

ACCURACY OF ULTRASOUND GUIDED FINE NEEDLE ASPIRATION IN PATIENTS WITH NODULAR THYROID DISEASE

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SUMMARY – The aim of the study was to evaluate effectiveness of ultrasound guided fine needle aspiration in patients with nodular thyroid disease. Over a 7-year period, there were 457 patients with nodular thyroid disease who underwent ultrasound guided fine needle aspiration with subsequent histologic verification. Diagnostic fine needle aspiration findings were classified into one of the following categories: benign, indeterminate and malignant. The cytologic diagnosis of benign finding was histologically confirmed in 206 (99.5%) of 207 patients. Of 166 patients with indeterminate cytology, 25 (15.1%) were shown to be malignant, 107 (64.4%) were adenomas, and 34 (20.5%) were non-neoplastic lesions. Of 76 patients with malignant fine needle aspiration cytology, histologic examination indicated carcinoma in 67 (88%), follicular adenoma in seven (9%) and nodular goiter in two (3%) patients. There were 246 true negative, 178 true positive, one false negative, and 24 false positive findings, yielding a sensitivity of 99%, specificity of 91%, accuracy of 94%, positive predictive value of 88% and negative predictive value of 99%, false negative rate of 0.2% and false positive rate of 5%. The study confirmed the ultrasound guided thyroid fine needle aspiration to be a reliable screening test for patients with thyroid nodules. Following a benign fine needle aspiration result of thyroid nodule the physician can be 99% sure that the lesion is indeed benign.

Key words: *Biopsy – needle; Thyroid nodule – diagnosis; Thyroid nodule – pathology*

Introduction

Clinically detectable thyroid nodules occur in approximately 4%-10% of the population^{1,2}. However, thyroid cancer occurs in fewer than 5% of thyroid nodules³. Fine needle aspiration (FNA) as the most accurate and cost-effective method of evaluating thyroid nodules⁴, has become a standard initial step for patients with thyroid nodules. The goal of the procedure is to distinguish nodules that require surgery from those that do not⁵. Its impact on the management of thyroid nodules has resulted in an overall decrease in the number of thyroidectomies, with a concomitant increase in the yield of malignancy for resect-

ed thyroid nodules⁶⁻⁹. Nevertheless, FNA has some limitations, and both false positive and false negative results occur¹⁰. A false positive result in thyroid cytology is not of major concern because, without this test, many more patients with solitary, 'cold' nodules would require excision for diagnosis. It is more important to maintain the lowest false negative rate possible to ensure that few carcinomas will be missed. A substantial proportion of FNA biopsy results are neither clearly benign nor clearly malignant and fall into the category of indeterminate results. FNA cytology has a wide range of sensitivity, specificity and diagnostic accuracy for thyroid nodules but average values for these three parameters were very high, i.e. 85.2%, 95.6% and 94.4%, respectively¹¹.

This study was undertaken to evaluate the effectiveness of ultrasound guided FNA in patients with nodular thyroid disease, done over a 7-year period in our laboratory.

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Patients and Methods

Methods

We undertook a computerized search for all patients who had preoperative thyroid FNA cytology performed at University Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital between March 1995 and April 2002, and underwent thyroid surgical procedure. Most FNA biopsies were performed by a cytopathologist. Routine FNA was done using a 25-gauge needle attached to a 10-mL syringe under continuous real-time sonographic guidance. Aspirated material was smeared onto glass slides, air-dried, stained by May-Grünwald-Giemsa stain, and examined under a light microscope. The histologic diagnoses were used as the 'gold standard' against which FNA results were compared.

Patients

A total of 6495 patients were examined by FNA of the thyroid in our institution and histologic specimens were available for 461 (7%) patients. These patients underwent thyroid surgical procedure at the same hospital. Among 461 patients with subsequent histologic verification there were 457 who presented with nodular thyroid disease. The other four patients presented with diffuse lesions of the thyroid and were excluded from any other calculations. There were 378 (82.6%) females and 79 (17.4%) males; the female : male ratio was 4.7:1. Age range was 11-78 years with a median of 48 and mean age of 47.7 ± 13.2 years.

FNA categories

For the purpose of this study, the original diagnostic FNA results were classified into one of the following categories:

- benign – including benign thyroid nodule, nodular goiter, cyst and Hashimoto's thyroiditis,
- indeterminate – cellular follicular lesion (surgical intervention not advised), suspicious of follicular neoplasm, follicular neoplasm, and suspicious of malignancy, and
- malignant – specimens in which an unequivocal diagnosis of malignancy can be made; papillary carcinoma, high-grade follicular carcinoma, medullary carcinoma, anaplastic carcinoma or metastases.

Specimens with either no diagnostic cellular element or insufficient cells for cytologic diagnosis were classified as inadequate or unsatisfactory.

The results were categorized on the basis of the findings made by the cytopathologist before the operation.

Statistical analysis

False negative (FN) and false positive (FP) results were evaluated using a definition proposed in the guidelines of the Papanicolaou Society of Cytopathology⁵. A true positive (TP) FNA was defined as suspicious (indeterminate cytologic result; thyroid surgical procedure was advised) or malignant cytologic results from a nodule determined to be malignant or follicular adenoma after thyroidectomy; a FP was defined as a cytologic diagnosis of neoplasm, which requires surgical excision, rendered on non-neoplastic lesion. A true negative (TN) FNA was defined as a benign cytologic result from a nodule determined to be benign after thyroid surgical procedure; a FN FNA was defined as a cytologic diagnosis of non-neoplastic lesion, which does not usually require surgical procedure, rendered on a malignant lesion. In most of the published series, the FN rate is computed as the number of FN diagnoses divided by the total number of FNAs in the series $\times 100$. The FP rate is computed as the number of FP diagnoses divided by the total number of FNAs in the series $\times 100$ ⁵. These data were used to compute the sensitivity, specificity, predictive values, FN and FP rate, and accuracy of thyroid FNA.

Results

Of the total of 457 patients with thyroid nodular disease with subsequent histologic verification there were eight (1.8%) considered insufficient for cytologic diagnosis. These inadequate or unsatisfactory FNA aspirates corresponded histologically to one Hashimoto's thyroiditis, four nodular goiters, two follicular adenomas and cystic lesion. They were not included in any other calculations.

The diagnostic results of FNAs in 449 patients are summarized in Table 1.

In the benign FNA category there were 207 (45.3%) cases and only one (FN) was histologically shown to be malignancy.

Of 166 (36.3%) patients with indeterminate cytology, 25 (15.1%) were shown to be malignancies (13 papillary, two follicular, five medullary, three Hürthle cell carcinomas, one metastasis of renal cell carcinoma and one follicular-medullary carcinoma), 107 (64.4%) were adenomas, 33 (19.9%) nodular goiters and one (0.6%) was Hashimoto's thyroiditis (Table 2). Patients with cytologic diagnosis of cellular follicular lesion were judged to be at a low risk and conservative treatment was advised. They were evaluated as a benign cytologic finding (40 TNs). Twenty-two patients (FPs) had non-neoplastic lesions on his-

Table 1. Correlation between cytology and histology in patients with preoperative fine needle aspiration

Fine needle aspiration	Pathohistologic diagnosis				Total
	Nodular goiter	Thyroiditis	Follicular adenoma	Malignant neoplasm	
Benign	172	2	32	1	207
Indeterminate	33	1	107	25	166
Malignant	2	0	7	67	76
Total	207	3	146	93	449

tology, and thyroid surgical procedure was advised after indeterminate cytologic findings.

Seventy-six (16.6%) patients with malignant FNA cytology corresponded histologically to 67 (88%) carcinomas (59 papillary, 4 medullary, 3 anaplastic and 1 follicular). There were seven (9%) follicular adenomas and two (3%) nodular goiters (FPs) (Table 3).

Therefore, in this study there were 246 true negative, 178 true positive, one false negative, and 24 false positive findings, yielding the following values for FNA cytology of the thyroid: sensitivity of 99%, specificity of 91%, accuracy of 94%, positive predictive value of 88% and negative predictive value of 99%, FN rate of 0.2% and FP rate of 5%.

Discussion

We report on a large, single center study of cytohistologic correlation for nodular thyroid disease, with histologic diagnosis of the nodule as the gold standard. The incidence of unsatisfactory or inadequate aspirates of 1.8% was relatively low in comparison to other reports, where it ranges

from 2% to 21%.³ The Papanicolaou Society⁵ suggests that inadequate rate should not exceed 15%. Inadequate biopsies are said to be less common when the cytopathologist reporting on biopsies does the aspiration personally, thus judging the specimen adequacy at the time of procedure. Currently, the criteria proposed for specimen adequacy vary slightly from institution to institution¹²⁻¹⁴, but most require the presence of follicular epithelial cells¹⁵. However, it may be misleading to adhere strictly to the definition of what constitutes an adequate specimen, so this remains subjective and dependent on both the skill of the person performing aspiration and the experience of the cytopathologist. In the present study, there were six operated patients with inadequate FNA reports and no carcinoma was missed (two follicular adenomas, three nodular goiters and one Hashimoto's thyroiditis). Previous reports describe the frequency of carcinomas to be 2%¹⁶, 5%^{17,18}, and even 9%¹⁹ of operated patients with inadequate FNA results. At our institution, most of FNAs are performed by the cytopathologist, always under ultrasound guidance, and we have large numbers of cases, so this could explain the

Table 2. Indeterminate fine needle aspiration cytology and corresponding histologic findings after thyroidectomy

Indeterminate fine needle aspiration	Pathohistologic diagnosis				Total
	Nodular goiter	Thyroiditis	Follicular adenoma	Malignant neoplasm	
CFL	12	0	28	0	40
FN?	7	1	31	2	41
FN	11	0	46	8	65
MN?	3	0	2	15	20
Total	33	1	107	25	166

CFL=cellular follicular lesion; FN?=suspicious of follicular neoplasm; FN=follicular neoplasm; MN?=suspicious of malignant neoplasm

Table 3. Correlation between malignant fine needle aspiration cytology and histologic findings

Pathohistologic diagnosis	Malignant fine needle aspiration findings	
	n	%
Papillary carcinoma	59	77.6
Medullary carcinoma	4	5.3
Follicular carcinoma	1	1.3
Anaplastic carcinoma	3	4.0
Adenoma	7	9.2
Non-neoplastic lesion	2	2.6
Total	76	100

low incidence of unsatisfactory aspirates.

A three-category system for thyroid FNA cytology as advocated in this study was used before^{20,21}. The need for indeterminate FNA diagnostic category is predominantly due to overlapping of the cytologic criteria for hyperplastic adenomatoid nodule in goiter, follicular adenoma, follicular carcinoma and follicular variant of papillary carcinoma^{9,22,23}. This shows that there is no clear distinction between unequivocally malignant cytology and the more or less suspicious one.

The present study demonstrated that 79.5% (132/166) of the indeterminate diagnoses correlated with thyroid neoplasm on histology (107 [81%] cases were benign and 25 [19%] were malignant), and 34 (20.5%) were non-neoplastic lesions. In comparison, 88% (67/76) of cases originally reported as malignant correlated histologically with thyroid carcinomas on subsequent thyroidectomy.

Our data showed a high percentage of patients (88%) to have been correctly operated upon the malignant FNA

result, and confirmed the high reliability of benign cytologic result (206/207 [99%]). An obvious limitation of every cytohistologic correlation is that only a small fraction of patients with benign FNA result underwent thyroid surgical procedure. This selection can cause a bias in the results; in this study, only 6% of the benign FNA findings could be verified histologically, in comparison to 70% of the malignant FNA findings. The patients with malignant FNA findings lacking histologic diagnosis were those who probably underwent thyroid surgical procedure in different hospitals.

Every technique will have FN and FP diagnoses. FN may occur because of missed sampling of a nodule or cytologic error in interpretation. The incidence of FN diagnosis is hard to gauge because approximately only 10% of patients with benign cytology undergo surgery³. The reported rate of FN diagnoses varies from 1% to 11%^{3,6,9}. On the other hand, FP diagnoses represent about 1% to 8% of the cases^{3,23-27}. FP can occur if a hyperplastic nodule is sampled producing relatively abundant, slightly atypical follicular epithelial cells and scant colloid. Because FNA is considered a screening procedure, particular attention should be given to minimizing FN diagnoses, even at the expense of accepting FP diagnoses⁵. In this study, there was only one FN and 24 FPs with calculated FN rate and FP rate 0.2% and 5%, respectively. The relatively high FP rate was due to indeterminate (22 FPs) rather than malignant FNA findings (two FPs).

FNA currently is the best procedure available for the evaluation of thyroid nodules, with the reported sensitivity and specificity rate varying from 65% to 98% and 52% to 100%, respectively (Table 4)^{18,21,23,26,28,29}. In the hands of experienced cytopathologists FNA of the thyroid achieves high diagnostic accuracy rate of more than 90%^{12,29}. In this study, the sensitivity, specificity and accuracy of ultrasound

Table 4. Comparison of our data with literature reports

Reference	No. of FNAs	No. of PHD	Sensitivity	Specificity	Accuracy	PPV	NPV
Čap <i>et al.</i> ¹⁸	2100	536	90(%)	79(%)	81(%)	51(%)	97(%)
Leonard and Melcher ²¹	335	184	88(%)	78(%)	80(%)	46(%)	97(%)
Hall <i>et al.</i> ²³	795	72	84(%)	90(%)	89(%)	98.7(%)	97(%)
Gharib <i>et al.</i> ²⁶	10971	–	98(%)	99(%)	–	98(%)	99.3(%)
Holleman <i>et al.</i> ²⁸	112	53	84(%)	52(%)	65(%)	53(%)	83(%)
Altavilla <i>et al.</i> ²⁹	1796	257	71(%)	100(%)	95(%)	100(%)	94.4(%)
Current study	6495	449	99(%)	91(%)	94(%)	88(%)	99(%)

FNA=fine needle aspiration; PHD=pathohistologic diagnosis; PPV=positive predictive value; NPV=negative predictive value

guided FNA were 99%, 94% and 96%, respectively.

In conclusion, despite its limitation, ultrasound guided thyroid FNA is a reliable screening test for patients with thyroid nodules. Following a benign FNA finding of thyroid nodule, the clinician can be more than 99% sure that the lesion is indeed benign, and many patients with benign thyroid nodules will be spared surgery.

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Sažetak

TOČNOST ULTRAZVUČNO VOĐENE ASPIRACIJE TANKOM IGLOM U BOLESNIKA S NODULARNOM BOLEŠĆU ŠTITNJAČE

I. Tabain, N. Mateša i Z. Kusić

Cilj studije bio je procijeniti pouzdanost ultrazvučno vođene aspiracije tankom iglom u bolesnika s nodularnom bolešću štitnjače. Tijekom 7-godišnjeg razdoblja bilo je 457 bolesnika s nodularnom bolešću štitnjače u kojih je učinjena ultrazvučno vođena tankoiglena aspiracija s naknadnom histološkom potvrdom. Dijagnostički tankoigleni aspirati su klasificirani u jednu od sljedećih kategorija: benigne, neodređene i maligne. Citološka dijagnoza benignog nalaza histološki je potvrđena u 206 (99,5%) od 207 bolesnika. Od 166 bolesnika s neodređenim citološkim nalazom 25 (15,1%) ih se je pokazalo malignim, 107 (64,4%) su bili adenomi, a 34 (20,5%) su bile ne-neoplastične promjene. Od 76 bolesnika s malignom citologijom tankoiglenog aspirata histološki je pregled utvrdio 67 (88%) karcinoma; sedmero (9%) ih je imalo folikularni adenom, a dvoje (3%) nodularnu strumu. Bilo je 246 stvarno negativnih, 178 stvarno pozitivnih, jedan lažno negativan i 24 lažno pozitivna nalaza, što je pokazalo osjetljivost od 99%, specifičnost od 91%, točnost od 94%, pozitivnu prediktivnu vrijednost od 88%, negativnu prediktivnu vrijednost od 99%, te stopu lažno negativnih i lažno pozitivnih nalaza od 0,2% odnosno 5%. Ova je studija potvrdila da je ultrazvučno vođena aspiracija tankom iglom pouzdan test probira za bolesnike s čvorovima štitnjače. Na osnovi benignog rezultata tankom iglom aspirata čvora štitnjače liječnik može biti 99% siguran da je promjena doista benigna.

Ključne riječi: *Biopsija – igla; Čvor štitnjače – dijagnostika; Čvor štitnjače – patologija*