

## Cervical ultrasound assessment of thyroid nodules at risk of malignancy: single-center experience

O.C. NEAGOE<sup>1</sup>, M. IONICA<sup>1</sup>, O. MAZILU<sup>1</sup>

**SUMMARY: Cervical ultrasound assessment of thyroid nodules at risk of malignancy: single-center experience.**

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*Aim. The increasing diagnosis of thyroid nodules makes proper assessment of their nature and course of treatment essential, considering that thyroidectomy may be unnecessary and only contribute to higher healthcare system costs. Although criteria have been proposed for the stratification of these patients according to risk by use of cervical ultrasound and fine needle aspiration biopsy (FNAB), not all medical units may be equipped or have access to trained medical professionals to perform FNAB. The aim of this study was to show that cervical ultrasound may be sufficient for the evaluation of thyroid nodules in the*

*treatment decision-making process.*

*Patients and methods. 206 patients with single thyroid nodules and nodular goiter were assessed through cervical ultrasound and FNAB for the correlation between pretreatment classification and final diagnosis on histological examination.*

*Results. 26.5% of single nodes proved malignant on paraffin studies, as compared to only 14% of nodular goiters. FNAB recorded a sensibility of 33.3%, specificity of 93.3%, false-negative rate of 50% and false-positive rate of 12.5%, whereas cervical ultrasound recorded a sensibility of 92.3%, specificity of 75.3%, false-negative rate of 2.8% and false-positive rate of 48.9%.*

*Conclusion. Cervical ultrasound evaluation is a reliable method in the preoperative diagnosis of thyroid cancer patients.*

KEY WORDS: Thyroid - Ultrasound - Cancer - Fine needle aspiration.

### Introduction

Although thyroid cancer represents less than 1% of all cancers (1), an increasing incidence has been recorded worldwide (2-4), becoming an issue for healthcare systems (5). Prevalence of thyroid nodules diagnosis has increased as a result of higher quality imaging equipment and more efficient screening methods (6).

The proper management of patients with thyroid nodules has long been debated in the international literature, especially when malignancy is suspected. Whether surgical treatment should be recommended and to what extent, depends on several factors such as clinical symptoms, sonographic appearance and cytology findings on fine needle aspiration biopsy (FNAB) (7, 8). Unfortu-

nately, this method may not be largely available in certain countries, or medical professionals from the Pathology Departments may not have sufficient training or experience with this type of examination. Another issue is represented by the false-negative results of FNAB, reported at up to 48% (9). This poses the problem of identifying an easy access and reliable evaluation method that will allow for a correct assessment of the risk of malignancy in patients with thyroid nodules. The American Thyroid Association (ATA) has recommended several imaging features that allow risk stratification and further diagnostic investigation (7).

The aim of our study is to evaluate the use of cervical ultrasound in the assessment of thyroid nodules. We have followed the correlation between preoperative imaging aspects, preoperative results of FNAB and final paraffin histopathological findings.

### Patients and methods

In this retrospective study performed at the Emergency Clinical County Hospital we have selected 206 pa-

First Department of Surgery, Second Discipline of Surgical Semiology and Medical and Surgical Oncology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

Corresponding author: Mihaela Ionica, e-mail: dr.mihaela.ionica@gmail.com

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tients admitted to our clinic for thyroid nodules or nodular goiters for surgical treatment, over a six year period, between January 2011 and December 2016. Approval for this study was obtained from the Ethical Committee of the hospital and the research was performed in accordance with the World Medical Association Declaration of Helsinki, revised in 2000, Edinburgh.

Patient inclusion criteria comprised the diagnosis of nodular goiter or single thyroid nodule, with ultrasound characteristics that allowed them to be included in the high, intermediate or low suspicion for malignancy categories as described by the ATA. Patients with thyroid hyperfunction, demonstrated by a low value of serum TSH, patients presenting with clinical lymphadenopathy, as well as patients with sonographic appearance classified as very low suspicion for malignancy and benign were excluded from the present study. An exception was a single patient with Graves Basedow with nodular goitre that after surgery was diagnosed with papillary carcinoma. Data was extracted from patient private medical records and hospital database and included demographic information, diagnosis at admission, cervical ultrasound characteristics, surgical procedure type, pathology report, that comprised several FNAB and all paraffin biopsies.

In this study the patient series was divided according to the ultrasound characteristics, as proposed by ATA (7), into three groups, high, intermediate and low suspicion of malignancy. Several patients have been evaluated also by FNAB and all patients underwent surgery with paraffin examination being performed on all surgical specimens. Surgical treatment was performed in all patients on recommendation of an endocrinologist, criteria for surgery comprised of patients with high or intermediate risk of malignancy ultrasound appearance and patients from any of the risk groups that presented with compressive symptomatology.

Statistical analysis was performed using SPSS software for Windows version 21 (Armonk, NY: IBM Corp.). Descriptive analysis of continuous data was presented as mean range, minimum and maximum values. Pearson's chi square test, student's t test and Fisher's exact test were used for the evaluation of correlation between ultrasound appearance, FNAB cytology results and final diagnosis on paraffin blocks. A p value of <0.05 was considered statistically significant.

## Results

The study series comprised 206 patients, among which 49 (23.8%) presented with a single thyroid nodule (STN) and 157 (76.2%) with nodular goiter (NG). The female/male ratio was 11.9:1, with 190 female patients (92.2%) and 16 male patients (7.8%). Mean age for the whole group was 49.3 years, with a minimum of 18 years and a maximum of 85 years. Mean age for female patients was of 48.9 years, while for male patients average age was of 54 years. Differences in age average were also seen when comparing mean age for female and male patients with SN and NG as shown in Table 1.

Total thyroidectomy was performed in 57 patients, while total lobectomy was performed in 86 patients and subtotal lobectomy was done in 55 patients. Total thyroidectomy with radical neck lymphadenectomy was performed in a total of 21 patients, eight of which were done as first surgical approach and 13 as a second surgery following a total lobectomy. The choice between the type of surgery was determined by the grade of suspicion, the presence of a single nodule, the clinical symptomatology, in several cases by the FNAB results and nonetheless the patients wish.

Paraffin postoperative hystopathological reports showed 171 patients with benign thyroid lesions and 35 patients with thyroid cancer, among which 25 with papillary thyroid carcinoma (PTC), six patients with follicular thyroid carcinoma (FTC), three with Hürtle cell carcinoma and one medullary carcinoma. Among these 32 were female patients (91.4%), with only three male patients (8.6%). Mean age for the two groups was statistically significant ( $P=0.04$ ) with a mean age of 56.1 years for female patients and 63.7 years for male patients.

From the whole series 40 patients have been evaluated through FNAB. This examination was performed only in patients evaluated with high or intermediate risk for malignancy ultrasound appearance. FNAB revealed, according to the Bethesda classification, six patients with cytologies suspicious for malignancy, four patients with atypia of undetermined significance or follicular lesion of undetermined significance, two patients with follicular neoplasm or suspicious for a follicular neoplasm and 28 patients with benign cytological aspects. For these patients ultrasound appearance was of high suspicion for malignancy in 24 cases and of intermediate risk in 16

TABLE 1 - AGE AND SEX DISTRIBUTION FOR WHOLE SERIES AND ACCORDING TO THYROID LESION TYPE.

	Female (No/Age)		Male (No/Age)		Total No/Age (mean)	
Whole series	190	48.9	16	54.1	206	49.3
Patients with single thyroid nodule	46	47.4	3	46	49	47.3
Patients with nodular goiter	144	51.6	13	57.8	157	51.9

TABLE 2 - PATIENT DISTRIBUTION ACCORDING TO FNAB RESULTS (\* FTC INCLUDES CASES OF HÜRTLE CELL CARCINOMA).

Paraffin hystopathological report \ FNAB cytology report	Suspicious for malignancy	Atypia of undetermined significance or follicular lesion of undetermined significance	Follicular neoplasm or suspicious for a follicular neoplasm	Benign
PTC	3	2	-	9
FTC*	1	-	1	5
Medullary carcinoma	1	-	-	-
Benign	1	2	1	14
	<b>Sensibility</b>	<b>33.3%</b>		
	<b>Specificity</b>	<b>93.3%</b>		
	<b>False +</b>	<b>12.5%</b>		
	<b>False -</b>	<b>50%</b>		
	<b>PPV</b>	<b>87.5%</b>		
	<b>NPV</b>	<b>50%</b>		

cases. Out of the eight cytologies indicating malignancy seven were confirmed postoperatively with only one false-positive. Among the 28 benign cytologies half were malignant on paraffin hystopathological analysis, resulting in 14 false-negatives. The sensitivity of FNAB was 33.3%, with a specificity of 93.3% with a false-positive and false-negative rate of 12.5%, respectively 50%. Positive and negative predictive values were of 87.5% and 50% (Table 2).

Cervical ultrasound examination was performed on all patients. According to the ATA criteria patients were grouped as follows: high suspicion for malignancy 47 patients, intermediate suspicion for malignancy 87 patients and low suspicion for malignancy 72 patients. Final postoperative paraffin examination respectively revealed 24, 9 and 2 patients with malignant lesions corresponding to the high, intermediate and low suspicion for malignancy groups. Cervical ultrasound sensitivity and specificity of identifying thyroid cancer were 92.3% and 75.3%, with a false-positive and false-negative rate of 48.9% and 2.8%. Positive and negative predictive values were of 51.1% and 97.2% (Table 3).

A total of two incidentalomas were diagnosed on final analysis of the series, both in patients with low grade ultrasound suspicion for malignancy. In our series there was a small group of three patients, that although presenting low grade ultrasound suspicion of malignancy in thyroid lesions, requested total thyroidectomy. Among these final paraffin examination revealed an incidentaloma (papillary carcinoma), with an incidence of 33.3%. The second incidentaloma was found following

total thyroidectomy performed in a patient know with Basedow-Graves disease, that associated a nodular goiter, surgical treatment being performed at the recommendation of the endocrinologist.

The type of initial lesion observed on ultrasound, SN or NG, was seen in our series to have an uneven rate of postoperative hystopathological thyroid cancer. Out of the total number of patients with SN 26.5% were diagnosed with a malignant thyroid lesion, as compared to patients with NG that recorded an incidence of only 14% (P=0.02). On FNAB analysis 26.1% of patients with SN were found to have cytological aspects suggestive for malignancies, whereas for patients with NG FNAB was positive for malignancy in only 7.4% of cases (P=0.01).

Over the period of this study an increase in the number of thyroid cancer patients per year has been recorded. An incidence of 12.8% has been noted for 2011, in 2012 a slight decrease has been seen with an incidence of 11.5%, followed in 2013 and 2014 by an incidence of 17.4% and respectively 19.5%. The highest values for incidence have been recorded in 2015 and 2016 reaching up to 21.4%, respectively 20% of the studied population.

## Discussions and conclusion

Although thyroid cancer is the most common type of neoplasia of the endocrine system, it represents less than 1% of all cancers (1). Over past years an increase in thyroid cancer incidence has been recorded

TABLE 3 - PATIENT DISTRIBUTION ACCORDING TO US REPORT (\* FTC INCLUDES CASES OF HÜRTLE CELL CARCINOMA).

Paraffin histopathological report \ US report	High suspicion for malignancy	Intermediate suspicion for malignancy	Low suspicion for malignancy
PTC	20	4	1
FTC*	3	5	1
Medullary carcinoma	1	-	-
Benign	23	78	70
<b>Sensibility</b>	<b>92.3%</b>		
<b>Specificity</b>	<b>75.3%</b>		
<b>False +</b>	<b>48.9%</b>		
<b>False -</b>	<b>2.8%</b>		
<b>PPV</b>	<b>51.1%</b>		
<b>NPV</b>	<b>97.2%</b>		

worldwide (2-4). This growing incidence has been attributed in part to more efficient screening protocols for thyroid pathology and secondary to incidental findings on imaging studies for other pathologies (2, 5). Thyroid nodule diagnostic prevalence has increased, depending on the study population, by 19-68% with a consequent increase in thyroid cancer diagnosis from 5 to 15% (6). In this series we have observed an increase by almost 8% in thyroid cancer incidence, from 12.8% in 2011 to 20% in 2016. Even in this context thyroid cancer related mortality has remained stable (2, 7). From a histological point of view this raise in thyroid cancer cases is reflected by an increased incidence of PTC, with a constant incidence of other histological types (2, 7). In this study PTC represented 71.4% of all diagnosed thyroid cancers.

The importance of establishing a reliable preoperative diagnosis in patients with thyroid lesions with regard to the presence of thyroid cancer, results from the fact that this will allow for a proper surgical treatment, avoiding thus re-interventions in the cervical region, which would significantly increase the rate of complications and implicitly prolong hospital stay. Choosing the proper surgical conduct has as well an important role in avoiding unnecessary surgery, which may lead to an increase in associated healthcare costs (3, 4).

Especially for middle income and developing countries, medical costs are a major problem, the raise in thyroid cancer incidence increasing the burden on the healthcare system by requiring more financial support (5, 7, 8). PTC being the most common histological type diagnosed, associated with the most favorable prognosis, as well as overall low mortality rates have led to a more con-

servative approach regarding the treatment of thyroid cancer. Oda et al. suggest that both patients and the healthcare system may benefit more from an active surveillance approach rather than from immediate surgical treatment, showing that for low-risk papillary microcarcinoma patients the cost increased by up to 6.5 times if immediate surgery was the initial choice of treatment (5). This approach is somewhat debatable, considering that an immediate treatment, especially in such early stages of disease, may exempt the patient from more ample surgical procedures, complications, and increase in morbidity, that would also reflect on healthcare costs.

Correctly treated, thyroid cancer is in most cases curable in the early stages (2, 3). In the case of loco-regional extension or lymphatic or systemic dissemination occurring as the result of therapeutic neglect, perioperative mortality and especially morbidity increase exponentially. Thus reducing the rate of curability and transforming this disease just in a manageable one regarding recurrent complications.

Therefore proper pretreatment assessment may lead to a more efficient management of costs without impacting patient treatment quality, survival and quality of life.

Cervical ultrasound and FNAB are the two main investigations recommended for the evaluation of thyroid nodules (7, 8). The Bethesda classification has offered the possibility of stratifying risk of cancer by offering uniform diagnostic criteria (10). The American Thyroid Association recommends FNAB evaluation even for highly suspicious nodules on cervical ultrasound examination, to properly assess patients and help in the decision-making process, avoiding for selected patients



surgical treatment and its subsequent morbidity and financial burden (7). In a single center study, Medici et al. (11) proposed that after an initial benign cytology patients could be reevaluated through FNAB after an interval of three years, without affecting patient safety or increasing mortality, implying a lowering of associated medical costs (11).

FNAB represents a cheap, easy to perform, minimally invasive, with little risk method of investigation that should allow for a better evaluation of thyroid nodules. FNAB has been supported as a highly useful investigation, with a sensitivity and specificity of up to 100% (12, 13), but numerous studies highlight several discrepancies between cytology results and final histological examination, with an increased rate of false-negative varying between 6.7% and 48% (9, 14-17). In this study we found that although FNAB has a very high specificity of 93.3%, it has a sensitivity of only 33.3%, with false-negative results in half the patients. These results suggest that active monitorization through FNAB, as proposed by some studies (11), may delay the diagnosis of thyroid cancer in a significant number of patients.

Not only false-negative results may adversely impact correct patient management but also difference in histological type reported on cytology readings and final paraffin examination, as shown by Janczak et al. (9). Considering the more conservative treatment approach tendency, such discrepancies in diagnosis may prove to be problematic due to the expected evolutions of different histological types of thyroid cancer, leading to an improper treatment. According to the results of this study, such a conservative approach, based on a method with false-negative results in 50% of cases, does not constitute an ideal attitude for the fundament of a proper therapeutic protocol.

Cervical ultrasonography is a mandatory evaluation tool for all patients with thyroid nodules, useful in both diagnostic and follow-up procedures. Compared to FNAB, which also requires ultrasound guidance, ultrasound is non-invasive and cheaper. The ATA has outlined five sonographic patterns that are suggestive of the risk of malignancy: high, intermediate, low, very low suspicion of malignancy and benign. The most common features suggestive of malignancy comprise of solid nodules with microcalcifications, rim calcifications with extrusive soft tissue component, irregular margins and evidence of extrathyroidal extension. Hypoechoigenity and intranodular hypervascularity are considered less specific criteria for the presence of malignancy. Cystic nodules are generally considered to be benign, but care must be taken as a small percentage proves to be malignant on histology studies. Shape may also be an indicator of thyroid cancer, nodules taller than wide measured on transverse view showing an increased risk of malignancy (7, 8). These international recommendations provide general

guidelines, that do not substitute good clinical judgment and that are continuously adapted in the light of new research. Risk of malignancy in the case of high suspicious ultrasound lesions has been estimated at more than 70-90%, whereas for intermediate and low suspicion lesions the risk is considered to be 10-20%, respectively 5-10% (7). In our series cervical ultrasound has shown a very high sensitivity of 92.3%, with a relatively high specificity of 75.3%. False-positive and false-negative rates were 48.9% and respectively 2.8%, whereas positive and negative predictive values were seen to be 51.1% and 97.2%.

In our experience, FNAB are not largely available to all medical facilities due to a lack in either the corresponding equipment or experienced medical professionals, or both. In choosing the best approach for patients with thyroid lesions, the low sensitivity and the high rate of false-negatives of FNAB seen in our series, has led us to rely more on the ultrasound characteristics.

On the whole, ultrasound, according to the results of this study, has proven to be the optimal method for establishing major suspicion of thyroid cancer, associating a low rate of false-negative results. In almost 50% of cases results are false-positive, implying that a high percentage of patients undergo radical surgeries for benign pathologies. One must not neglect however that in some of these cases the surgical indication was given also by loco-regional compressive phenomena, which on their own would have represented a reason for an extensive surgery. From an oncological standpoint cervical ultrasound proves its efficiency in the possibility of an initial radical surgical approach of thyroid cancer. As for FNAB, although the specificity is high, a 50% false-negative results and a low sensibility, make this diagnostic method unreliable from the surgical approach of malignant diseases.

In medical centers with an increased experience of performing FNAB, it is possible that the correlation of FNAB and cervical ultrasound may optimize the diagnostic procedure, by reducing the false-positive rate of ultrasound evaluation and the false-negative rate of FNAB. Based on the results obtained from this study we suggest that proper preoperative diagnosis of malignant thyroid lesions may be improved by correlating several clinical and paraclinical factors, such as gender, females showing a net predominance (91.4%); age - lower mean values for female than male patients and type of thyroid lesion - SN being diagnosed as thyroid cancer in over a quarter of cases.

The weakness of our study lies in the relatively small sample of patients that have undergone FNAB and the corresponding correlation between cytology and final histology report, as well as the correlation to ultrasound appearance. This highlights the need for further research on the proper interpretation of these exploration

methods and a more extensive and through preoperative investigation of patients presenting with thyroid nodules or goiters.

In conclusion, it is our opinion that ultrasound evaluation of thyroid nodules is a reliable and useful dia-

gnostic method, with a high sensitivity and low false-negative rates, which may prove sufficient in the management of these patients, especially for centers with low experience or limited access to fine needle aspiration biopsies.

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