

Aim of the study: Fine-needle aspiration biopsy (FNAB) is the most accurate and cost-effective method to evaluate the risk of malignancy of thyroid nodules, but approximately 1–24% of FNABs generate a nondiagnostic result (ND-FNAB). The aim of this study was to determine the predictive factors of a repeated nondiagnostic result of FNAB.

Material and methods: A total of 4018 FNABs performed in a territorial referral centre were analysed, of which 288 (7.17%) were nondiagnostic. Medical records were available for 245 biopsies performed in 228 patients. The retrospective analysis of factors that may influence a repeat ND-FNAB, including demographic, clinical and ultrasound characteristics, was performed.

Results: A repeat FNAB was performed in 159 nodules giving a diagnostic result in 79.2% of cases. The time between the biopsies ranged from 1 to 611 days (mean 154.4, median 119). The timing of a repeat FNAB did not significantly alter the diagnostic output ($p = 0.29$). In the univariate analysis, significant predictors of a repeat ND-FNAB were older patient age ($p = 0.02$), L-thyroxine supplementation ($p = 0.05$), and a history of ^{131}I therapy ($p < 0.0001$). In the multivariate analysis, only a history of ^{131}I therapy was a statistically significant risk factor for a repeat ND-FNAB ($p = 0.002$).

Conclusions: Patients with a history of ^{131}I therapy and ND-FNAB should undergo periodic ultrasonographic assessment rather than a repeat biopsy. The interval between repeated FNABs recommended by guidelines does not affect the diagnostic output.

Key words: nondiagnostic FNAB, thyroid nodules, ultrasound-guided biopsy, ^{131}I therapy.

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Repeated nondiagnostic result of thyroid fine-needle aspiration biopsy

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Introduction

Thyroid nodular disease (TND) is a common medical condition. Ultrasonographic examination can identify nodules in 35–68 % of asymptomatic patients [1, 2]. The prevalence of TND is higher in women and increases with age [1]. Thyroid nodules are typically benign but the risk of thyroid cancer in the nodule is not negligible (0.45% to 13%, mean \pm SD, 3.9% \pm 4.1%) [3]. The most accurate and cost-effective method to evaluate the risk of malignancy of thyroid nodules is fine-needle aspiration biopsy (FNAB), but approximately 1–24% of FNABs generate nondiagnostic results (ND-FNAB) [4–10].

There are conflicting reports in the literature on risk factors of nondiagnostic FNAB, but most researchers agree that older patient age, diameter of nodule, history of thyroid surgery and hypoechoogenicity and cystic portion > 50% in ultrasound imaging seem to significantly increase the risk of ND-FNAB [11–15].

According to current guidelines, a solid nodule with a nondiagnostic FNAB result requires a repeated FNAB within 3–12 months, depending on clinical risk factors for malignancy [16]. However, the risk of obtaining nondiagnostic material in repeated biopsy is high [17–21] and the nondiagnostic results of subsequent biopsies pose a relevant clinical problem.

The aim of this study was to determine the factors predicting a repeated nondiagnostic result of FNAB.

Material and methods

A total of 4018 FNABs performed in Holycross Cancer Centre in Kielce from 1.01.2013 to 31.08.2014 (20 months) were analysed, of which 288 (7.17%) were nondiagnostic (Fig. 1). Medical records were available for 245 biopsies performed in 228 patients (78.8% women 21.2% men). The patients' age ranged from 20 to 85 years (mean 59, median 61 years). A retrospective analysis of factors that could influence a repeated ND-FNAB result, including demographic, clinical and ultrasound characteristics, was performed:

Demographic and clinical characteristics: age, sex, thyroid function, presence of autoimmune thyroiditis, L-thyroxine supplementation, antithyroid drugs, history of ^{131}I therapy, radiation therapy, and surgery in the neck region.

Ultrasound characteristics: nodule size, sonographic findings suggesting malignancy according to the classification proposed by Kim *et al.* (U1-U5) [22].

Neck ultrasonography was performed using a Siemens Versa pro and a Hitachi EUB-6500 (both featuring a colour Doppler function), with a high frequency linear probe (7.5 MHz). Patients were qualified for biopsy according to current guidelines [16]. Fine-needle aspiration biopsy was obtained by a pathologist under ultrasonographic guidance of a radiologist. Either the radiologist or the pathologist was certified to perform the thyroid biopsies. The

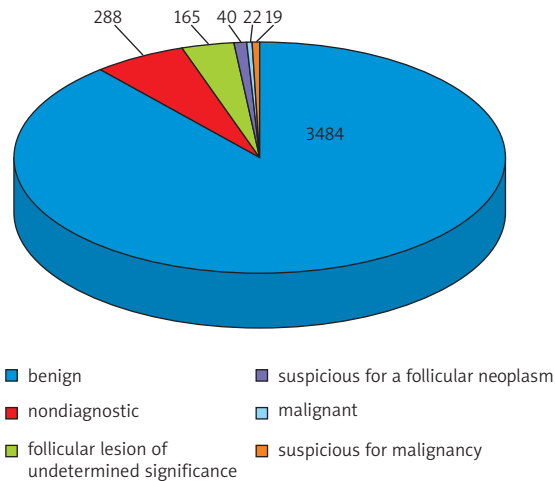


Fig. 1. Results of fine needle aspiration biopsies performed in Holycross Cancer Centre in Kielce from 1.01.2013 to 31.08.2014 (20 months): benign – 3484 (86.71%), follicular lesion of undetermined significance – 165 (4.11%), suspicious for a follicular neoplasm – 40 (0.99%), suspicious for malignancy – 19 (0.47%), malignant – 22 (0.55%), nondiagnostic – 288 (7.17%)

smears were obtained by using 27-gauge needles fitted to a 2-ml syringe. In each case, two smears were prepared and fixed in 86% ethanol and stained with HE stain. In our Centre a minimum of six clusters of 10 epithelial cells had to be found on two smears, based on two separate aspirations, for the specimen to be considered satisfactory. The smears were evaluated according to the Bethesda Thyroid Cytology Classification.

Statistical analysis was performed. Descriptive statistics and frequency analysis were used to characterise this group of patients (Table 1). Univariate and multivariate logistic regression models were used to determine the risk factors of repeated nondiagnostic biopsy results. Odds ratios, 95% confidence intervals, and statistical significance levels were calculated. All statistical analyses were performed using MedCalc Statistical Software version 15.6.1 (MedCalc Software bvba, Ostend, Belgium; <https://www.medcalc.org>; 2015). We considered a p -value < 0.05 to be statistically significant.

Results

A repeated FNAB was performed in 159 nodules giving a diagnostic result in 79.2% of cases (Fig. 2). The results of statistical analysis are presented in Table 2. The time between biopsies ranged from 1 to 611 days (mean 154.4, median 119). The timing of repeated FNAB did not significantly alter the diagnostic output ($p = 0.29$). On the univariate analysis, significant predictors of repeated ND-FNAB result were older patient age ($p = 0.02$), L-thyroxine supplementation ($p = 0.05$) and history of ^{131}I therapy ($p < 0.0001$). As shown in Table 2, the risk of a nondiagnostic biopsy increases every year by 4% (OR = 1.04). For patients with history of ^{131}I therapy the risk of a nondiagnostic result is more than 6 times higher than in those without this

Table 1. Characteristics of the patients with nondiagnostic result of FNAB

	Characteristic	Values	Number of patients
Age (years)	Mean (SD)	59 (13)	
	Median (Q ₁ –Q ₃)	61 (52–67)	
	Range	20–85	
Sex	Male	19.5%	31
	Female	80.5%	128
Thyroid function	Hyperthyroidism	8.8%	14
	Hypothyroidism	8.8%	14
	Euthyroidism	82.4%	131
Antithyroid drugs	Yes	3.2%	5
	No	96.8%	154
L-thyroxine supplementation	Yes	28.3%	45
	No	71.1%	113
	Not data	0.6%	1
Autoimmune thyroiditis	Yes	9.4%	15
	No	18.9%	30
	Not data	71.7%	114
^{131}I therapy	Yes	22.0%	35
	No	78.0%	124
Surgery in the neck region	Yes	10.7%	17
	No	89.3%	142
Radiation therapy in the neck region	Yes	6.9%	11
	No	92.5%	147
	Not data	0.6	1
Nodule size (mm)	Mean (SD)	15.3 (10.9)	
	Median (Q ₁ –Q ₃)	12.5 (9–18.5)	
	Range	3–56	
Sonographic findings according to Kim's classification	U2	26.1%	45
	U3	59.2%	96
	U4	9.8%	17
	U5	0.4%	1
Time between the biopsies (days)	Mean (SD)	154.4 (100.6)	
	Median (Q ₁ –Q ₃)	119 (94–172)	
	Range	1–611	

risk factor (OR = 6.32). Sex, thyroid function, autoimmune thyroiditis, antithyroid drugs, a history of radiation therapy and surgery in the neck region, nodule size and ultrasonographic classification according to Kim *et al.* were not statistically significant ($p > 0.05$). In the multivariate analysis, only a history of ^{131}I therapy was a statistically significant risk factor for a repeated ND-FNAB result ($p = 0.002$).

Discussion

According to current Polish guidelines [16] a nodule with a nondiagnostic FNAB result requires clinical and/or ultrasonographic follow-up and a repeated FNAB performed

Table 2. The univariate and multivariate logistic regression analysis

Risk factor	Univariate logistic regression		Multivariate logistic regression	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age (in years)	1.04 (1.01–1.08)	0.0223	1.03 (0.99–1.03)	0.1181
Sex (female = 1, male = 2)	0.51 (0.16–1.56)	0.2365	Not included	–
Thyroid function (1 – euthyroidism, 2 – hyperthyroidism, 3 – hypothyroidism)	1.35 (0.76–2.40)	0.3048	Not included	–
Antithyroid drugs (1 – no, 2 – yes)	0.95 (0.10–8.75)	0.9605	Not included	–
L-thyroxine supplementation (1 – no, 2 – yes)	2.23 (1.00–4.98)	0.0491	0.80 (0.29–2.27)	0.6818
Autoimmune thyroiditis (1 – no, 2 – yes)	0.61 (0.12–3.19)	0.5631	Not included	–
¹³¹ I therapy (1 – no, 2 – yes)	6.32 (2.71–14.72)	< 0.0001	4.84 (1.82–12.87)	0.0016
Surgery in the neck region (1 – no, 2 – yes)	0.79 (0.21–2.94)	0.7285	Not included	–
Radiation therapy in the neck region (1 – no, 2 – yes)	0.36 (0.04–2.91)	0.3378	Not included	–
Nodule size (mm)	1.01 (0.97–1.05)	0.6207	Not included	–
Sonographic findings according to Kim’s classification (U2, U3, U4, U5)	0.80 (0.42–1.53)	0.5022	Not included	–
Time between the biopsies (days)	1.0 (1.00–1.01)	0.2916	Not included	–

no sooner than three months after the initial FNAB unless clinical features indicate a particularly high risk of malignancy. When two FNABs are nondiagnostic in a solid lesion, surgery should be considered, depending on clinical risk assessment due to the lack of cancer exclusion and a possible higher probability of its detection [16]. According to the American Thyroid Association guidelines, a repeated US-guided biopsy and on-site cytological evaluation is recommended [23]. Surgery should be considered for a histopathological diagnosis if a cytologically nondiagnostic nodule has a high suspicion sonographic pattern, nodule growth (> 20% in two dimensions) is detected during US surveillance, or clinical risk factors for malignancy are present [23]. Repeatedly nondiagnostic nodules without a highly suspicious sonographic pattern require close observation or surgical excision for a histopathological diagnosis [23]. At least a 3-month interval between an initial and repeated biopsy has been suggested to avoid reparative cellular atypia after the previous biopsy that could make cytological assessment difficult, even leading to a misdiagnosis [24, 25]. In this study we demonstrate that the interval between the biopsies does not alter the diagnostic output. Other authors have also questioned the need for a 3-month waiting period after the initial biopsy [26–28].

The risk of a nondiagnostic result in a second biopsy is as high as 20.8% – almost threefold higher than in an initial biopsy. Other authors report up to 17–67.5% risk of obtaining nondiagnostic material in a repeated biopsy [17–21]. Furthermore, we found that patients with a history

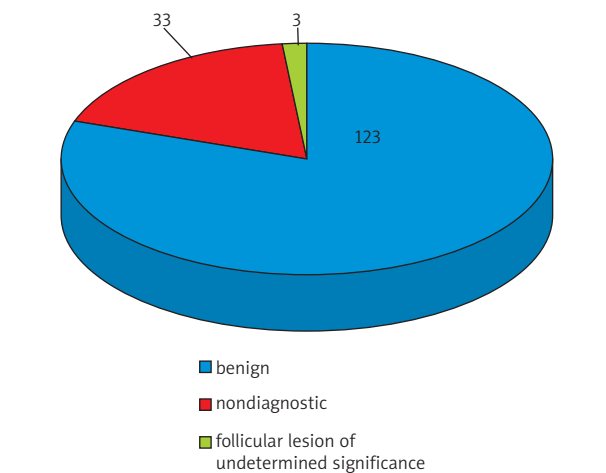


Fig. 2. Results of the second biopsy: nondiagnostic – 33 (20.75%), benign – 123 (77.36%), follicular lesion of undetermined significance – 3 (1.89%)

of ¹³¹I therapy had over a sixfold higher risk compared with patients without this factor (OR = 6.32). In the available literature, no influence of ¹³¹I therapy on nondiagnostic FNAB results rate has been reported. This phenomenon may result from radiation-induced cell degeneration and vascular damage associated with inflammation and fibrosis of the thyroid gland. Shih *et al.* described the histopathologic changes confirming atrophy and fibrosis of the thyroid gland following ¹³¹I exposure [29]. Due to the increasing

popularity of ^{131}I therapy we can expect the problem of repeatedly nondiagnostic results in subsequent FNAB in this group of patients to become more common.

The nondiagnostic results of subsequent biopsies pose a relevant clinical problem since the presence of malignancy cannot be excluded. According to the available reports, the frequency of malignancy among all N-FNABs was 1–4% [30] and among those N-FNABs that were subjected to surgical pathological examination it was 8–33% [21, 31–33]. Due to the high risk of a repeated nondiagnostic biopsy result on the one hand and an uncertain risk of malignancy in N-FNAB on the other, the question arises – should we repeat the biopsy once again, monitor the lesion, or refer the patient for surgery? Some authors [26, 34–35] propose attempting to obtain the diagnostic material, and if not possible – refer the patient for surgery, because it is the only way to exclude the presence of malignancy in the lesion. Coorough *et al.* in a retrospective study of 259 patients found that patients with nondiagnostic FNAs had a significantly higher rate of all types of thyroid cancer, compared with those with diagnostic FNAs – 12% vs. 5% [34]. Furthermore, Arpacı *et al.* proved that the risk of malignancy in patients who had 2 or more N-FNABs and finally underwent surgical resection was as high as 24%, although the study included only 75 patients [35]. In contrast, other researchers recommend conservative management [18, 36]. In the study by Hryhorczuk *et al.* 256 nodules with a nondiagnostic result of an initial biopsy received a repeated FNAB, surgical excision, or at least 24 months of follow-up, which enabled diagnosing 5 cancers (representing 2% of the population that received an initial N-FNAB) [18]. According to the authors these findings show that a nondiagnostic thyroid biopsy result should not be interpreted as suspicion of cancer [18]. Anderson *et al.* demonstrated that a repeated FNA following a nondiagnostic result of an initial FNA gave the likelihood of detecting malignancy as low as 0.6%; therefore, the authors suggested a clinical and US follow-up rather than a repeated FNA [36]. The diagnostic performance of ultrasound for initially nondiagnostic thyroid nodules has a sensitivity of 90% and specificity of 65% for predicting malignancy [37]. Other authors also emphasize the diagnostic value of ultrasound evaluation in this group of patients [38].

An alternative to a repeated fine-needle biopsy can be a core-needle biopsy (CNB). According to recent studies, ultrasound-guided CNB is safe and less likely to result in nondiagnostic results [39], with sensitivity and specificity of 94.6% and 100%, respectively, and it can also prevent unnecessary diagnostic surgery [40]. In contrast, reports on the needle lumen diameter affecting the diagnostic output of a fine-needle biopsy are inconsistent [41, 42]. A recently published meta-analysis that included eleven studies comparing diagnostic yield of FNAB and CNB showed significantly higher diagnostic effectiveness of CNB, also in case of nodules with a prior nondiagnostic result of FNAB [43]. According to the study, the probability of obtaining a nondiagnostic result using CNB is almost four times lower and may decrease the amount of unnecessary thyroidectomies [43].

Another method enhancing the efficiency rate of a thyroid FNAB is rapid on-site adequacy assessment (ROSAA, also known as on-site evaluation of adequacy – OSEA) of specimens by a cytopathologist and – in the case of inadequate material – immediate re-biopsy [44–47]. Simsek *et al.* in a prospective randomised study on 204 patients demonstrated that immediate on-site evaluation can significantly decrease the nondiagnostic rate of thyroid FNAB specimens compared with a regular biopsy – 2% vs. 15.7% [46]. Moreover, ROSAA seems to be a more effective method compared with performing at least 3 needle passes [47]. Ceresini *et al.*, in turn, obtained an impressive rate of 0.6% of nondiagnostic thyroid FNAB by combining ultrasound guidance, no-aspiration technique and on-site review of specimens [44].

In conclusion, according to the current study and available literature, the most rational approach towards repeatedly nondiagnostic nodules results seems to be a close clinical and US follow-up as well as considering indications for a repeated biopsy or surgical treatment in case of nodule growth or a change of ultrasonographic pattern detected during US surveillance. A history of ^{131}I therapy, which increases the risk of nondiagnostic FNAB result, should be an additional argument for a more conservative approach. Such a decision should be made individually in accordance with patient's preferences.

The authors declare no conflict of interest.

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