



How to select nodules for fine-needle aspiration biopsy in multinodular goitre. Role of conventional ultrasonography and shear wave elastography — a preliminary study

Jak typować guzy do biopsji aspiracyjnej cienkoigłowej w wolu wieloguzkowym? Rola konwencjonalnej ultrasonografii oraz elastografii fali poprzecznej — badanie pilotażowe

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Abstract

Introduction: The wide prevalence and relatively low malignancy ratio of thyroid nodular disease (TND) make the selection of suspicious lesions for fine-needle aspiration biopsy (FNAB) a vital problem in endocrinology. Apart from the decision as to whether FNAB is necessary, there is often a second problem — which nodule or nodules to choose in a case of multinodular goitre (MNG), when the number of lesions may be high.

The aim of this study was to compare the usefulness of conventional ultrasonography (US) to that of a novel method of tissue stiffness assessment — shear wave elastography (SWE) — in differentiating between malignant and benign nodules and in selecting the most suspicious lesions in MNG.

Material and methods: Patients with MNG, referred for thyroidectomy irrespectively of indications for surgery, underwent thyroid US and SWE examination before surgery, between August and December 2010. Results of these examinations were correlated with the histopathological outcomes.

Results: 80 patients with 339 thyroid nodules were included. Ten thyroid cancers (TCs) in ten patients were diagnosed in histopathology. All ten cancers were the least elastic lesions in MNG (using quantitative data on maximal tissue stiffness). Four cancers appeared as the biggest lesions in MNG, while one was equally the biggest in a particular goitre (there were other lesions of the same size) taking into account maximal diameter. Three of ten cancers possessed the highest number of suspicious features in MNG, a further four had the highest number equally, with at least one other lesion in the same goitre.

Conclusions: On the basis of our results, the relatively high stiffness of a lesion compared to other nodules from the same MNG should be considered as a strong argument for choosing that particular one for FNAB. (*Endokryol Pol* 2014; 65 (2): 114–118)

Key words: shear wave elastography; ultrasonography; thyroid nodules

Streszczenie

Wstęp: Wysoka częstość choroby guzkowej tarczycy oraz stosunkowo niskie ryzyko złośliwości czyni wybór zmian, które powinny być poddane biopsji cienkoigłowej żywotnym problemem w endokrynologii. Oprócz decyzji czy biopsja cienkoigłowa jest wskazana, często powstaje kolejny problem — który guzek lub guzki wybrać w przypadku wola wieloguzkowego, w którym liczba zmian bywa wysoka. Celem tego badania było porównanie użyteczności konwencjonalnej ultrasonografii oraz nowej metody oceny sztywności tkanek — elastografii fali poprzecznej — w różnicowaniu guzków łagodnych i złośliwych oraz selekcji najbardziej podejrzanych zmian w wolu wieloguzkowym.

Materiał i metody: Pacjenci z wolem wieloguzkowym kierowani do tyroidektomii pomiędzy sierpniem a grudniem 2010 roku, niezależnie od wskazań do zabiegu, przechodzili przedoperacyjne badanie sonograficzne i elastograficzne. Wyniki tych badań porównano z rozpoznaniem histopatologicznym.

Wyniki: Do badania włączono 80 pacjentów z 339 guzkami tarczycy. W badaniu histopatologicznym zdiagnozowano dziesięć raków tarczycy. Wszystkie raki stanowiły najmniej elastyczną zmianę w obrębie wola wieloguzkowego (uwzględniając ilościowe dane dotyczące maksymalnej sztywności zmiany). Cztery raki okazały się największymi zmianami w obrębie wola wieloguzkowego, jeden był największym na równi z innymi guzkami z danego wola (tzn. istniały guzki w obrębie danego wola o takiej samej wielkości), uwzględniając maksymalny wymiar guzka. Trzy z dziesięciu raków posiadało największą liczbę podejrzanych cech sonograficznych, kolejne cztery największą liczbę na równi z co najmniej jedną inną zmianą w obrębie danego wola.

Wnioski: Na bazie wyników badań stosunkowo wysoka sztywność zmiany — w porównaniu z innymi guzkami u danego pacjenta, powinna być rozpatrywana jako silny argument za wyborem tej zmiany do biopsji cienkoigłowej. (*Endokryol Pol* 2014; 65 (2): 114–118)

Słowa kluczowe: elastografia fali poprzecznej; ultrasonografia; guzki tarczycy

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Introduction

Thyroid nodular disease (TND) is one of the most widespread endocrine disorders. According to available studies, thyroid lesions are present in 10–70% of adults, and even more in women and some particular groups (e.g. acromegalic patients, patients with type 2 diabetes) [1–5]. As the risk of malignancy is quite low but noticeable, there is a great need for diagnostic tools allowing for reliable distinction of benign and malignant nodules. There have been numerous studies assessing the usefulness of particular ultrasonographic (US) features in the prediction of malignancy [6–8]. Also some new techniques, such as elastography, are believed to improve the reliability of diagnosis. This has been described as a very useful tool in differentiating between benign and malignant thyroid lesions [9–11] and diagnostics of other thyroid diseases, such as Graves' disease, chronic or subacute thyroiditis [12–14]. Especially shear wave elastography (SWE), a new variant of thyroid imaging, is considered as more objective, reliable and reproducible. Shear waves emission is induced by an ultrasonic beam, hence it does not require any mechanical sources of pressure [15–16].

Fine-needle aspiration biopsy (FNAB) is a routine and valuable diagnostic procedure in a case of thyroid nodules with disquieting US appearance [17–18]. Apart from the decision as to whether FNAB is necessary, the selection of the most suspicious lesions in a case of multinodular goitre (MNG) is a challenge in everyday practice. To date, most studies have regarded all analysed thyroid lesions in the studied group as independent. Few studies have compared the features of multiple nodules in one patient and how to select those at highest risk of malignancy. In particular, no study has assessed the usefulness of SWE in selecting the most suspicious lesions in MNG.

The aim of this study was to assess the usefulness of US and SWE in selecting nodules representing the highest risk of malignancy for fine-needle aspiration biopsy in patients with MNG.

Material and methods

Patients

The patients with MNG were selected from a group of subjects referred for thyroidectomy between August and December 2010, irrespectively of indications for surgery, described previously [19]. All patients underwent thyroid US and SWE examination prospectively before surgery. Indications for surgery encompassed suspicion of malignancy (according to the FNAB results), repeating non-diagnostic or indeterminate results of cytopathology, Graves' disease, large MNG,

toxic nodular goitre or hyperparathyroidism coexisting with MNG. Data about conventional sonographic markers of malignancy, mean and maximal elasticity, size and precise location was collected to ensure exact assignment between results of US, SWE and histopathology. Histopathological examination was performed by two pathologists as a routine medical procedure after thyroidectomy. All participants gave informed written consent. This study was approved by The Poznan University of Medical Sciences Ethical Committee.

Conventional ultrasound and SWE

US and SWE examination were performed using an AIXPLORER system by Supersonic Imagine with 2–10 MHz linear transducer. The presence of the following markers of malignancy — solid composition, microcalcifications, hypoechogenicity, 'taller than wide' shape and diffused margins were assessed. Suspicion in conventional US appearance was determined by the number of the features listed above present in a particular lesion. Elasticity of nodules was assessed quantitatively. Quantitative assessment included measurement of maximal and mean values of areas of interest, expressed in kPa. We compared the results of histopathology, US and SWE for every nodule in order to compare diagnostic values of several sonographic features; the main objective of the study was to compare sonographic characteristics of cancers and benign nodules collocated in multinodular goitres in order to find the most effective algorithms for selecting thyroid lesions for FNAB. As a first step, we compared mean size, tissue stiffness and number of sonographic malignancy features (solid composition, microcalcifications, hypoechogenicity, 'taller than wide' shape and diffused margins were considered) between the groups of benign and malignant nodules. Next, we compared three algorithms of selection nodules for FNAB in MNG — number of US malignancy features, size of the nodule and stiffness of the lesion as the primary criterion.

Statistical analysis

The calculations were performed using Statistica 10 from StatSoft. A *P* level of less than 0.05 was considered statistically significant. Significance of difference between two means was calculated by t-test for independent samples.

Results

80 patients with MNG, possessing 339 thyroid nodules, were included. There were 67 women and 13 men. Mean age was 53.4 years, standard deviation (SD) 13.0, age range: 26–78 years. Ten cancers in ten patients were

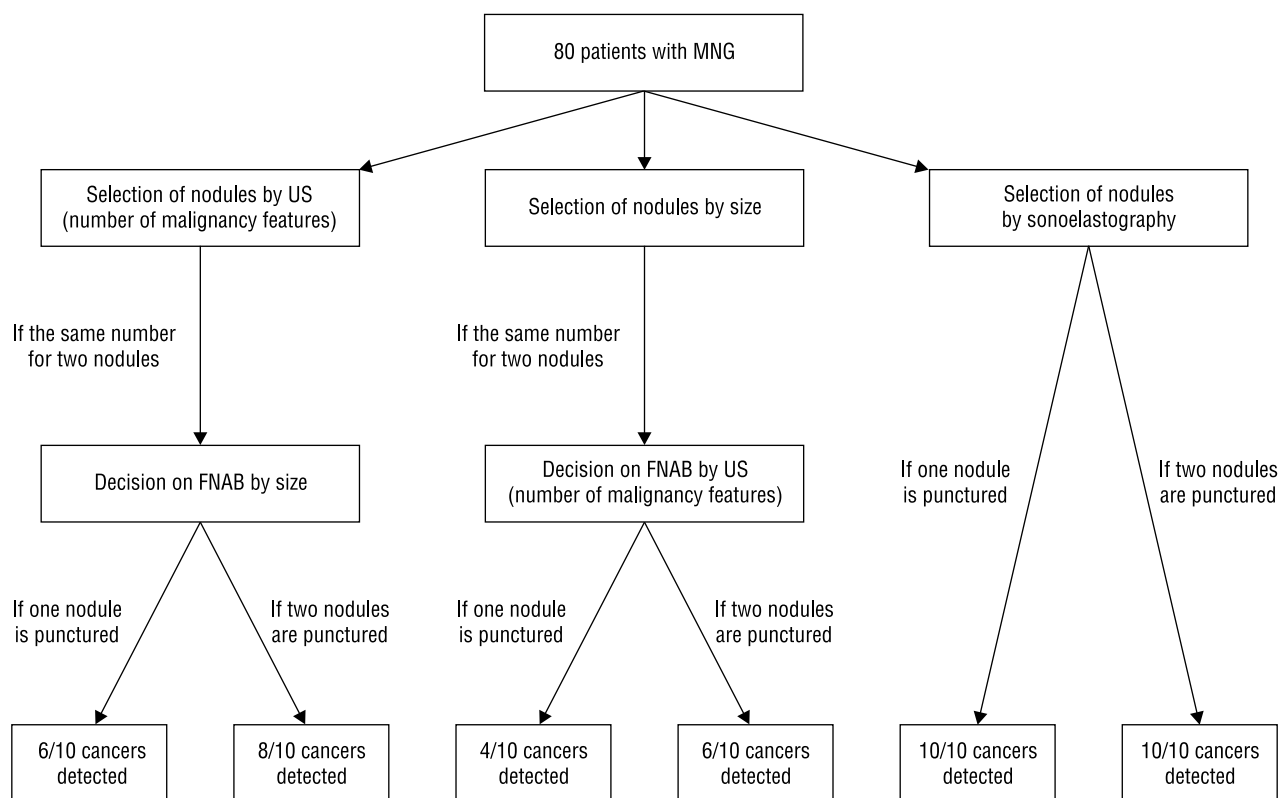


Figure 1. The three different algorithms for selecting the most suspicious nodules for fine-needle aspiration biopsy (FNAB) in patients with multinodular goitre (MNG). The three are: number of malignancy markers on ultrasonography (US), size, and sonoelastography (quantitative scale)

Rycina 1. Porównanie trzech algorytmów wyboru najbardziej podejrzanych zmian do biopsji cienkoigłowej w przypadku wola wieloguzkowego uwzględniające wielkość, liczbę podejrzanych cech sonograficznych oraz elastyczność zmiany

diagnosed on histopathology. Seven of them were papillary thyroid cancers (PTCs), two follicular thyroid cancers (FTCs), and one medullary thyroid cancer (MTC). Among patients with thyroid cancer (TC), there were three men and seven women. Mean age was 48.4 years with SD of 12.5 years for patients with TC and 53.4 with SD 11.8 for those with benign lesions. This difference was not significant ($p = 0.22$).

Mean size of TC was 15.6 mm, SD 12.0 mm, standard error of mean (SEM) 3.8 mm. In the whole group of benign nodules, the mean size was 16.5 mm with SD 10.4 and SEM 0.6. The differences between two groups were non-significant ($p = 0.79$). Four cancers were the biggest lesions in MNG, while one was one of the two equally biggest (taking into account maximal diameter).

The median of suspected US features was 2.5 for TCs (range 2–4) and 2 for benign lesions (range 0–5). Three of ten cancers possessed the highest number of suspicious features in MNG, a further four had the same number of suspicious features as at least one benign lesion in the same patient. For the whole investigated group, median tissue stiffness in SWE was 88.16 kPa for cancers (range 26.0–294.0 kPa) and 36.44 kPa (range 1.2–144.7 kPa) for benign nodules ($p = 0.0002$). All ten cancers were the

least elastic lesions in MNG (using quantitative data on maximal tissue stiffness).

Two diagnosed follicular TCs had mean stiffness equal to 38.8 and 83.7 respectively. Their sizes were 48 and 9 mm respectively. The first one had two suspected features (solid character, hypoechogenicity), and the second one had three features (solid character, hypoechogenicity, microcalcifications). In the case of the only one diagnosed medullary TC, mean stiffness was 294 kPa — it was the least elastic lesion found in our study. Maximal diameter of this nodule was 12 mm, it had only one suspected feature (diffused margins). All ten cancers were the least elastic lesions in MNG (using quantitative data on maximal tissue stiffness).

Figure 1 compares the effectiveness of three various algorithms for selecting nodules for FNAB in MNG. The first algorithm demonstrates how many of ten cancers from the studied group would undergo biopsy if the number of US malignancy features was used as the main criterion (and size as a secondary criterion in a case of an equal number of malignancy features for two or more lesions). The second algorithm presents how many of ten cancers from the studied group would undergo biopsy if size was used

as the main criterion (and US as a secondary criterion in a case of an equal size of two or more lesions). The last algorithm depicts how many of ten cancers from the studied group would undergo biopsy if elasticity assessed in quantitative scale was used as the main criterion.

Discussion

According to our results, the size of the nodule, being rather historical but still traditionally considered as a criterion for the selection of nodules for biopsy, partially present in most guidelines containing some size thresholds influencing the diagnostic procedures did not prove to be a predictor of malignancy at all. Thyroid cancers were even insignificantly smaller than benign lesions. This outcome is in concordance with many other studies indicating that small size is not a predictor of benignancy. A large retrospective study performed by Ahn et al. [20] reported that mean size of benign nodules was 17.9 mm, malignant — 12.1 mm. In a prospective study performed by Bojunga et al. [21], TCs were slightly bigger than other lesions but the difference was statistically insignificant. According to our results, taking into account the size as the most important feature, and US features of malignancy only in a case of lesions presenting equal size, would lead to the omission of 60% of cancers in MNG if one puncture is performed and 40% in case of two punctures per procedure.

Conventional US malignancy markers turned out to be more helpful than size. However, markers of malignancy were very often present also in cases of benign nodules. If we assume that two punctures during one procedure in a patient are performed, taking the US appearance as the main criterion of selection, we would omit 20% of cancers. This is a considerable amount, as the mean nodularity in patients with TCs was 3.9 nodules per patient, hence if performing two biopsies per patient, more than half of the nodules would be punctured. If one biopsy was performed in a patient, as much as 40% of cancers would be omitted.

According to our results, SWE turned out to be a valuable tool in selecting nodules for biopsy in a case of MNG, superior to size or conventional US features of malignancy. All TCs were the stiffest lesions in MNG. It is worth noting that even nodules of which the stiffness was quite low in an absolute quantitative scale were the hardest in particular MNGs. Previously published papers on the topic of SWE in the differentiation of malignant and benign nodules brought promising results. Veyrieres et al. [22] achieved sensitivity of 80.0% and specificity of 90.5% taking 66 kPa as a cut-off point and reported high inter-observer

agreement. Sebag et al. [23] gained sensitivity of 85.2% and specificity of 93.9% using 65 kPa as threshold value of maximal stiffness. Kim et al. [24] reported slightly lower sensitivity (76.1%) and markedly lower specificity (64.1%) for 65 kPa. However, none of the above studies considered the issue of nodules co-located in MNG.

The background to these findings requires further studies. According to the results of many molecular researchers, there are significant changes in the expression of numerous proteins participating in extracellular matrix formation, cellular adhesion etc. beginning in the early stages of TC development [25–26]. These changes may lead to an increase of the stiffness of lesions and elastographic changes parallel to molecular ones. At some point, stiffness of a nodule becomes outstanding from other lesions.

To the best of our knowledge, this is the first report on the utility of shear-wave elastography in differential diagnostics of malignant and benign thyroid lesions performed on a sizable group of patients published in the Polish medical literature.

On the basis of our results, the relatively high stiffness of a lesion, compared to other nodules from same MNG, should be considered as a strong argument for choosing that particular one for FNAB. However, although our included group could be considered large, the number of TCs in MNGs remains insufficient to arrive at a definite conclusion. This issue requires further investigations on larger groups of patients.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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