

ORIGINAL PAPER

The Value of Fine-Needle Aspiration Biopsy (FNAB) in Differential Diagnosis of Scintigraphic Cold Thyroid Nodule

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ABSTRACT

Introduction: Pathology of thyroid nodules is present in all ages and it is frequently encountered in clinical practice. Thyroid nodules do not represent a single disease, but they are the clinical manifestation of a wide range of different thyroid diseases. **Aim:** The objective of this study is to evaluate the frequency and localization of malignancy in solitary scintigraphic cold nodules, as well as the sensitivity, specificity and diagnostic accuracy of FNAB in comparison with histopathological findings. **Methods:** The study was included 49 patients with palpatory findings of the solitary nodule located in the both lobes or isthmus of thyroid gland. All subjects underwent the scintigraphy and FNAB, followed by a cytologic results that was compared to the final histopathological diagnosis, after surgery. **Results:** The study results show that the highest number of solitary nodules (81,6%) is localized in the lower pole of the both lobes of the thyroid gland. The cytologic results were benign 8 cases, malignant in 23 and indeterminate (follicular neoplasm) in 18 cases. The highest number of thyroid cancer is histopathologically confirmed in the patients with cytological diagnosis of follicular neoplasms, i.e. follicular cancer is found in 66.7% and papillary cancer is found in 33.3% of subjects. The most common cancer is papillary cancer found in 61,2%. Since the pathohistological diagnosis of all our patients responded to cancer, it was done indirect statistical evaluation of the diagnostic sensitivity of cytological method in the estimation of malignant thyroid lesion, which was 83,7%. **Conclusion:** FNAB is a highly sensitive method in the diagnostics of malignant thyroid lesions with the sensitivity $Se=83,7\%$. The highest number of thyroid cancer is histopathologically confirmed in the patients with cytological diagnosis of follicular neoplasm (66.7%). The highest number of patients had a cytological diagnosis of papillary cancer.

Keywords: solitary thyroid nodule, scintigraphy, Fine-needle aspiration biopsy-FNAB, papillary cancer, follicular cancer.

1. INTRODUCTION

Pathology of thyroid nodules is present in all ages and it is frequently encountered in clinical practice (1-10). Thyroid nodules do not represent a single disease, but they are the clinical manifestation of a wide range of different thyroid diseases (11-20). They are categorized as non-neoplastic nodules including hyperplastic and inflammatory nodules, or as neoplastic nodules that can be benign or malignant (21-27). Most of thyroid nodules are benign lesions, especially in the cases of multinodular goitre. A solitary nodule is an isolated palpable nodule, whose size is different from other thyroid parts, where the remaining tissue is normal or diffusely increased (4, 15).

Approximately 3/5 solitary nodules are follicular adenomas, 1/5 is a cyst, and 1/5 is thyroid cancer (15). The prevalence of malignant tumours in solitary nodules and in multinodular goitres is in the range of 13-20% and up to 13%, respectively (25).

The prevalence of thyroid nodules is higher in the countries with iodine deficiencies, where there is also endemic goitre (5, 26). In developed countries, e.g. in the USA, where iodine deficiency is adequately corrected by iodine prophylaxis, the prevalence of clinically manifested thyroid nodules in adult population is in the range from 4 to 7% (17, 20, 23). The incidence of clinically palpable goitre is 2 to 10 times more frequent in women than in men (25, 26).

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Scintigraphy is one of the most commonly used methods in the evaluation of thyroid nodules. The importance of scintigraphy is the identification of cold nodules since they are more frequently malignant in comparison to hot nodules. The incidence of malignancy in cold nodules varies from 5 to 15% and is higher in patients under 40 years of age (17, 27). Scintigraphic identification of cold nodule requires a FNAB, which is very important in the evaluation of thyroid nodules in selection of patients for surgical treatment (15, 19). Based on their results (4) show that the total sensitivity of the cytological method is (80%) and the specificity is 97.7%.

2. AIM

The objective of this study is to determine the frequency and localization of malignancy in solitary scintigraphic cold nodules, as well as the sensitivity, specificity and diagnostic accuracy of FNAC in the evaluation of solitary thyroid nodule in comparison to histopathological findings.

3. METHODS

The prospective study included 49 subjects treated in the Department for Thyroid Gland Diseases, Radiology and Nuclear Medicine Clinic. The subject population included 7 male subjects and 42 female subjects aged 15-79. Clinical examination, thyroid scintigraphy and FNAC were considered.

Clinical findings were based on medical history data, inspection and palpation of the thyroid gland and surrounding structures of the neck. Medical history data included data on age, sex, time of occurrence and change in nodule size. The inspection and palpation of thyroid gland were performed with the usual procedure, where a special attention was drawn to a number and size of nodules, their consistency and movability. A finding of solitary cold nodule located in the right or left lobe and in the isthmus of thyroid gland was considered a positive palpatory finding.

Thyroid scintigraphy was performed 30 minutes after IV administration of $3\text{-}5\text{mCi}$ technetium pertechnetate. Scintigraphic imaging was performed with GEMillennium gamma camera with parallel-hole collimator LEHR. The imaging lasted 5-15 minutes, depending on functional activity of thyroid gland. Scintigraphic cold nodules are defined as nodules that poorly accumulate or do not accumulate any radioactivity in comparison to the remaining part of the thyroid gland. Scintigraphic malignant lesion is defined as cold nodule with irregular contours in relation to the surrounding tissue, and a scintigraphic finding of extrathyroidal accumulation of 99mTc pertechnetate. Ultrasound guided FNAB is performed with 21-22 gauge needles attached to 10-20ml plastic syringes, by the "free-hand technique", without a puncture adapter (21) and with previous disinfection of the neck skin with ethanol. Every punctured nodule in the thyroid gland is localized accurately (in relation to a scintigraphic finding), to compare it with a cytological finding.

A needle was constantly in the ultrasound beam and it was obliquely introduced into the thyroid gland before the middle part of the probe. When a needle tip reaches a certain pathological change, cytological material is aspirated. Aspiration was

performed with syringes of 10-20ml. Immediately after punctures, the aspirates were smeared on slides, wet fixed (in 95% ethanol), left to dry at the room temperature (approximately 30 minutes to 1 hour), and stained with the Papanicolaou method. After that, cytologic specimens were microscopically analyzed in the Institute of Pathological Anatomy, University Clinical Centre in Tuzla. Based on the cytological analyses, the findings were categorized into three categories: benign, suspected malignant, and malignant lesions. The findings were interpreted according to the DeMay's diagnostic protocol (11).

A benign lesion was represented by a cytological finding of the colloid and cellular nodule; A suspected malignant lesion was represented by a cytological finding of the follicular neoplasm; A malignant lesion was represented by cytological findings which, according to cytomorphic criteria, indicate to the malignant tumour of the thyroid gland. A surgery was performed in the Clinic of Otorhinolaryngology. After a surgery, material was sent to histopathological analysis done by the Institute of Pathology, University Clinical Centre in Tuzla. Slices were taken from a nodule for microscopic analysis, fixed in formaldehyde, embedded in paraffin, and then cut to the thickness of 5 microns. After that, the slices were stained with the standard hematoxylin and eosin (HE) method.

According to the World Health Organization classification (1, 2), histopathological findings were divided into three groups: the first group included malignant thyroid tumours (follicular, papillary, medullary, and anaplastic cancer); the second group included benign thyroid tumours (follicular, trabecular, non-follicular, macrofollicular, and oxyphilic adenoma); and the third group included tumour-like lesions (non-neoplastic lesions: diffuse hyperplasia, nodular goitre, Basedow's disease, endemic goitre, cystic lesions, ectopic thyroid tissues and chronic thyroiditis). Benign lesions will be represented by histopathological findings of colloid thyroid nodules.

Patients with clinical findings of diffuse, multinodular goitre, functional disorders of thyroid gland and patients without complete medical documentation (including clinical findings of scintigraphic cold nodule and cytological puncture findings) were excluded from the study.

Statistical evaluation of data was performed with the descriptive statistical methods (central tendency measures, dispersion measures, and graphs), as well as the t -test and χ^2 test for calculation of significance of the tested differences, where differences at the level of $p < 0.05$ would be statistically significant. Parameter (χ^2 test) and non-parameter tests of significance (z and t -test) were used for testing the statistical significance of differences among the samples. The statistical significance of the differences in quantitative sizes was tested with the t -test, and the qualitative samples were tested with the hi -square test (χ^2). Tests of diagnostic sensitivity and specificity, were used for the evaluation of values of the applied tests.

4. RESULTS

The prospective study to evaluate the presence of clinically palpable nodule of thyroid gland, conducted in the Department for Thyroid Gland Diseases, Radiology and Nuclear Medicine Clinic, included a total of 49 subjects, of which 7 were male subjects (14.3%) and 42 were female subjects (85.7%). The average age of the complete sample was 53 years and within the range of 15-79 years of age.

Clinical examination and scintigraphy showed that the highest number of thyroid nodules (81,6%) is localised in the lower pole of the both lobes. The data are shown in Table 1.

FNAC was performed in all subjects, and the highest number of subjects, i.e. 22 subjects (44.9%) had a cytological diagnosis of papillary cancer. The data are shown in Table 2.

After the operative therapy in all subjects, histopathological diagnoses indicated that the most common cancer was papillary cancer, found in 30 subjects or 61.2%, while follicular cancer was found in 19 subjects or 38.8%.

The study compared the results of cytological and histopathological diagnoses, where the highest number of the thyroid cancer was histopathologically confirmed in the subjects with cytological diagnosis of the follicular neoplasm, i.e. with the histopathological method, the follicular cancer was found in 66.7% of patient, and the papillary thyroid cancer was found in 33.3% of patient. The data are shown in Table 3.

Since the histopathological method of all our subjects corresponded to the thyroid cancer, the indirect statistical evaluation of diagnostic sensitivity of cytological analysis (FNAB) was performed as the analysis of malignant vs. benign categories. Based on the numeric values, only the sensitivity of the cytological method was calculated in the evaluation of malignant thyroid lesions, and it was 83.7%.

In predicting the occurrence of papillary cancer, FNAB shows the sensitivity of 66.7%, the specificity of 89.5%, the positive predictive value (PPV) of 90.9%, and the negative predictive value of 63%.

The correlation of localization of thyroid nodules with palpatory and scintigraphic methods (Figures 1 and 2) with cytological diagnosis showed that the highest number of the thyroid cancer in our subjects was localized in the lower pole of the both thyroid lobes, in total 40% or 16 subjects, while the lowest number of cancer was found in the middle third of the lobes, in total one or 2%. The data are shown in Table 4.

The correlation of localization of thyroid nodules with palpatory and scintigraphic methods with histopathological diagnosis showed that the highest number of the thyroid cancer confirmed by the histopathological findings, was localized in the lower pole of the both lobes in 40 subjects or 81.64%.

In the localization of the upper pole, the histopathological findings confirmed the thyroid cancer in 5 subjects or 10.20%; in the localization of the isthmus, the thyroid cancer was confirmed in 3 subjects or 6.12%; and the lowest number of the thyroid cancer was found in the localization of the middle third of the lobes in one subject or 2.04%. The data are shown in Table 5.

5. DISCUSSION

Thyroid nodules are frequently present in all ages. According to the general clinical judgment, solitary thyroid nodules bear a higher risk of cancer (6, 10). Palpable thyroid nodules are present in approximately 10% of the population, and their malignancy percentage is in the range

Nodule localization	N	%
Lower pole	40	81.6
Upper pole	5	10.2
Isthmus	3	6.1
Middle third	1	2.0

Table 1. Localization of thyroid nodules by palpatory method and scintigraphy

Cytological method	N
Cellular nodule	2
Follicular neoplasm	18
Colloid nodule	6
Medullary cancer	1
Papillary cancer	22

Table 2. Cytological findings of the subjects

		Histopathological findings	
		Follicular cancer	
		N	%
FNAC	Cellular nodule	0	.0%
	Follicular neoplasm	12	66.7%
	Colloid nodule	4	66.7%
	Medullary cancer	1	100.0%
	Papillary cancer	2	9.1%

Table 3. Comparison of cytological and histopathological methods

		FNAC				
		Cellular nodule	Follicular neoplasm	Colloid nodule	Medullary cancer	Papillary cancer
Scintigraphy	Lower pole	N 1	18	5	0	16
		% 2.5%	45.0%	12.5%	.0%	40.0%
	Upper pole	N 0	0	1	1	3
		% .0%	.0%	20.0%	20.0%	60.0%
	Isthmus	N 0	0	0	0	3
		% .0%	.0%	.0%	.0%	100.0%
Middle third	N 1	0	0	0	0	
	% 100.0%	.0%	.0%	.0%	.0%	
Total	N 2	18	6	1	22	
	% 4.1%	36.7%	12.2%	2.0%	44.9%	

Table 4. The correlation of localization of thyroid nodules with palpatory and scintigraphic methods with cytological diagnosis.

of 5-10% in the iodine-sufficient areas (26). Lansford observes that if a thyroid nodule is present, the risk of malignancy is two times higher in men than in women (16). Most authors report that the cancer incidence ranges from 3:1 to 13:1 in favor of females in differentiated thyroid tumours (25). In the study conducted on 184 subjects in our region, Čičkušić reports the ratio of females and males of 2.7:1 (i.e. 72.8%: 27.2%) (28). In the study conducted on 112 patients, Radović et al. analyzed the ratio of the cytological puncture findings and the scintigraphic cold nodule findings, and the derived ratio of females and males was 13:1, with equal distribution of malignant findings in both sexes (24). The results of this study also indicate that the incidence of nodular thyroid disease is

		Histopathological findings		
			Follicular cancer	Papillary cancer
Scintigraphy	Lower pole	N	17	23
		%	42.5%	57.5%
	Upper pole	N	1	4
		%	20.0%	80.0%
	Isthmus	N	1	2
		%	33.3%	66.7%
	Middle third	N	0	1
		%	.0%	100.0%
	Total	N	19	30
		%	38.8%	61.2%

Table 5. The correlation of localization of thyroid nodules with palpatory and scintigraphic methods with histopathological diagnosis.

higher in women in comparison to men (85.7%: 14.3%, i.e. 6:1). The youngest subject in this study was a male patient aged 15 with a histopathological diagnosis of papillary cancer, and the oldest subject was a female patient aged 79. This is also confirmed by Lansford's study, where the most common malignant thyroid lesion refers to solitary thyroid nodules in patients younger than 20 years and older than 70 years, which is also confirmed by the results of this study (16). The incidence of malignancy in the scintigraphic cold nodules varies in studies and it ranges from 5 to 20% (3, 13, 22). This study analyzed only the scintigraphic cold nodules, and the obtained results indicate that all cases of thyroid malignancy were found in the scintigraphic cold nodules, confirming the importance of the thyroid scintigraphy in the identification of cold nodules, which are more frequently malignant in relation to hot nodules. Scintigraphic findings correlate to palpatory findings in the evaluation of the number and size of nodules in the nodular thyroid disease (1, 8). These reports are confirmed by this study whose obtained results indicate to 100% coincidence of these two methods. This study, as well as the palpatory and scintigraphic methods show that the highest number of the thyroid nodules is located in the lower poles of the both lobes in 40 subjects or 81.6%. Ultrasound guidance FNAB is the gold standard in the diagnostic evaluation of nodules larger than 1cm (16, 24). According to the reference data, the sensitivity of this method ranges from 50 to 95%, the specificity is 72-100%, the diagnostic accuracy is in the range of 85-95%, the false positive results range from 0 to 25%, and the false negative results range from 0.3 to 50% (7, 13, 18). On the other hand, the sensitivity of the clinical method in the evaluation of malignant thyroid lesions is 61.3%, the specificity is 57.1%, and the diagnostic accuracy is 60% (28). In this study, the highest number of the subjects includes cytomorphologic findings indicative of the thyroid cancer found in 22 subject (44.8%); cytological findings of the follicular neoplasm are found in 18 subjects (36.7%); and the lowest number of the subjects includes cytological findings of the colloid goitre in 6 subjects (12.2%) and the cellular nodule in 2 subjects (4.1%). The thyroid cancer was confirmed in all subjects by the histopathology. The most common cancer in our group was papillary cancer, found in 30 subjects or 61.2%, while follicular cancer was

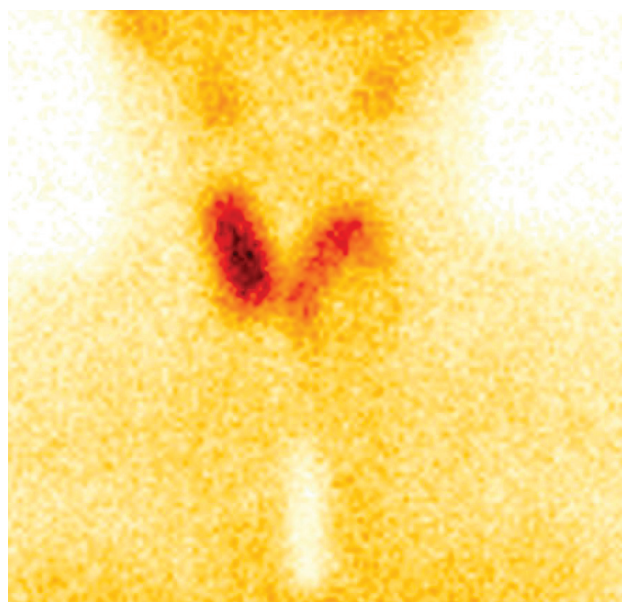


Figure 1. Thyroid nodules examined scintigraphy - cold thyroid nodules

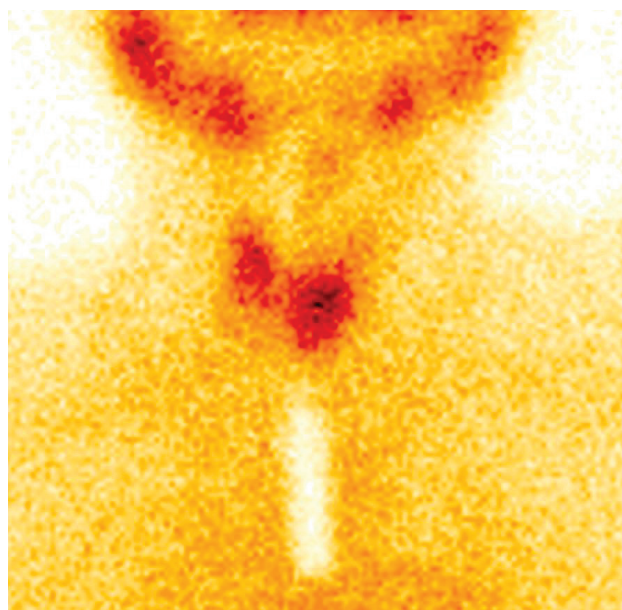


Figure 2. Thyroid nodules examined scintigraphy - cold thyroid nodules

found in 19 subjects or 38.8%. The highest number of thyroid cancer is histopathologically confirmed in the subjects with cytological diagnosis of follicular neoplasm, i.e. with the histopathological method, follicular cancer is found in 66.7% of subjects, and papillary cancer is found in 33.3% of subjects. According to the USA reference, the average age of patients with the differentiated thyroid tumours is in the range of 45-50 years (9). This is also confirmed by this study, where the average age of the subjects is 53 years. Differentiated cancers represent approximately 98% of all thyroid cancers in the USA (9). The same percentage share of differentiated cancers (follicular and papillary) of the total number of the malignant thyroid tumours was also obtained in this study. Caron and Clark report that papillary cancer includes 70-80% of all differentiated thyroid cancer in the iodine-sufficient regions (4). Since our region is iodine-deficient, the percentage share of follicular cancer is somewhat higher than in the studies reporting the sufficient iodine intake,

and it is 38.8% (or in 19 subjects). The percentage share of papillary cancer of 60% in this study is closer to the European reference data.

6. CONCLUSION

Ultra sound guided FNAB a highly sensitive method in the diagnostics of malignant thyroid lesions with the sensitivity $Se=83.7\%$. Based on the results of this study, it can be concluded that the clinical findings of the thyroid nodules require a special attention, as well as the implementation of additional tests, including scintigraphy and FNAB as the first methods in the diagnostic protocol. Furthermore, FNAB is a feasible, highly sensitive and specific method with a low cost for evaluation of the scintigraphic cold solitary nodules, and it can be partly considered as the sophisticated screening test for the selection of a large number of patients with thyroid nodules into a small group that will require a surgery, because it is the only method to obtain direct and specific information, i.e. it allows an early diagnosis of the solitary scintigraphic cold nodule

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