total thyroidectomy or lobectomy was performed in all patients and findings from histologic examination of the nodules showed them to be the same as the index nodule, which was confirmed by a clinician (N.E.G.), a surgeon (M.A.G. or B.K.), and a pathologist. Informed consent was obtained from all patients according to the Declaration of Helsinki. The institutional review board of our hospital approved the study design.

A comparison of characteristics of patients and nodules were made by $\chi^2$ or Fisher exact test. Clinical indices such as age and nodule size were compared with the Independent Samples $t$ test. Statistical analyses were performed using SPSS statistical software (version 10.05; SPSS Inc, Chicago, Illinois). $P<.05$ was considered significant.

**RESULTS**

A total of 98 consecutive patients with follicular neoplasm on FNAC (16 men and 82 women) were included in the study. Their mean (SD) age was 46.7 (13.0) years. The mean nodule size was 26.6 (12.2) mm. Total or near-total thyroidectomy was performed in 78 patients (80%) and thyroid lobectomy was performed in 20 patients (20%). Thyroid cancer was diagnosed in 26 patients (27%). Papillary cancer was the most common cytologic findings (20 patients [77%]) and 6 patients (23%) had a diagnosis of follicular cancer. Of the 20 patients with papillary cancer, 6 (30%) had a follicular variant of papillary cancer. The benign histologic diagnoses were follicular adenoma in 22 cases (22%), Hashimoto thyroiditis in 12 cases (12%), and nodular goiter in 38 (38%).

The mean nodule size was slightly larger in malignant nodules than in benign nodules, but the difference did not reach statistical significance (29.3 [12.6] mm vs 25.6 [11.7] mm, respectively; $P=.76$). The mean age was similar in patients with malignant disease vs those with benign disease (46.3 [12.8] years vs 48.2 [13.8] years, respectively; $P=.98$). In patients older than 45 years, the risk of malignant neoplasms did not increase (Table 1). Male sex was not predictive for thyroid cancer. The percentage of atypical cells was similar in malignant (26%) and benign nodules (23%). The presence of a solitary nodule was not predictive for malignancy ($P=.57$). Solid echo structure, presence of microcalcifications, and hypoechoic nodules on ultrasonography were predictive for malignancy (Table 1). Sensitivity, specificity, positive predictive values, and negative predictive values of ultrasonographic features are given in Table 2. The variable associated with the highest sensitivity was the presence of a solid nodule (88.5%), and that, associated with the highest specificity, was the presence of microcalcifications (94.4%). When we combined the 3 ultrasono-
graphic features (a solid echo, a hypoechoic pattern, and microcalcifications) sensitivity was 95.0%, and specificity was 98.6%.

**COMMENT**

Fine-needle aspiration, although very sensitive for the discrimination of malignant and benign nodules, has limited accuracy with follicular lesions. The cytological diagnosis of follicular neoplasm has continued to be a frustrating entity for pathologists, surgeons, and patients. The recommended treatment for follicular neoplasm is surgery, and up to 70% of these patients undergo surgery for benign disease. In this case, besides the increased costs, the patients are prone to increased risk of surgical morbidity. Moreover, in the case of a malignant lesion, the need for a completion thyroidectomy increases the risk of complications and doubles the cost.

We prospectively studied 98 patients with thyroid nodules initially read as follicular neoplasm by FNAC; all patients underwent the procedure. In 26 cases (27%), nodules were diagnosed as being malignant, which is consistent with other studies. Papillary carcinoma was the most common cytologic finding (20 of 26 patients [77%], of whom 6 [23%] were diagnosed as having the follicular variant of papillary carcinoma). This finding is in line with other studies.

Several studies investigated clinical, ultrasonographic, and cytologic criteria to predict malignancy in follicular lesions. Many of these studies have suggested that the cases diagnosed as follicular neoplasm with a lower risk of malignancy can be managed by close follow-up and repeated FNAB. However, the topic of risk factors predicting malignancy in thyroid nodules with a diagnosis of follicular neoplasm is still controversial. In the current study, our findings extend previous reports that noted the increased, especially when the presence of solid nodule, microcalcifications, and hypoechogenicity was combined (98.6% and 95.0%, respectively).

The presence of atypical cells in follicular lesions and its relationship with malignant lesions had been investigated previously. Some investigators found that the presence of atypia is predictive for malignancy in nodules diagnosed as follicular neoplasm. However, some authors could not find an association between atypia and malignancy in follicular neoplasms. In the current study, we could not find an association between the presence of atypia and malignancy.

In thyroid nodules with a diagnosis of follicular neoplasm on FNAC, the assessment of risk can be based on an integration of multiple clinical features and ultrasonographic findings. We confirmed that the best compromise between the risk of missing carcinomas and the need for reducing unnecessary surgical procedures would consist of surgically treating those nodules presenting a solid echo structure, microcalcifications, or hypoechoic pattern. Given the relatively indolent behavior of differentiated thyroid cancers, the decision for close follow-up and repeated FNAB may be useful in patients with a low-risk of having malignant neoplasms. Nevertheless, it will be a strict decision to leave nodules with a probability of cancer alone. In this case, there may be psychological problems for patients who know that they have a potentially malignant tumor; the malignant potential of follicular adenomas is still unclear. Low-risk patients, especially those reluctant to undergo surgery or those with clinically significant underlying medical conditions may be observed closely if the patients are willing to accept a small risk of cancer and if they appreciate the need for careful follow-up, including repeated biopsies.

**Table 2. Sensitivity, Specificity, and Predictive Value for Malignant Neoplasms in Patients With Thyroid Nodules With a Diagnosis of Follicular Neoplasm**

<table>
<thead>
<tr>
<th>Ultrasonographic Findings</th>
<th>No.</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid nodule</td>
<td>56</td>
<td>88.5</td>
<td>54.2</td>
<td>41.4</td>
<td>92.9</td>
</tr>
<tr>
<td>Hypoechoic pattern</td>
<td>40</td>
<td>84.6</td>
<td>61.5</td>
<td>55.0</td>
<td>75.0</td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>21</td>
<td>65.4</td>
<td>94.4</td>
<td>81.0</td>
<td>87.2</td>
</tr>
<tr>
<td>Solid and hypoechoic nodule with microcalcification</td>
<td>21</td>
<td>73.1</td>
<td>98.6</td>
<td>95.0</td>
<td>91.0</td>
</tr>
</tbody>
</table>

Abbreviations: NPV, Negative predictive value; PPV, positive predictive value.

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Correspondence: Mehmet Ali Gulcelik, MD, 41. cadde 12/34, Cukurambar, Ankara, Turkey (mgulcelik@yahoo.com).

Author Contributions: All authors had full access to all...
the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: N. E. Gulcelik and M. A. Gulcelik. Acquisition of data: N. E. Gulcelik. Analysis and interpretation of data: N. E. Gulcelik and Kuru. Drafting of the manuscript: N. E. Gulcelik and M. A. Gulcelik. Critical revision of the manuscript for important intellectual content: N. E. Gulcelik and Kuru. Statistical analysis: N. E. Gulcelik and Kuru. Administrative, technical, and material support: N. E. Gulcelik and M. A. Gulcelik.

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REFERENCES