Preoperative Evaluation of Solitary Thyroid Nodule in Patients with Ultrasound and Fine-Needle Aspiration Biopsy

**INTRODUCTION**

Thyroid nodules (TNs) are a common medical problem. Prevalence of TNs found by palpation at neck examination in patients with or without suspected thyroid disease is 3–8%, while prevalence of non-palpable thyroid nodules (i.e., <1 cm in diameter) detected by thyroid ultrasonography in the general population is 20–76% \(^{1,2}\). In addition, in about 50% of patients with a clinically palpable solitary nodule one or more additional non-palpable thyroid nodules may be found by thyroid ultrasonography, or detected incidentally by imaging studies performed for various reasons \(^3\).

Large thyroid nodules may cause local compressive symptoms or may be accompanied with the symptoms and signs of hyperthyroidism. However, TNs are often asymptomatic. Thus non-palpable TNs are frequently detected incidentally during physical or radiological examination. However, given that a risk of thyroid malignancy is 5–13% all thyroid nodules need to be clinically evaluated. High-resolution thyroid ultrasound (US) has enhanced evaluation of nodular thyroid disease. It is found that microcalcifications are associated with an increased risk of thyroid gland malignancy. Nonetheless, none of these US findings is diagnostic, and fine-needle aspiration biopsy (FNAB) remains the cornerstone of thyroid cancer diagnosis. Which nodules exactly should be targeted for FNAB remains controversial. According to American Thyroid Association (ATA) guidelines, FNAB should be routinely performed for all the thyroid nodules 10 mm or greater in diameter. Guidelines of the Society of Radiologists in Ultrasound (SRU) recommend FNAB when: TNs are 10 mm or greater in diameter only when microcalcifications are present; TNs are 15 mm or greater in diameter if completely or predominantly solid or if coarse calcifications are present; and TNs are 20 mm or greater if predominantly cystic with a solid component. Based on the American Association of Clinical
Endocrinologists (AACE) guidelines FNAB should be performed on all hypoechoic nodules 10 mm or greater with one or more of the following US characteristics: irregular margins, chaotic intranodular vascular spots, a more-tall-than-wide shape, and microcalcifications. Recommendations of the National Cooperative Cancer Network Thyroid Carcinoma Clinical Practice Guidelines are similar to AACE guidelines ⁸. These guidelines’ differences partially reflect disagreement in estimating the magnitude of two primary risks: the risk of delaying appropriate surgical treatment when thyroid cancer is present and the risk of undergoing hemithyroidectomy/isthmusectomy for a benign, asymptomatic thyroid nodule.

Thus, the approach to small (<10mm) thyroid nodules could vary, depending on the guidelines.

Within the last ten years Serbia recorded a doubled number of thyroid cancer patients. In a large number of patients more and more malignant and aggressive forms of this carcinoma were diagnosed ⁹. It is difficult to say is the increase of patients with this type of carcinoma the consequence of the Chernobyl disaster of the high burden of stress lasting already two decades (due to war and disintegration of Yugoslavia, hyperinflation and sinking of local currency, depleted uranium radiation resulting from NATO bombings).

**OBJECTIVE**

The aim of this study is to find how much ultrasound alone and how much ultrasound jointly with FNAB, can differentiate benign from malignant nodules u in our working conditions.

**PATIENTS AND METHODS**

A prospective study was conducted at the Department of Endocrine Surgery, Clinical Center Belgrade, in four-year period, in accordance with Good Clinical Practice and Declaration of Helsinki. To be eligible to participate in the study, patients had to be at least 18 years old and the patients were referred for ultrasound evaluation of thyroid nodules if: their ambulatory physician found neck lumps by palpation, patients requested further examination due to impression of neck swelling, if they were treated due to hyper or hypothyroidism, and if they had a genetic predisposition.

The exclusion criteria were: history of neck irradiation, cervical lymphadenopathy, patients who underwent surgery and those who already knew their thyroid gland was malignant.

In total 290 patients with solitary solid (or predominantly solid) thyroid nodules were included in the study. All patients with suspicious or malignant FNAB underwent surgery, and surgery was also performed on those 53 patients with benign FNABs.

The FNAB were performed by endocrinologists or radiologists without anesthesia, using a 23-25 gauge needle mounted on a syringe using a freehand technique.

Ultrasound investigations used an ultrasonographic scanner (Toshiba SS 270A and

**FIGURE 1**

**ULTRASOUND EVALUATION : BENIGN, MALIGN, SUSPECT**

Acuson XP 128) equipped with a 7, 5 MHz linear transducer for morphological studies and for color-Doppler evaluation.

The following ultrasound parameters were assessed in all nodules:

1. nodule size (maximum diameter as evaluated by sagittal and transverse scans);
2. echographic structure (solid, mixed or cystic);
3. echogenicity (iso-, hyper- or hypoechoic);
4. presence/absence of calcification;
5. lesion margins well-defined or blurred
6. as small nodules up to 10 mm, over 10 mm as large nodules.

By ultrasound characteristics, our patients were classified into two groups according to TIRADS classification: normal ultrasound findings – nodules in TIRADS 1 and 2 groups - they were reviewed by 6 and 12 months and three years later and there were no significant changes in appearance and size of nodules; nodules in the TIRADS 3 group – suspect to be malignant; nodules in TIRADS 4 and 5 groups – proved malignant. The FNAB were performed for all nodules in the TIRADS 3, 4 and 5 groups.

**TIRADS**

US criteria may help to decide cost-effective management. Our objective was to develop a standardized US characterization and reporting data system of thyroid lesions for clinical management: (TIRADS). In Horvath et al. ¹⁰ proposed the thyroid imaging reporting and data system (TIRADS). They established six categories (TRIADS 1 to TIRADS 6) based on US patterns and estimated the incidence of malignancy for each TIRADS class:

1. TIRADS 1 - normal findings
2. TIRADS 2 - there is a change, but malignancy risk is 0%
3. TIRADS 3 - malignancy risk < 5%
4. TIRADS 4A - malignancy risk 5-10%
5. TIRADS 4B - malignancy risk 10-80%
6. TIRADS 5 - malignancy risk over 80%
TABLE 2  
FNAB COMPARED TO FINAL HISTOPATHOLOGY RESULTS

<table>
<thead>
<tr>
<th></th>
<th>No of patients</th>
<th>Benign</th>
<th>Susp malignant</th>
<th>Malignant</th>
<th>Malignant + susp</th>
</tr>
</thead>
<tbody>
<tr>
<td>UZ</td>
<td>206</td>
<td>87 (42.86%)</td>
<td>49 (24.1%)</td>
<td>67 (33.00%)</td>
<td>166 (57.1%)</td>
</tr>
<tr>
<td>FNAB</td>
<td>116</td>
<td>53 (45.7%)</td>
<td>30 (25.9%)</td>
<td>33 (28.5%)</td>
<td>66 (56.9%)</td>
</tr>
<tr>
<td>PH</td>
<td>116</td>
<td>70 (60.3%)</td>
<td>/</td>
<td>46 (39.7%)</td>
<td>203 (22.7%)</td>
</tr>
</tbody>
</table>

7. TIRADS 6 – change already PH verified as 100% malignant.
They diagnosed nodules with TIRADS 4 or greater as suspected of malignancy; they compared their classification results and FNAB findings and showed that the sensitivity, specificity, PPV, and NPV were 88, 49, 49, and 88%, respectively. In both studies, follicular lesions according to FNAB findings were classified as suspicious of malignancy.

FNAB was performed in all patients with solitary solid (or predominantly solid) nodule with diameter to or greater than 10 mm, where US resulted by suspect or malignant findings. Biopsies were done under sonographic guidance. Cytological specimens were smeared according to the Papanicolaou technique, and evaluated by experienced cytopathologists. When the smear was inadequate (<6 clusters with 10 cells each)11, FNAB was repeated once; only technically satisfactory results were considered.

Adequate cytological material was classified as benign (colloid nodules, thyroid cysts, lymphocytic thyroiditis, cystic goiters, adenoma – except for follicular carcinoma and Hurthle cell carcinoma–), normal thyroid tissue and benign hyperplasia.) as malignant (papillary carcinoma, medullary carcinoma, Hurthle cell carcinoma and anaplastic carcinoma). Suspicious findings included atypical follicular cells or Hurthle cells. Histopathological findings were reviewed by two independent pathologists. All patients with benign, suspicious or malignant FNAB underwent surgery. The diagnosis of cancer was based on the final confirmation of patho-histological findings after surgery12. Five factors were analyzed when comparing the preoperative FNAB results with the final histologic findings: sensitivity, specificity, accuracy, positive and negative predictive values. Neoplastic lesions outside the nodule examined by FNAB were considered incidental and not included in the analysis. Clinical, ultrasound, cytological and histological findings were separately recorded and analyzed. The diagnostic value of ultrasound criteria was also assessed in terms of sensitivity, specificity, positive/negative predictive value and accuracy 13.

RESULTS
Out of 290 patients 49 (16.9%) were excluded from further analysis due to inadequate cytological specimens after a second round of FNAB and for 38 (13.1%) patients there were missing data (such as size of nodules, ultrasound findings, FNAB, or final findings of HP). Finally, a single nodule was examined in 203 patients.

Out of 203 ultrasound examined patients 127(62.6%) were females; 76(37.4%) males; 87(42.8%) nodules were benign (TIRADS 1 i 2), 67(33%) malignant (TIRADS 4 i 5) and the remaining 49(24.2%) suspicious (TIRADS 3). Patients were aged between 26 and 88 (mean age 49 years). Nodule size (as evaluated by ultrasound) ranged from 6 to 30 mm (mean ± SD 16.7 ± 9.8 mm), 124 were classified as large nodules and the remaining 79 as small.

Inadequate samples were significantly more common for "small nodules" (<10 mm in diameter) than for "large nodules" (>10 mm) (calculated only for patients with inadequate material for FNAB; 73.4%vs.26.6%,p<0.001).

Cytological and histological features
All cases underwent by FNAB were underwent surgery and all were confirmed by the final histologic evaluation. FNAB were underwent in 116 (57.2%) nodules (all benign, suspicious or overtly malignant nodules underwent surgery).

87 (42.8%) nodules benign on ultrasound were not operated, they were reviewed by 6 and 12 months and three years later and there were no significant changes in appearance and size of nodules. The prevalence of cancer was lower in small than in large nodules (p<0.01). However, follicular and medullary histotypes were more common in small than in large nodules (p = 0.01).

Preoperative (by FNAB) benign lesions were diagnosed in 53 (45.7%) cases, but all of these multiple endocrine neoplasia (MEN-II) patients and patients with positive family history both insisted on surgery.
Malignancy (by FNAB) was in 33 (28.5%) specimens. The remaining 30 (25.8%) cases were defined as suspicious.
From the 30 suspicious cases, 8 proved to be malignant, the remaining 22 were benign lesions, while 48 of the 53 lesions found benign on preoperative FNAB were verified as such by histologic evaluation, while the remaining 5 were malignant. All cases of papillary carcinoma on FNAB were positive according to the final histologic evaluation, two cases were found to be papillary carcinoma, seven cases of follicular adenoma were found to be papillary carcinoma and one case of follicular adenoma proved to be follicular carcinoma. Final histology results showed that, of the 30 suspicious and 53 benign cases on FNAB, 13 cases proved to be malignant.

On final histologic evaluation, 70 (60.3%) cases proved to be benign lesions and 46 (39.7%) were found as malignant.

The sensitivity of FNAB was 72%, specificity 100%, positive predictive value 100%, negative predictive value 84% and accuracy 89%.

**DISCUSSION**

Martin was in 1930s a pioneer in the application of FNAB as preoperative diagnostic technique in the assessment of choice in patients with thyroid nodules as candidates for surgery treatment. He first noted that FNAB with clinical findings, laboratory and imaging data, reduced the number of thyroidectomias 21% to 75%. FNAB has an accuracy between 69% and 95%, and a specificity between 58% and 90%31, and became a first-line tool in the investigation of nodular thyroid disease16,17. Solitary nodules are found in approximately 4-7% of adult population8,19,20, malignancy incidence in solitary thyroid nodules is up to 10%. In autopsies, thyroid gland carcinoma was found in 6% cases, mostly as a multifocal alteration in the gland while often also as neck metastase. These were in most cases small tumors, 4 to10 mm in diameter21. Selection of patients to undergo surgery is a very important preoperative histologic evaluation. Decisions made in the past on the basis of thyroid glands scanning were of poor specificity as a method22, with a large number of false positive findings and many cases of unnecessary surgical interventions, where final histologic evaluation proved low malignancy incidence8. Mayo Clinic studies indicate FNAB usefulness as a routine diagnosis in the treatment of thyroid gland malignancies, and also a reduction of gland resections in suspect cases from 67% to 43%. Studies also showed a rise of malignancy evaluation in final histologic evaluation from 14% to 25%, resulting in a reduction of surgical interventions and consequently a reduction of costs by 25%-23. Garcia et al.,24 indicate that surgical interventions on suspect thyroid nodules were reduced by half in the period from 1980 to 1993 and that cancer confirmation rate in final pathologic evaluation increased from 14.7% to 32.9%.

Most authors indicate FNAB sensitivity from 80 to 95%, specificity from 70 to 100%, and false positive and false negative results in 5-25% cases28,29. Accuracy is estimated to be between 92% and 95%, and varies according to the histologic evaluation. In case of papillary carcinoma the accuracy is about 80%22, due to pathognomonic features on histologic specimen examination.

In cases of follicular cancer, FNAB is lower and estimated to be between 10% and 40%, mainly because structural features of cell groups and the capsule of the nodule are essential to the diagnosis, and are not seen on FNAB cytology. However, a few pathologists were able to identify cytologic features corresponding to follicular malignancy14. In follicular cancer cases, lack of tissues for diagnoses are indicated as main factors of lower accuracy, which also goes for Hurthle cell carcinoma and follicular tumors. Insufficient tissue taken for FNAB was in about 13.3% cases, usually in cystic lesions with blood or fluid being present, where FNAB should be repeated. In cases of follicular or Hurthle cell tumors, the tissue makes impossible the differentiation between benign and malignant, so that FNAB is insufficient here. FNAB cannot evaluate penetration of blood vessels or capsule35. The frequency of histologically malignant lesions was slightly less in small than in large nodules, but clinically relevant in absolute terms. Follicular and medullary carcinomas, (histological types with a less favorable prognosis) were more frequent in small nodules. Gharib et al.,36 reported 17% suspicious results on their FNAB evaluation, 20-25% of which proved to be malignant on final histologic evaluation. In our report, of 30 nodule cases suspect to be malignant, 8 (26.6%) were malignant in the final histologic evaluation. Compared to fine-needle biopsy, ultrasound-controlled FNAB resulted in better FNAB results but usefulness was not confirmed36; a possible reason for this could be that the person carrying out the ultrasound-controlled biopsy was poorly trained. In ultrasound-controlled biopsy in this study, in 11 cases (9.5%) specificity was 100%, sensitivity 83.3%, positive predictive value 100%, negative predictive value 83.3% and accuracy 90.9%. Small, deeply located nodules, where taking of material was very difficult, were the reason of poor accuracy.

The discrepancy between the low prevalence of clinically evident thyroid neoplasia compared with the high rate of cancers under 10–15mm at autopsy37, prompts many physicians to believe that in most cases occult thyroid cancer has no clinical relevance. In addition, several reports have suggested that incidentally discovered thyroid papillary carcinomas follow an indolent course38,39,40,41. On the other hand, some studies support our finding that evidence of extrathyroidal spread and/or nodal metastasis is equally common in large and small nodules41,42,43, and that no valid dimensional cut-off for neoplastic aggressive behaviour can be identified.

**CONCLUSION**

Many studies have investigated whether the ultrasonographic characteristics of thyroid nodules are useful indicators of histological malignancy. The prevalence of malignant lesions in thyroid nodules referred for US-FNAB is now a gold standard in the evaluation of thyroid nodules, but not substantially different in nodules above 1 cm vs. below 1 cm in size. In this study it was
shown for the FNAB technique to be accurate, efficient and reliable in the diagnosis and evaluation of thyroid nodules. Histological type and local aggressiveness are not more favorable in microcarcinomas than in larger thyroid cancers. A cost-effective approach to the use of FNAB should not depend solely upon nodule size; specific ultrasound patterns (microcalcifications, blurred margins and hypoechogenic appearance) appear to be useful indicators.

SUMMARY

PREOPERATIVNA PROCENA SOLITALNIH TIROIDNIH NODULA KOD BOLESNIKA POMOĆU ULTRAZVUKA I IGLENE BIOPSIJE


Rezultati: Bolesnici su bili starosnog doba između 26-88 godina (prosečno 49 godina). Od 203 bolesnika, 49 je imalo neadekvatnu FNAB, 87 su proveravani tj. praćeni na 6-12-36 meseci. Zbog nepotpunih podataka potrebno je izražavanja. Od ukupno 116 nodula kojima je učinjen FNAB, 53 su bili benignog porekla, 30 sumnjivog i 33 maligna. Na završnoj postoperativnoj histološkoj obradi utvrđeno je 70 i 46 benigne i maligne TNs, odnosno učestalos malignih TNs je bio nešto veći u nodula prečnika preko 10 mm nego kod onih ispod 10 mm (p < 0.01). Parametri kao što su veličina ili mikrokalcifikacije nisu dovoljni da obezbide procenu maligniteta ili čak i FNAB nije dovoljan, ali se tačnost povećava korišćenjem ultrazvučnog vodjenja FNABa.

Zaključak: U ovoj studiji je da FNAB tehnika može biti precizna, efikasna i pouzdana u dijagnostici i evaluaciji tiroidnih nodusa. Histološki tip i lokalna agresivnost nisu dovoljni da obezbede procenu maligniteta ili čak i FNAB nije dovoljan, ali se tačnost povećava korišćenjem ultrazvučnog vodjenja FNABa.

Ključne reči: TIRADS, FNAB, štitna zlede

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