

## Risk of malignancy in non-diagnostic thyroid fine-needle aspiration biopsy in multinodular goitre patients

AKGUL O, OCAK S, KESKEK M, KOC M, TEZ M

*5<sup>th</sup> Department of Surgery, Ankara Numune Training and Research Hospital, Ankara, Turkey  
e-mail: mesuttez@yahoo.com*

**Objective.** Although the majority of biopsies is adequate for a cytological diagnosis, 5-20 % will be insufficient or nondiagnostic. Patients with nondiagnostic FNABs (ND-FNAB) may be further managed by continued observation, repeated FNAB, or thyroidectomy. The aim of this study was to determine the risk of malignancy in ND-FNAB, and to determine if there are any clinical factors that can be used to distinguish malignant versus benign disease in multinodular goitre patients with ND-FNAB.

**Methods.** A total of 411 multinodular goiter patients who underwent both a FNAB and thyroidectomy was the subject of study. Seventy nine of these patients with ND-FNAB were further reviewed retrospectively, and demographical and clinical factors were investigated to determine if there is any predictor of malignancy in this group of patients. Among these patients, FNAB has been repeated one more time in 5 (6.3 %) patients, and two more times in 9 (11.3 %) patients.

**Results.** Among 79 patients with ND-FNAB, 10 patients (12.6 %) had malignancy as found postoperatively. There were no differences in age, sex, functional status of the thyroid gland, and nodule size between patients with benign versus malignant disease.

**Conclusion.** Nondiagnostic FNAB remains a significant problem in the evaluation of thyroid nodules. Despite ultrasound guidance, clinicians should inform patients that there is a 5-15 % malignancy risk of initial nondiagnostic specimens.

**Keywords:** nondiagnostic FNA biopsy, multinodular goitre

Thyroid nodules constitute the main indication for FNAB, the goal of this diagnostic procedure being to detect thyroid neoplasms for surgical resection and to identify non-neoplastic lesions that may be managed conservatively (Suen 1996). Although the majority of biopsies is adequate for a cytological diagnosis, 5-20 % will be insufficient or nondiagnostic (Alexander et al. 2008). Patients with nondiagnostic FNAB (ND-FNAB) may be managed by continued observation, repeated FNAB and/or thyroidectomy. This management spectrum is likely related to a broad range of malignancy rates, from 2 % to 37 % in patients undergoing thy-

roidectomy (Chow et al. 2001). The studies that have attempted to assess the risk of malignancy in patients with ND-FNABs are limited by having a subset of patients followed up clinically. To understand the true incidence of malignancy in a ND-FNA it is necessary to have pathological confirmation (Chow et al. 2001; Richards et al. 2008).

The aim of this study was to determine the risk of malignancy in ND-FNAB and to determine if there are any clinical factors that can be used to distinguish malignant versus benign disease in multinodular goitre patients with a ND-FNAB.

### Patients and Methods

A total of 411 multinodular goiter patients who underwent both FNAB and thyroidectomy at Ankara Numune Training and Research Hospital between July 2004 and March 2009 was the subject of study. Out of these 411 patients, 79 patients had a nondiagnostic FNAB and underwent further analysis. Medical records of these patients including age, gender, dominant nodule size, preoperative serum thyroid-stimulating hormone (TSH) level, thyroid hormone therapy, and final pathological diagnosis were collected retrospectively.

All 411 patients underwent ultrasound examination. Ultrasound-guided FNAB was performed by an endocrinologist using a 25-gauge needle with three or four aspirations per nodule. A thyroid FNAB biopsy was reported as nondiagnostic when there were too few or absent follicular cells and an interpretation was not possible. A specimen was satisfactory for diagnosis if there were at least 6 groups of 10 to 15 follicular cells. All cytology was reviewed by in-house cytopathologists.

Among a total of 411, in 79 patients (19.2 %) the findings obtained by FNAB were classified as non diagnostic. Among those 79 patients, FNAB has been repeated one more times in 5 (6.3 %) patients (FNAB #2), and two more times in 9 (11.3 %) patients (FNAB #3).

Patients with suspicious findings by ultrasonography or by clinical examination as well as those with ND-FNAB went directly for surgery. All other patients with ND-FNABs were referred for thyroidectomy if the repeated FNAB was nondiagnostic. Patients were also grouped according to benign versus malignant disease as diagnosed by postoperative final pathology.

Statistical evaluation. Descriptive statistics are presented according to nodule and patient characteristics

as appropriate and were compared using the two-sample t-test (for continuous data) or the chi-square test (for categorical data). Significance was accepted at  $p < 0.05$ .

### Results

A total of 411 multinodular goiter patients underwent both the FNAB and thyroidectomy. There were 343 (83.4 %) women and 68 (16.6 %) men. The mean age was  $44.9 \pm 13.1$  years. There were 403 (98 %) euthyroid, 6 (1.5 %) hyperthyroid and 2 (0.5 %) hypothyroid patients. The surgeries performed included total thyroidectomy (72.5 %), thyroid lobectomy (12 %), one side total lobectomy and other side subtotal lobectomy (5.5 %), and subtotal thyroidectomy (0.5 %). Overall, 78 of 411 (18.9 %) patients had malignancy. Characteristics of patients and nodules with initial nondiagnostic cytology were not different from those with diagnostic cytology (Table 1). Age, gender, nodule size, and nodule location were not predictive of a nondiagnostic ultrasound-guided FNAB.

By the final pathology, ten patients (12.6 %) with a ND-FNAB had malignancy, compared with 68 (20.4 %) in patients with a diagnostic FNAB ( $p = 0.11$ ; not significant). Of the malignant patients with a ND-FNAB, one patient (1.2 %) had Hürthle cell carcinoma, one patient had medullary carcinoma (1.2 %), 7 patients (8.8 %) had papillary microcarcinoma (papillary carcinoma <1 cm), and one patient (1.2 %) had papillary carcinoma. The rate of malignant disease in patients with suspicious findings on ultrasonography or on clinical examination, and a ND-FNAB was 13.8 % (9 of 65). Moreover, the rate of malignancy in patients with repeated ND-FNABs and no other suspicious findings for malignancy was 7.1 % (1 of 14).

**Table 1**  
Comparison of patients with a ND-FNAB and with a diagnostic FNAB

Characteristic	ND-FNAB (n =79)	Diagnostic FNAB (n =332 )	p
Age, years	47.4 ± 14.8	46.5 ± 12.8	NS
Gender	10 males, 69 females	58 males, 274 females	NS
Thyroid function			
Euthyroid	71	326	
Hyperthyroid	8	3	NS
Hypothyroid	0	3	
Size of nodule biopsied (mm)	22.7 ± 10.1	24 ± 7.8	NS
Final pathology (malignant/benign)	10/79 (12.6 %)	68/332 (20.4 %)	NS

NS: Not significant

When we arbitrarily grouped cancer patients according to nodule size; one patient had nodules  $\leq 1$  cm; 8 patients had nodules 1 to 4 cm in size and one patient had nodules  $\geq 4$  cm.

There were no differences in age, gender, functional status of the thyroid gland, and nodule size between patients with ND-FNABs in relation to benign versus malignant disease (Table 2).

### Discussion

Thyroid nodules are present in more than 50 % of adult population and their prevalence is increasing with age (Mazzaferrri 1993). In the last two decades, FNAB has gained widespread acceptance as a diagnostic tool in the management of thyroid nodules. Several authors have shown its remarkable sensitivity and specificity compared to other tools such as radiology and laboratory tests (Silverman et al. 1986).

Despite improved aspiration techniques and ultrasound guidance, up to 20 % of initial aspirations may be still nondiagnostic. During a 5 year period, we experienced 19 % rate of ND-FNABs of thyroid nodules, a finding consistent with previous studies (Alexander et al. 2002). One study has reported near-perfect success in obtaining diagnostic specimens using ultrasound guidance in such patients (Braga et al. 2001). Factors have been reported to influence the success of FNAB, including small nodule size, position of the nodule within the thyroid, and patient age and body habitus (Alexander et al. 2002). However, our data did not confirm these findings.

In the study from Mayo Clinic a total of 153 patients had nondiagnostic thyroid FNAB; 60 patients underwent repeated FNAB, and 6 were found to be malignant; 93 patients did not undergo a second biopsy and 4 patients were found to have a malignancy (Chow et al. 2001). Some authors suggest that as the number of

aspirations increased, false-negative results decreased, and they propose to take at least six aspirations (Hamburger et al. 1986).

Several studies have shown varying rates of malignancy among nondiagnostic thyroid biopsies. Thus, MacDonald and Yazdi (1996) studied 114 patients with nondiagnostic FNAB, while histological follow-up was available in 91 patients, and malignancy rate was 2 %. In addition, McHenry et al. (1993) studied 411 patients with a solitary cold thyroid nodule that underwent thyroidectomy, including 92 with a “non-diagnostic” repeated FNAB. They reported a malignancy rate of 9 % in this subgroup of patients with persistent nondiagnostic cytology. Among 709 patients with FNABs 50 nondiagnostic cases were found and among them 31 patients underwent thyroidectomy and 5 had malignant lesions (16.1%) (Goldstein et al. 2002).

In our study, among a total of 411 patients the nondiagnostic FNAB appeared in 79 patients (19.2 %) and 10 patients (12.6 %) with a ND-FNAB had a malignancy. These findings were similar to the above listed findings by others in patients with nodular goitre. Though our study differs from those by others by the fact that all our patients had multinodular goitre, it should be suggested that the patients with nodular goitre and multinodular goitre show a great similarity in the malignancy rates and rate of non diagnostic FNAB.

We acknowledge potential concerns related to our study methods that should be kept in mind. Patients returning for follow-up ultrasound-guided FNAB were not selected randomly, allowing for potential physician (or patient) selection bias.

In summary, nondiagnostic FNABs remain a significant problem in the evaluation of thyroid nodules. Despite ultrasound guidance, clinicians should advise the patients that there is a 5-15 % risk of initial nondiagnostic specimens.

Table 2

Comparison of patients with a ND-FNAB in relation to benign versus malignant disease

Characteristic	Benign (n =69 )	Malignant (n =10 )	P value
Age, y	44.4± 19.1	49.8 ± 19.7	NS
Gender	10 males, 59 females	0 males, 10 females	NS
Thyroid function			
<i>Euthyroid</i>	61	9	
<i>Hyperthyroid</i>	7	1	NS
<i>Hypothyroid</i>	1	0	
Size of nodule biopsied (mm)	23.6 ± 13.1	21.6 ± 9.9	NS

NS: Not significant

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