INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Evaluation of Thyroid Nodules in Turkish Population

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Abstract

Objective To determine the characteristics of thyroid nodules by using fine needle aspiration (FNA) biopsy and ultrasonography.

Patients and Methods FNAs of 1,004 patients with thyroid nodules between 2000 and 2007 were evaluated retrospectively. The surgical records of 101 of the patients were available and reviewed. The Odds ratios for nodule characteristics were calculated individually.

Results The sensitivity of FNA was 66.7% and the specifity was 95.2%. Positive predictive value was 72.7% and negative predictive value was 93.7%. Our diagnostic accuracy was 90.5%. Solitary nodules, irregular margins and microcalcifications were associated with increased risk of malignancy with Odds ratios 3.61 (95% CI: 1.25-10.42; p= 0,017); 5.44 (95% CI: 1.76-16.78; p= 0,003) and 39.29 (95% CI 8.32-185.47; p< 0.001) respectively. Macrocalcification, age, gender and thyroid status were not associated with increased risk of malignancy.

Conclusion Our data suggest that FNA is a reliable, reproducible and valid method to evaluate thyroid nodules and ultrasonographic features, especially microcalcification is a very important predictor of malignancy.

Key words: thyroid nodules, fine needle aspiration biopsy, ultrasonography, microcalcification

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Introduction

The prevalence of thyroid nodules is estimated as 4-7% in general population on the basis of palpation (1). Since ultrasonography was introduced for clinical application, the prevalence of thyroid nodules has increased to 20-76% and approached 50% based on data reported in an autopsy series (2-6). In Turkey, the prevalence of thyroid nodules was reported as 33% in a study which included 1,831 subjects screened for thyroid nodules (7). The clinical importance of thyroid nodules is to define a malignant lesion, which accounts for 5% of all thyroid nodules (8). Fine needle aspiration (FNA) is the method of choice for cytologic evaluation of a thyroid nodule. FNA is reported to be a good screening method for detecting malignant lesions (9). Due to the high prevalence of thyroid nodules, a cost-effective and reliable strategy for the management of nodular thyroid disease is necessary. It is generally accepted that ultrasonographic features, e. g. irregular shape, spiculated or ill-defined margin status, marked hypoechogenicity, presence of micro- or macrocalcification and shape (taller in height than its width) are ominious signs of malignancy. The current guidelines have broadened the role of USG in the evaluation of nodules (10). In the present study, we correlated the findings of ultrasonography, scintigraphy, FNA and thyroidectomy in patients with nodular thyroid disease.

Patients and Methods

Patients:

We retrospectively evaluated 1,004 patients with thyroid nodules, admitted to the Outpatient Clinic of Istanbul University, Cerrahpasa Medical Faculty, betweeen 2000 and 2007.

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Since our institution is a referral center, the patients came from every region of Turkey. We did not measure the urinary iodine excretion of the patients, and therefore we could not determine whether our study group was iodine deficient. Since Turkey is an iodine deficient region, salt iodination has been mandatory since 1999 (11). Currently iodine deficiency is still present as mild or moderate after salt iodination (12).

Patients with thyroid stimulating hormone (TSH) levels higher than 3.5 mIU/ml were defined as hypothyroid, and lower than 0.3 uIU/ml as hyperthyroid, TSH levels between 0.3- 3.5 uIU/ml as euthyroid (13). The patients with palpable thyroid glands were evaluated using ultrasonography in the first visit. 298 patients had solitary nodules and 706 had multiple nodules. If the patient was euthyroid or hypothyroid, the largest nodule of patients with multiple nodules was defined as the dominant nodule and biopsied;as one nodule from each patient was examined, a total of 1,004 nodules was examined. Also, a nodule was biopsied, if it had at least one of the following features:irregular shape, spiculated or ill-defined margin status, marked hypoechogenicity, and presence of micro- or macrocalcification. In the follow-up of patients with known thyroid nodules, these nodules were also biopsied if the nodule had grown more than 2 milimeters in at least two dimensions or if any feature of malignancy was detected on ultrasonography (14). Medical history and findings of physical examination were obtained from medical records of the patients. Age, gender, thyroid status, number and diameters of nodules, ultrasonographic and cytologic features of the nodules were recorded. Also, surgical records of 101 patients, who underwent thyroidectomy were reviewed.

Methods:

Ultrasonography, ^{99m}TC scintigraphy and FNA findings were used to determine the features of nodules. Irregular shape, spiculated or ill-defined margin status, marked hypoechogenicity, and presence of micro- or macrocalcification were regarded as USG features of malignancy (10). In ^{99m}TC scintigraphy, the nodules were classified as hyperactive, hypoactive and normoactive. FNA material was spread on glass and air-dried, then stained using May Grünwald-Giemsa. In FNA, malignant nodules were defined as cytologic findings unequivocal for malignancy. Cytologic findings consistent with papillary, follicular, medullary and anaplastic thyroid cancers were classified in this group. Suspicious malignant nodules were defined as cytologic findings showing some of the features of malignancy, e.g., intranuclear inclusions or nuclear grooves, but insufficient for a definitive diagnosis of malignacy. This group consisted of aspirates including dyskaryotic thyrocytes and consistent with Hurthle cell neoplasm. Benign nodules were defined as nonneoplastic cytologic findings, including colloidal nodules, lymphocytic thyroiditis, benign cysts and granulomatous thyroiditis. Aspirates with less than six clusters of well preserved follicular epithelial cells on two slides were defined as unsatisfactory (15). The pathologic examination of thyroidectomy material from the patients, who underwent surgery, was recorded and classified as benign and malignant.

Statistical analysis was performed using Student's t test, Chi-square test, logistic regression test; $p<0,05$ was defined as significant.

Results

The mean age was 48.41±13,36 SD years. Of 1,004 patients, 856 (85.3%) were females and 148 (14.7%) were males. A total of 298 (29.6%) patients had solitary nodules and 706 (70.3%) had multiple nodules. 97 of the patients were hypothyroid, 129 were hyperthyroid, and 778 were euthyroid. 101patients (10.1%)underwent thyroidectomy, and their records were available. Of 101 patients who underwent surgery, 63 FNA materials (62.3%) were benign, 11 (10.8%) were malignant, 23 (22.7%) were suspicious for malignancy and 4 (3.9%) were unsatisfactory. On pathologic examination of thyroidectomy material, 83 (82.2%) of these patients had benign features and 18 (17,8%) had thyroid cancer. Of 18 patients with thyroid cancer 15 had papillary, 1 had medullary and 2 had follicular cancer.

In ultrasonography, 97 of 706 patients with multiple nodules had two nodules and 609 had three or more than three nodules.

Thyroid scintigraphy using Tc99 m was performed on 575 patients. 354 (61.6%) of these 575 patients had hypoactive nodules, 50 (8.7%) had normoactive and 171 (29.7%) had hyperactivenodules.

Of 1,004 FNA materials, 828 (82.5%)were benign, 33 (3.35%)were malignant, 101 (10.1%)were suspicious for malignancy, 42 (4.2%)were unsatisfactory. For determining the possible impact of nodule characteristics on benignity or malignity, we excluded suspicious andunsatisfactory FNAs and the remaining 861 FNA materials were evaluated along with ultrasonographic findings.

The mean age was 48.94±13.11 years in patients with nodules proven benign in FNA and 46.18±14.69 years in patients with nodules proven malign in FNA. The age was not different between patients' groups with benign and malign nodules ($p= 0.237$).

25 (3.4%) of 739 women with definitive FNAs and 8 (6.6%) of 114 men with definitive FNAs had malignant cytologic findings. Although men seemed to have slightly higher risk of malignancy compared to women, the difference was not statistically significant ($p= 0.091$).

Thyroid status did not affect the risk of malignancy in FNA. Free T4 (FT4) and TSH were similar in both patients' groups with benign and malignant nodules ($p= 0.737$ and $p= 0.920$, respectively).

The risk of having a malignant FNA material was significantly higher in patients with one or two nodules compared to those with three or more nodules ($p= 0.027$).

The echogenity of nodules did not affect the risk of ma-

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Table 1. Ultrasonographic Features Predicting Malignancy in Patients with Thyroid Nodules in FNA

	Odds ratio (95% CI)	p
Macrocalcification	1,75(0,47-6,43)	0,4
Microcalcification	39,29 (8,32-185,47)	<0.001
Solitary nodule	3,61(1,25-10,42)	0,017
Two and more nodules	2,89(0,72-11,65)	0,134
Irregular margins	5,44(1,76-16,78)	0,003

Table 2. Relation of FNA Diagnosis and Histopathological Diagnosis of Thyroidectomy Material

		Histolopathology		
		Malignant	Benign	Total
FNA	Malignant	8 (10,8%)	3 (4,1%)	11 (14,9%)
	benign	4 (5,4%)	59 (79,7%)	63(85,1%)
	Total	12 (16,2%)	62(83,8%)	74 (100%)

lignancy in FNA. The risk was similar in hypo-. hyper-, iso- and mixed echoic nodules (p=0.918).

We could reach scintigraphic records of 573 patients, and 496 of them were eligible, because of exclusion of suspicious and unsatisfactory FNAs; 150 patients had hyperactive, 45 had normoactive and 301 had hypoactive nodules.

Nodules with irregular margins had significantly higher risk of malignancy in FNA compared to nodules with regular margins (p<0.001).

Nodules with cystic degeneration had a similar risk of malignancy in FNA with nodules without cystic degeneration (p=0.938).

The nodules with a surrounding hypoechoic rim had a similar risk of malignancy in FNA with nodules without hypoechoic rim (p=0.943). The nodules with the diameter greater than 1 cm had similar risk of malignancy in FNA with nodules smaller than 1 cm in diameter (p=0.123). The nodules proven malignant in FNA were similar size with those proven benign in FNA when calculated using Student's t test (p=0.338). The presence of microcalcification in nodules was associated with significantly higher risk of malignancy compared to both nodules without calcification and nodules with macrocalcifications (p<0.001). The presence of macrocalcification was not associated with increased risk of malignancy in FNA compared to nodules without macrocalcification (p=0.52).

Logistic regression and odds ratio was calculated for the number of nodules, calcification and irregular margins and shown in Table 1.

We reached the surgical records of 101 patients, who underwent surgery, in our group of 1,004 patients with nodules. In 101 patients, who underwent thyroidectomy, 4 unsatisfactory FNAs were excluded and the probability of malignancy in thyroidectomy material with FNA classified as benign preoperatively, was 6.3%. The probability of malignancy in thyroidectomy material with FNA classified as malignant preoperatively was 72.7%. The probability of malignancy in thyroidectomy material with FNA classified as suspicious for malignancy preoperatively was 26.1%. When 23 FNAs suspicious for malignancy were also excluded, only FNAs classified as benign and malign were used to calculate the sensitivity, specifity, negative and positive predictive value. The sensitivity of FNA was 66.7% and the specifity was 95.2%. Positive predictive value was 72.7% and negative predictive value was 93.7%. Our diagnostic accuracy was 90.5%. FNA and histopathological examination of thyroidectomy material were compared and shown in Table 2. The sensitivity of FNA was 77.8 and the specifity was 74.7%, when FNAs classified as suspicious for malignancy were included in malignant group. The positive predictive value was 41.2% and the negative predictive value 93.7%. Total accuracy was calculated as 75.2%.

Discussion

According to the criteria of European Thyroid Association, there is no geographical region in Turkey, which is free of a goiter problem. Thyroid nodules are a very common clinical finding, with an estimated prevalence ranges from 3% to 7% during palpation (8).

Erdogan et al reported that the patient's age, sex, initial serum TSH level and time between evaluations did not influence growth of a benign nodule in moderately iodine-deficient area (16). In our study, we found that age and gender were not associated with increased risk of malignancy in thyroid nodules. This finding was inconsistent with the literature stating that male gender and age below 20 and above 70 are associated with higher risk of having malignant thyroid nodules (17). Mazeh et al found no correlation between age and gender and malignancy, either (18). Sundram et al

reported a female preponderance of mortality of thyroid malignancies in Bangladesh, Laos, and Malaysia, whereas lower mortality in women is reported in China, Cambodia, Viet Nam, and New Zealand in the expert consensus conference concerning thyroid cancer in Asia-Pacific region. In the mentioned conference, thyroid cancer incidence in Singapore was reported to be growing at a disproportionately higher rate in men than in women. Thyroid cancer in Singapore also tended to be more common in younger people compared to other cancers (19).

Thyroid status defined as FT4 and TSH had no effect on the risk of malignancy in our study. Scintigraphic findings were not associated with the risk of malignancy in thyroid nodules, either. Harach et al reported six cases of 73 (8.2%) scintigraphically proven hot nodules were malignant. They could explain this finding with the known frequency of follicular carcinoma in goitrous areas and emphasized that their number of cases was too small to draw a definitive conclusion. Also, 2 cases of malignancy with hyperactive nodules had follicular cancer proven surgically, which was consistent with the pathology of endemic goitrous region (20).

In our group of 101 patients treated surgically, follicular cancer was seen only in these patients, and the majority of 18 malignancies consisted of papillary cancers. In the series of 518 thyroidectomized cases reported by Taneri et al, papillary cancer was also the most frequent, followed by follicular carcinoma (21). When we divided nodules as the ones bigger than 1 cm in diameter and smaller than 1 cm, we could not find any significant difference between the groups in the risk of malignancy. This finding is consistent with the recent literature, which states that the size of a nodule is not a predictor of malignancy (17, 22).

Sahin et al classified 472 nodules from 207 patients, who eventually underwent surgery, as supracentimetric and infracentimetric. There were no significant differences between infracentimetric and supracentimetric nodules. They concluded that infracentimetric nodules were not associated with a lower risk of malignancy (23).

The risk of malignancy is found to be similar in palpable and nonpalpable nodules (23). Sundram et al stated that, patients in the Asia Pacific region were most likely to be diagnosed with palpable thyroid nodularity, with a relative low but growing incidence of cancers first detected incidentally (19). Taneri et al reported that multiple nodules in thyroid glands were associated with malignancy in Turkish patients with a relatively higher incidence compared to the data in the literature (21). Inconsistent with this finding, in our study, having one or two thyroid nodules was associated with significantly higher risk of malignancy compared to having three or more nodules.

Therefore, it is recommended to evaluate the nodules for ultrasonographic features suggesting malignancy in order to avoid unnecessary US-guided FNAs (22). In the present study group, we biopsied the biggest nodule in the majority of patient with multiple nodules, unless there was a suspicious feature for malignancy in another nodule. When none of the nodules has a suspicious sonographic appearance and multiple sonographically similar coalescent nodules are present, the likelihood of malignancy is low and it is reasonable to aspirate only the largest nodules (14, 17). However, we might have still missed any malignancy, which could be hidden in a nodule other than the one we biopsied. Consistent with the literature, our patients had higher risk of malignancy in the presence of microcalcification, with a very high Odds ratio, irregular margins and solitary nodule. Inconsistent with the literature, hypoechogenity and the presence of hypoechoic rim did not affect the risk of malignancy. Also, the presence of macrocalcification had no effect on the risk of malignancy in our study, whereas Moon et al defined macrocalcification as an ultrasonographic feature suggesting malignancy in their study with 853 patients with thyroid nodules (10).

The sensitivity and specifity of our FNAs are 66.7% and 95.2%, respectively. Positive predictive value was 72.7% and negative predictive value was 93.7% (10). Chang et al reported a sensitivity of 100% and a specificity of 63%. They explained the high sensitivity and low specifity by including suspicious FNAs in definitely malignant group. They suggested that one cause of low specificity might be associated with statistical problem (9). Amrikachi et al suggested that because most cases with a negative FNAB result were followed up clinically, it was difficult to estimate the true negative diagnosis in the follow-up group (24). We excluded suspicious FNAs for determining positive predictive value. Our high specifity and diagnostic accuracy might result from this exclusion. Consistently, the sensitivity of FNA increased to 77.8 and the specifity decreased to 74.7%, when FNAs classified as suspicious for malignancy were included in malignant group. The positive predictive value was 41.2% and the negative predictive value 93.7%. Total accuracy also decreased to 75.2%.

Moon et al reported sensitivity and specifity of FNAs 95.1 and 79.7, respectively, true positive 77, true negative 4 in children and adolescents (10). Mazeh et al had overall accuracy 75%, sensitivity 87%, specifity 89%, the negative predictive value 87% and positive predictive value was 89% (18). Baloch et al reviewed the results of 662 FNAs and reported a sensitivity and specificity of 92% and 84%, respectively (25). Hamburger et al reported a sensitivity and specificity of 85% and 80%, respectively (26). Şahin et al reported the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of US-FNAB for infracentrimetric nodules were 96.3%, 71.2%, 44.8%, 98.8%, and 76.1%; and for supracentimetric nodules, these values were 98.1%, 63.1%, 35.6%, 99.4, and 69.1%, respectively (23). The sensitivity of FNA is reported between 65% to 98% and the specifity 72% to 100% in various studies (17, 27). The present results are also in this range. These data indicate that FNA is the method of choice for evaluation of thyroid nodules.

In conclusion, thyroid nodules are common in general population, especially in iodine-deficient regions. To identify

nodules with malignant features, FNA is a reliable, reproducible and minimally invasive method and along with ultrasonography, its diagnostic accuracy approaches to that of surgical excision. In the present study, we evaluated 1,004 patients, 101 of which had been operated, in a 7-year time course. Our results demonstrate the characteristics of thyroid nodules in an iodine-deficient region. According to our findings, among all features of malignancy, microcalcification is a very important sign and should alert the physician.

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