The prognostic value of fine-needle aspiration biopsy of the thyroid gland – analysis of results of 1078 patients.

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Abstract

OBJECTIVE: We aimed to evaluate the prognostic value of thyroid fine needle aspiration biopsy (FNAB) in the diagnosis of pathologic lesions.
METHODS: Data from 1 078 consecutive patients (female : male ratio, 9:1) who underwent thyroidectomy were retrospectively analyzed. All patients had preoperative thyroid FNAB. Unilateral and bilateral FNAB were performed in 872 and 206 patients, respectively, resulting in 1 284 cytologic aspirates, which were compared to postoperative histology. Risk factors for malignancy (age, sex, single nodule, or nodule in multinodular goiter) were evaluated.
RESULTS: 203 (15.81%) aspirates were non-diagnostic. 768 (59.81%) were benign; 112 (8.72%) were atypical; 170 (13.24%) were follicular neoplasms, 5 (0.4%) had suspicion of malignancy; and 26 (2.02%) were malignant tumors on FNAB. The calculated risk of malignancy in each group was: 1.97%, 1.84%, 7.15%, 12.35%, 60%, and 100%. There were 2.02% false negative and 0.15% false positive results. Diagnostic discrepancies occurred in the follicular neoplasm group, of 86 biopsies (0.15%).
CONCLUSION: FNAB is the primary method of preoperative diagnostics of thyroid tumors, as it allows many patients to avoid thyroidectomy. In addition, it helps the operating surgeon to decide the extent of surgical resection.

ORIGINAL ARTICLE

INTRODUCTION

The fine needle aspiration biopsy (FNAB) of the thyroid is the fundamental and most commonly accepted preoperative diagnostic examination for thyroid nodules (Kim *et al.* 2007; Layfield *et al.* 2009; Nayar & Ivanovic 2009). Thyroid nodules can be palpated in approximately 4–7% of adults, less than 5% of which are malignant neoplastic lesions (Gharib & Goellner 1993; Gharib 1997; Sherman 2003). As ultrasound has advanced, access to imaging has become more widespread, and the population has aged, the number of patients with an incidentally diagnosed thy-

roid nodule has been increasing (Ogilvie *et al.* 2006). Because of the potential for dedifferentiation of a benign from a neoplastic lesion, a significant number of patients could avoid thyroidectomy and its associated risks, namely recurrent laryngeal nerve palsy and hypoparathyroidism (Hadi *et al.* 1997; Ogilvie *et al.* 2006).

The first FNAB was performed by Franzen in the 1950s at Karolinska University in Sweden, further developed by Zajicek and Soderstrom (Löwhagen *et al.* 1979; Lundgren *et al.* 2008). FNAB became popular in the United States in the 1970s, and in Europe in the 1980s. Currently, it is commonly performed in the outpatient clinic due to its ease of application, low cost, and high sensitivity and specificity (Sclabs *et al.* 2003; Ogilvie *et al.* 2006; Yang *et al.* 2007; Lundgren *et al.* 2008).

The indications for thyroid FNAB are: single nodule, high risk lesion in a multinodular goiter, nodule with a halo, increased vascularization, and microcalcifications on thyroid ultrasound. Risk factors for malignancy include male gender, age below 20 or above 70, past medical or family history of thyroid cancer or multiple endocrine neoplasia type 2A or 2B, and enlarged cervical lymph nodes (Ogilvie *et al.* 2006; Cooper *et al.* 2006; Lundgren *et al.* 2008). We aimed to evaluate the prognostic value of FNAB in the diagnosis of thyroid lesions, on the basis of histological results.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of 1078 patients who underwent thyroid surgery at our institution from 1996 to 2003. All clinical data, including patient demographics, disease course, diagnostics, and surgical treatment were queried via a survey, then recorded in an electronic database using Microsoft Access software (Table 1).

Tab. 1. Demographic data of the patients.

	Total	%
No. Patient	1 078	100%
Sex		
- female	961	89%
- male	117	11%
Mean age (years)		
- female	49.65±12.18	
- male	52.51±11.34	
Age (years)		
<20	24	2%
21-30	68	6%
31-40	138	13%
41-50	308	28%
51-60	276	26%
61-70	166	16%
>70	98	9%

All study patients underwent preoperative thyroid FNAB, performed at various research centers; therefore histologic evaluation was made by many cytopathologists. Because these FNABs were performed and evaluated in different centers over 8 years, the results were grouped according to the latest Bethesda classification (Cibas & Ali 2009). These included: nondiagnostic biopsies, benign lesions, atypia or follicular lesions difficult to interpret, follicular neoplasms or suspicion thereof, lesions suspicious for malignancy, and malignant lesions (Table 2). Postoperative histologic results were evaluated by a group of pathologists of the same clinic.

In order to assess the prognostic value of FNAB, cytology was compared with histologic results, and any correlation was observed. Risk factors for malignancy were also evaluated. The chi-squared test, the chi-squared test with Yates modification, and the V-squared test were used for statistical analysis. A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

Patients' demographic data are presented in Table 1. Out of 1 078 patients, unilateral FNAB was performed in 872 patients and bilateral FNAB in 206 patients, obtaining 1284 cytological aspirates.

FNAB results were as follows: 203 (15.81%) nondiagnostic, 768 (59.81%) benign, 112 (8.72%) atypical, 170 (13.24%) follicular neoplasms, 5 (0.4%) suspicious for malignancy, 26 (2.02%) malignant (Table 3). The correlations between thyroid FNAB cytology and postoperative histological results are presented in Tables 4 and 5.

Among 203 preoperative non-diagnostic aspirates, 198 (98.03%) and 4 (1.97%) cases were benign and malignant, respectively. Of the 4 patients with malignant lesions, 3 were papillary carcinomas and one was Hurthle cell carcinoma.

In the largest group of lesions that were benign on cytology (n=768), multi-nodular goiter was found in 660 (85.92%), adenoma in 72 (9.38%), thyroiditis in 22 (2.86%), and thyroid carcinoma in 14 (1.82%) cases post-thyroidectomy. Among the neoplastic lesions, papillary carcinoma was the most frequent (9 cases, 1.17%), followed by follicular carcinoma (4 cases, 0.52%), and anaplastic carcinoma (1 case, 0.13%).

In Group III of the Bethesda classification, which includes atypical cells, postoperative benign lesions were found in 104 preparations (92.85%), 10% of which had thyroiditis. In 8 (7.14%) cases, thyroid carcinoma was found. Papillary carcinoma was diagnosed in 6 (5.36%) cases. There was one case of medullary thyroid carcinoma and one case of anaplastic carcinoma.

In 170 FNABs, follicular neoplasms were found. Post-thyroidectomy, histological results showed multinodular goiter in 73 (42.94%), adenoma in 63 (37.06%), thyroiditis in 13 (7.65%) and thyroid carcinoma in 21

Tab. 2. The Bethesda System for Reporting Thyroid Cytopathology; Recommended Diagnostic Categories.

I. Nondiagnostic or Unsatisfactory	Cyst fluid only Virtually acellular specimen Other (obscuring blood, clotting artifact, etc)
II. Benign	Consistent with a benign follicular nodule (includes adenomatoid nodule, Colloid nodule, etc) Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context Consistent with granulomatous (subacute) thyroiditis Other
III. Atypia of undetermined significance or follicular lesion of undetermined significance	
IV. Follicular neoplasm or suspicious for a follicular neoplasm	specify if Hurthle cell (oncocytic) type
V. Suspicious for malignancy	Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma Other
VI. Malignant	Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma Undifferentiated (anaplastic) carcinoma Squamosus cell carcinoma Carcinoma with mixed features (specify) Metastatic carcinoma Non-Hodgkin lymphoma Other

(12.35%) cases. In the group with thyroid carcinoma, 11 (6.47%) were papillary carcinoma, 8 (4.71%) were follicular carcinoma, and 2 (1.17%) were Hurthle cell carcinoma.

There were 5 biopsies in Bethesda Group IV. In this group, 2 cases (40.0%) were diagnosed as benign lesions postoperatively. Metastatic renal carcinoma was found in one patient. Preoperative malignant thyroid neoplastic lesions were diagnosed in 26 preparations and malignancy was confirmed in all cases postoperatively. Histological results were following: 16 (61.54%) papillary carcinoma, 5 (19.32%) medullary carcinoma, 1 (3.85%) anaplastic carcinoma, 3 (11.54%) lymphoma, and 1 (3.85%) lung cancer metastasis.

Twenty-six (2.02%) cytological results were falsely negative and 2 results (0.15%) were falsely positive. Diagnostic discrepancies occurred in the group of follicular lesions, in 86 (6.8%) biopsies.

The following risk factors were taken into consideration: single or multinodular type, age, and sex. Among 1284 aspirates, in 618 cases material was taken from a single nodule; in 666 cases from a multinodular goiter. FNAB results based on nodule type are shown in Table 6.

There were a significantly higher number of benign lesions in multinodular goiter than in solitary thyroid nodules ($p<0.05$) by the chi-squared test. Atypical cells, follicular lesions, and malignant neoplastic lesions were more frequent in single nodules ($p<0.05$). Among the 618 preparations from single nodules, thyroid carcinoma was found in 50 (8.1%) cases whereas in nodules from multinodular goiter, malignant lesions were found in 26 (3.9%) patients ($p<0.05$). Thyroid carcinoma occurred more often in men than in women (11% vs. 6.5%), although this difference was not found to be statistically significant. The mean age of men with thyroid carcinoma was higher than in women (59.16 vs. 50.19 years). Malignant neoplasms occurred most often in patients under 20 years of age (12%), but this was not found to be statistically significant. The risk of cancer depending on the type of nodule, sex, and age is presented in Table 7.

Tab. 3. Fine-needle aspiration (FNA) cytologic diagnosis.

FNA cytologic diagnosis	Aspirates	
	No.	%
Nondiagnostic or unsatisfactory	203	15.81
Benign	768	59.81
Atypia	112	8.72
Follicular neoplasm	170	13.24
Suspicious for malignancy	5	0.4
Malignant	26	2.02
Total	1284	100

Tab. 4. Fine-needle aspiration (FNA) cytologic diagnosis and corresponding histologic findings after thyroid surgery.

FNA cytologic diagnosis	Histologic diagnosis					
	Nodular goiter	Adenoma	Thyroiditis	Thyroid carcinoma	Lymphoma / Metastatic carcinoma	Total
Nondiagnostic or Unsatisfactory	192 (94.58%)	1 (0.49%)	6 (2.96%)	4 (1.97%)	–	203
Benign	660 (85.92%)	72 (9.38%)	22 (2.86%)	14 (1.82%)	–	768
Atypia	75 (66.96%)	18 (16.07%)	11 (9.82%)	8 (7.14%)	–	112
Follicular neoplasm	73 (42.94%)	63 (37.06%)	13 (7.65%)	21 (12.35%)	–	170
Suspicious for malignancy	–	1 (20%)	1 (20%)	2 (40%)	1 (20%)	5
Malignant	–	–	–	22 (84.61%)	4 (15.39%)	26
Total	1000 (78%)	155 (12%)	53 (4.13%)	71 (5.53%)	5 (0.39%)	1284 (100%)

Tab. 5. Fine-needle aspiration (FNA) cytologic diagnosis and corresponding histologic findings after thyroid surgery.

FNA cytologic diagnosis	Histologic diagnosis: thyroid carcinoma							
	Papillar carcinoma	Follicular carcinoma	Hurthle cell carcinoma	Medullary carcinoma	Anaplastic carcinoma	Lymphoma	Metastatic carcinoma	Total
Nondiagnostic or Unsatisfactory	3 (1.47%)	–	1 (0.49%)	–	–	–	–	4 (1.96%)
Benign	9 (1.17%)	4 (0.52%)	–	–	1 (0.13%)	–	–	14 (1.82%)
Atypia	6 (5.36%)	–	–	1 (0.89%)	1 (0.89%)	–	–	8 (7.14%)
Follicular neoplasm	11 (6.47%)	8 (4.71%)	2 (1.17%)	–	–	–	–	21 (12.35%)
Suspicious for malignancy	2 (40.0%)	–	–	–	–	–	1 (20.0%)	3 (60.0%)
Malignant	16 (61.54%)	–	–	5 (19.23%)	1 (3.85%)	3 (11.54%)	1 (3.85%)	26 (100%)
Total	47 (3.7%)	12 (0.92%)	3 (0.22%)	6 (0.47%)	3 (0.33%)	3 (0.22%)	2 (0.15%)	76 (5.9%)

Tab. 6. Fine-needle aspiration (FNA) cytologic diagnosis in multinodular goiter and in a single nodule.

FNA cytology result	Single nodule	Multinodular goiter	*p*-value
Nondiagnostic or unsatisfactory	87 (14.05%)	116 (17.42%)	$p<0.05$
Benign	360 (58.23%)	452 (6787%)	$p<0.05$
Atypia	69 (11.14%)	43 (6.45%)	$p<0.05$
Follicular neoplasm	121 (19.56%)	49 (7.35%)	$p<0.05$
Suspicious for malignancy	3 (0.47%)	2 (0.3%)	$p<0.05$
Malignant	22 (3.45%)	4 (0.6%)	$p<0.05$
Total	618 (100%)	666 (100%)	

Tab. 7. The risk of carcinoma depending on the kind of the nodule, sex and age.

	Total (100%)	Risk of malignancy	*p*-value
Sex			
- female	961	63 (6.5%)	$p>0.05$
- male	117	13 (11%)	
Age (years)			
<20	24	3 (12.5%)	$p>0.05$
20-60	670	59 (8.8%)	
>60	222	14 (6.31%)	
Female mean age (years) /cancer disease/		50.92±16.36	
Male mean age (years) /cancer disease/		59.16±14.31	
Single nodule	618	50 (8.1%)	$p<0.05$
Multinodular goiter	666	26 (3.9%)	

DISCUSSION

Thyroid FNAB is a fundamental procedure in the diagnosis of thyroid disease (Ogilvie *et al.* 2006; Lundgren *et al.* 2008; Theoharis *et al.* 2009). Its results determine the method of treatment (conservative vs. operative) and influences the extent of surgical resection. The American Thyroid Association recommends FNAB as the most important examination due to its significant clinical value and low cost (Wu *et al.* 2006). We have recently observed an increase in the number of FNABs performed in our department and in other centers (Wu *et al.* 2006). However, FNAB has some limitations and should be treated as a medical consultation; therefore, it requires the support of as much clinical data as possible (Giard & Hermans 2000; Ravetto *et al.* 2000). Insufficient data makes cytological diagnosis difficult and sometimes impossible.

In our clinical data, we used the six-stage Bethesda classification (Theoharis *et al.* 2009). In our cohort, approximately 15% of biopsies were non-diagnostic. According to many authors, nondiagnostic results range from 4 to 20% (Gharib & Goellner 1993; Giard & Hermans 2000; Berner 2006; Yassa *et al.* 2007; Yang *et al.* 2007; Theoharis *et al.* 2009).

The appropriate number of follicular cells in the smear to obtain a diagnostic preparation has been a matter of discussion (Ranshaw 2003). In our and other departments (Wu *et al.* 2006), the presence of 8 groups of cells, each containing at least 10 thyrocytes, is assumed to be diagnostic. In our opinion in the case of the multinodular goiter, material should be taken from 3 nodules; subsequent aspirations make preparations difficult to assess due to excess of blood in the preparation. Apart from the technical aspects, the art of sampling the material is important for every physician who performs the biopsy, provided that he does it well. In addition, in order to avoid overdiagnosis it is necessary to gain adequate experience and exchange it with the others.

In our FNABs, benign lesions occurred in 60% of patients. A similar percentage of benign lesions was observed by Yassa (60%) and Yang (64%) (Yang *et al.* 2007; Yassa *et al.* 2007). The Bethesda classification determines the risk of malignancy within 0–3%. In our data, this risk was 1.82%; however, in other medical centers it ranged from 0.3–8% (Yang *et al.* 2007, Yassa *et al.* 2007).

Particular attention should be paid to Bethesda Group III, covering all types of atypical cells diagnosed in the FNAB. In this group, the risk of carcinoma is about 5–15%, and in our material, it was 7%. Because of high percentage of malignant changes in this group, these patients should undergo frequent biopsies (Kim *et al.* 2007).

Follicular thyroid neoplasms are among the most difficult to make a proper diagnosis before surgical treatment. There is no possibility of differentiating an adenoma from follicular thyroid carcinoma on cytology (Goldstein *et al.* 2002). In order to diagnose follicular thyroid carcinoma, it is necessary to assess capsule infiltration and vascular invasion (LiVolsi & Baloch 2004). Among our patients, follicular carcinoma was diagnosed in 13%.

The extent of surgical resection for follicular carcinoma is the topic of many academic discussions (Sclabs *et al.* 2003). In most of these cases, we perform total thyroidectomy on the tumor side and a subtotal or near total on the contralateral side. There are many recent publications recommending total thyroidectomy for follicular neoplasms, especially in the elderly and in multinodular goiter (Agarwal & Aggarwal 2008; Efremidou *et al.* 2009). In our cohort, the risk of cancer in the follicular lesion group was 12.35%; other authors estimated a rate of 20–60% (Yang *et al.* 2003; Miller *et al.* 2004; Daveci *et al.* 2006; Sahin *et al.* 2006; Yang *et al.* 2007; Yassa *et al.* 2007; Cibas & Ali 2009). This low percentage of malignancy seen in follicular neoplasms results from overdiagnosis of these lesions. The diagnostic discrepancies in this group reached about 50% – postoperatively, multinodular goiter was diagnosed in 42.94% and thyroiditis in 7.65% of cases. The follicular variant of papillary carcinoma was diagnosed postoperatively in 6.47% cases. Follicular carcinoma was diagnosed in 4.71% cases. The frequent incidence of papillary carcinoma in the group of follicular neoplasms should be an indication for intraoperative frozen section.

Suspicion of a malignant lesion on cytology is associated with high percentage of carcinoma on postoperative pathology (up to 60–75%). False positive results on FNAB occur rarely, up to 2% (Yang *et al.* 2007). In this study, all malignant lesions that were diagnosed preoperatively were confirmed on histopathology. On the other hand, within the group suspicious for malignancy, 2 of 5 were false positives (0.15%). False negative results ranged from 2–7% in the literature (Bakhos *et al.* 2000; Sclabs *et al.* 2003;) and in our cohort they were close to 2%. Low cell numbers on the smears appear to be the main reason for diagnosis of malignant changes.

In equivocal results (atypical cells, follicular neoplasm, or suspicion of malignant lesion), clinical data are of great importance to make an appropriate decision about surgery. We showed that a solitary nodule in a non-toxic goiter is a significant risk factor for malignancy. We did not find a significant association between male sex and patient age, as described in previous publications (Monteros *et al.* 2009).

CONCLUSIONS

FNAB is the primary method of preoperative diagnostics of thyroid tumors, as it allows many patients to avoid thyroidectomy. In addition, it helps the operating surgeon to decide the extent of surgical resection.

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