Value of ultrasound-guided fine-needle aspiration biopsy of thyroid nodules in an endemic goitre area

P. Mikosch[1], H.J. Gallowitsch[1], E. Kresnik[1], J. Jester[2], FG. Würtz[2], K. Kerschbaumer[2], O. Unterweger[1], HP. Dinges[2], P. Lind[1]

[1] Department of Nuclear Medicine and Special Endocrinology, LKH Klagenfurt, St. Veiterstr. 47, A-9020 Klagenfurt, Austria
[2] Department of Pathology, LKH Klagenfurt, St. Veiterstr. 47, A-9020 Klagenfurt, Austria

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Abstract. The aim of this study was to determine the value, advantages and limitations of ultrasound-guided fine-needle aspiration biopsy (US-FNAB) in an endemic goitre area. US-FNAB was performed on all outpatients who presented with hypoechoic and/or hypofunctional and/or growing nodules. A total of 4518 US-FNABs were performed and 718 patients from this series underwent surgery. Cytological results of the primarily performed US-FNAB of these patients were compared retrospectively with the histological results. US-FNAB results were grouped as (1) non-malignant (*n*=303), (2) non-malignant follicular proliferation (*n*=177), (3) malignancy cannot be ruled out (*n*=133), (4) malignant (*n*=61), (5) inadequate (*n*=34), and (6) sampling error; biopsy of a non-malignant nodule (*n*=10). Nodules as small as 5 mm in diameter could be biopsied, gaining representative material. US-FNAB found a malignant or suspicious cytology in 65 out of 87 cases with malignant histology (74.71%). Diagnosis of early tumour stages was often possible: 12 of 18 thyroid carcinomas biopsied and smaller than 10 mm in diameter had malignant or suspicious cytology (groups 3 and 4). US-FNAB was performed incorrectly within non-malignant nodules in ten patients (1.39%) with multinodular goitre (ten papillary carcinomas, nine smaller than 10 mm). Regarding the cytology of groups 1 and 2 as benign and those of groups 3 and 4 as malignant, US-FNAB performance was as follows: sensitivity 87.84%, specificity 78.50%, negative predictive values 98.13%, positive predictive values 33.51% and accuracy 79.53%. Biopsies with inadequate material were obtained in 4.73% of all biopsies. No major adverse effects occurred. Re-biopsies in 61 cases did not alter the cytological outcome in those cases where adequate material was obtained. US-FNAB is a valuable method in the pre-operative assessment of thyroid nodules in order to select patients for surgery, as malignancy can often be detected even in early tumour stages. However, even with ultrasonographic guidance, the minimal tumour size detectable by US-FNAB is around 5 mm. The cytological interpretation in cases with regression and microfollicular proliferation also sets limits on the method. However, patients with non-malignant cytologies can be followed up safely by sonography due to the high NPV of US-FNAB as long as thyroid nodules do not become larger. Re-biopsies seem to be of limited value as long as adequate material was obtained by US-FNAB.

Key words: Thyroid carcinoma – Thyroid nodules – Fine-needle aspiration biopsy – Ultrasonographic guidance – Preoperative management

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Introduction

The reliability of palpation in the detection of thyroid nodules is poor [1–3]. A major step forward in the assessment of the thyroid gland's morphology has been the broad introduction of ultrasonography [4]. The prevalence of thyroid nodules rises from 4–7% using palpation alone to 30–50% using ultrasonography [5]. Although interobserver variations are great [6, 7], today the method is regarded as the "golden standard" of routine morphological evaluation for the thyroid gland [6]. Although thyroid nodules are only malignant in 3–5% [6, 8], especially hypoechoic nodules have to be regarded as potentially malignant. However, ultrasonography can only image [1], but not distinguish between benign and malig-

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Correspondence to: P. Mikosch, Department of Nuclear Medicine and Special Endocrinology, Landeskrankenhaus Klagenfurt, St. Veiterstr. 47, A-9020 Klagenfurt, Austria

nant lesions [5, 6]. Clinical or ultrasonographic controls include the major risk of a loss of time in cases of potential malignancies. Consequently, the best method for a preoperative diagnostic evaluation is fine-needle aspiration biopsy (FNAB) [1, 5, 9–11]. This method allows patients to be detected with suspicious and malignant nodules, who need to have surgery, out of the great number of patients with thyroid nodules [6, 8, 9, 12]. The efficacy of this diagnostic approach is already well established [8, 9]. However, the performance of conventional FNAB without ultrasonographic guidance (C-FNAB) has shown limitations for different reasons [4, 11, 13], with sampling errors in small, non-palpable nodules [4, 13] being the most eminent one. Moreover, C-FNAB shows non-diagnostic aspirates in up to 20% [14].

Austria is an endemic goitre area. Although the increase of iodine supplementation to 20 mg KI/kg salt in 1990 already normalised iodine excretion [15, 16] and decreased goitre size [15], thyroid nodules are still a common problem, especially in the elderly who had an iodine deficiency for a long time during their lives. Thus, patients with nodular goitre, most of them with multinodular goitre, are still common in Austria. In such an endemic goitre area, ultrasonography combined with ultrasound-guided fine-needle aspiration biopsy (US-FNAB) seems to be the method of choice for broad-scale evaluation of thyroid nodules [10] in order to select patients who should undergo surgery.

This study was based on a comparison of cytological results obtained by US-FNAB with the histological diagnoses with the aim of determining the sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and accuracy for US-FNAB in an endemic goitre area and to analyse the values, advantages, limitations and sources of errors of the method.

Materials and methods

Ultrasonography of the thyroid gland was performed after clinical examination and palpation. Thyroid nodules were defined by their sonographic properties in terms of their echogenity, homogeneity of structure, microcalcifications and their boundaries. Ultrasound scanners were either a Picker 9100 or Kretz Technik ACA 5.0 equipped with a 5 MHz (Picker 9100) and a 7.5 MHz curved array transducer (Kretz Technik ACA 5.0). Moreover, technetium-99m-pertechnetate scintigraphy gave additional information about the nodules' functions.

In order to select patients for surgery, US-FNAB was performed in all outpatients who presented with hypoechoic nodules by ultrasound and/or hypofunctional nodules in the scintiscan. Other criteria for a "suspicious nodule" were irregular margins, intranodular microcalcifications and growth of the nodule during the follow-up investigations. In patients with more than one hypoechoic nodule, the most suspicious one was biopsied according to the criteria mentioned.

The biopsy was performed free-handed with a 21-gauge needle attached to a 20 ml syringe by four physicians experienced in the performance of US-FNAB. The biopsy procedure was in general comparable to the method described recently by Yokozawa et al. [13]. However, in our study, biopsy material was acquired by a "poking" technique rather than by a "drill" one. Moreover, ultrasonographic guidance was maintained during all phases of the biopsy procedure (Figs 1–3). Four specimens were placed on glass slides. Three smears were stained by May-Grünwald-Giemsa and one by Papanicolaou stain. Cytological interpretation was performed by nine experienced cytopathologists based on the guidelines of cytopathology diagnosis published by DeMay [17].

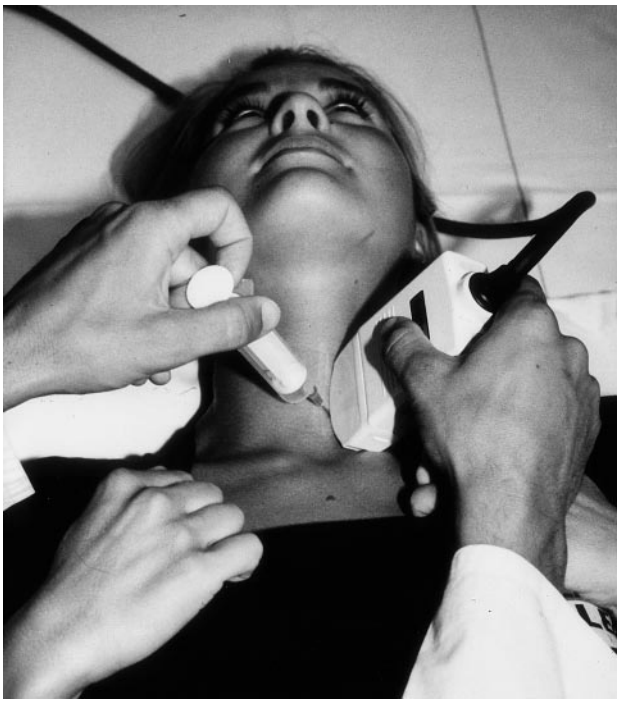

Fig. 1. The patient is positioned in a supine position. After obtaining the ultrasonographic status, the ultrasound gel is cleared from the neck, and an antiseptic solution is applied over the biopsy area. Afterwards the transducer is placed over the nodule of interest and the fine-needle is inserted beside the centre of the transducer. The transducer is held by the right and the biopsy equipment by the left hand

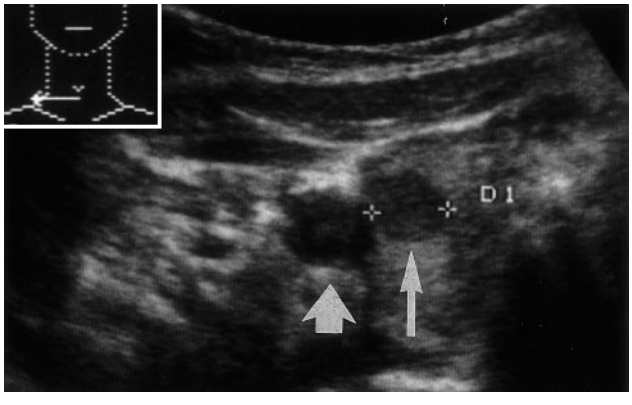

Fig. 2. Ultrasonography, transversal section: hypoechoic nodule in the lateral portion of the right lobe (*thin arrow*). Close to the nodule, the right carotid artery can be seen (*thick arrow*)

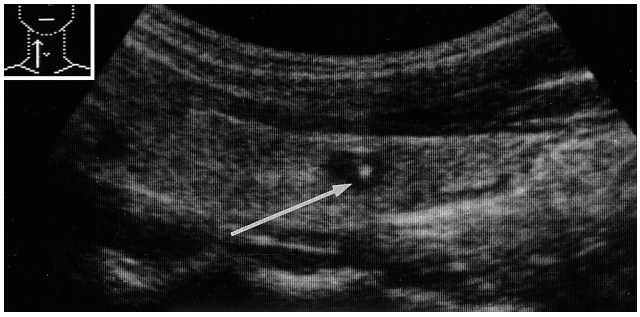

Fig. 3. Ultrasound, longitudinal section of the hypoechoic nodule seen in Fig. 2 during the US-FNAB. In the centre of the nodule the needle tip can be seen as a bright spot (*arrow*). The whole biopsy procedure is visualized, as the ultrasound transducer remains in position over the nodule of interest during the whole biopsy. This technique minimizes the possibility of aspiration of perinodular material and injury to other adjacent neck structures. Moreover, it allows material in large thyroid nodules to be sampled from the most suspicious area

Table 1. The groups of cytological results obtained by US-FNAB of 718 patients who underwent thyroid surgery.

Groups	Cytological results	US-FNAB
1	Non-malignant	303
2	Non-malignant follicular proliferation	177
3	Malignancy not to be ruled out (suspicious)	133
4	Malignant	61
5	Inadequate material	34
6	Sampling error (non-malignant nodule biopsied)	10

Tumour staging was performed according to the pTNM classification [pathological tumour-node metastasis classification proposed by the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC)] [18]. Reasons for surgery were either malignant or suspicious cytological findings or mechanical obstruction within the thyroid region as a result of the goitre.

Between August 1994 and December 1996, 41,735 outpatients were seen in the thyroid ward. During this period, 4518 US-FNABs were performed. For this study, the US-FNAB results of 718 patients who underwent surgery afterwards were compared retrospectively with the histological results. Because Austria is an endemic goitre area, most of the biopsied patients had more than one nodule in sonography (188 patients with two nodules, 267 more than two nodules); 263 patients had one thyroid nodule.

The US-FNAB results of the 718 patients were grouped as: (1) non-malignant (n=303), (2) non-malignant follicular proliferation (polymorphic micro- and macrofollicular proliferations with colloid) (n=177), (3) malignancy cannot be ruled out (smears with oxyphilic cells, atypical cells and monomorphic microfollicular lesions with few or no colloid) (n=133), (4) malignant (n=61), (5) inadequate (less than five clusters of follicular cells on at least two smears; n=34), and (6) sampling and selection error (biopsy of a non-malignant nodule in a multinodular goitre; n=10; Table 1).

For statistical analysis, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for US-FNAB were calculated as previously described [19, 20]. Cytological results of group 1 and 2 were regarded as benign and of group 3 and 4 as potentially malignant or malignant. Inadequate cytological preparations (group 5) and patients with multinodular goitre where US-FNAB was performed within a non-malignant nodule (group 6) were excluded for the statistical calculations on the performance of US-FNAB [10, 21].

Results

The histological findings in correlation with the different cytological groups were as follows: The non-malignant status of US-FNAB of group 1 (non-malignant) was confirmed in 300 patients (300/303; 99.01%). Among the patients in group 2 (non-malignant follicular proliferation), two had a minimally invasive follicular thyroid carcinoma (2/177; 1.13%). However, in this group another three papillary (three pT1) and one medullary (pT2) thyroid carcinoma were found in the final histology (4/177; 2.26%). In group 3 (malignancy cannot be ruled out), histology was malignant in 11 patients (11/133; 8.27%), and in group 4 (malignant), malignancy was confirmed by histology in 54 out of 61 patients (54/61; 88.52%). Regarding the cytological results of groups 1 and 2 as benign and the results of groups 3 and 4 as malignant, the performance of US-FNAB was as follows: sensitivity 87.84%, specificity 78.50%, NPV 98.13%, PPV 33.51%, accuracy 79.53%.

US-FNAB allowed biopsy nodules as small as 5 mm in diameter to be obtained with representative cytological results. A cytological diagnosis of thyroid carcinomas with a nodule size smaller than 10 mm (all pT1 carcinomas and those pT4 carcinomas with a diameter smaller 10 mm) was often possible (Table 2). Eighteen of 27 carcinomas with a diameter smaller than 10 mm were biopsied and in 12 out of 18 cases a malignant or suspicious cytological result was established. However, as only the most suspicious nodules were biopsied, US-FNAB was performed incorrectly within non-malignant nodules (1.39% of all US-FNAB) in ten patients with multinodular goitre (group 6) and in whom malignancy was proved by histology (ten papillary thyroid carcinomas, nine smaller than 10 mm, diameter range: 1.5–13 mm, median: 7 mm; mean: 6.3 mm).

Adequate cytological results were obtained in 95.27%. The frequency of inadequate biopsies (group 5) was very low (4.73%). In this group three patients had a thyroid carcinoma (3/34; 8.82%) (Table 3).

Besides inadequate biopsies and sampling errors, other pitfalls were minimally invasive carcinomas (n=4), thyroid carcinomas smaller than 5 mm (n=1), regressive and cystic nodules (n=2), immunothyroiditis (Hashimoto; n=1) and large, inhomogeneous thyroid nodules (n=1; Table 3).

In large thyroid nodules, US-FNAB showed advantages in the biopsy of sonographically inhomogeneous

Table 2. Results of US-FNAB in patients with malignant histologies of the thyroid gland. The results are grouped according to the cytological results of US-FNAB and the final histological outcome

Tumour type/stage	Diagnosed (groups 3,4)	Undiagnosed (groups 1,2)	Inadequate material (group 5)	Not biopsied (group 6)
Papillary thyroid cancer				
pT1	5	4	1	6
pT2	13	1		1
pT3	2			
pT4<1 cm	5		1	3
pT4>1cm	23		1	
Follicular thyroid cancer				
pT1	2			
pT2	4	2		
pT3	1	1		
pT4>1 cm	1			
Non-differentiated thyroid cancer	4			
Medullary thyroid cancer	1	1		
Metastases	2			
Parathyroid cancer	1			

Table 3. Reasons for non-diagnosed thyroid carcinomas by US-FNAB. The cases also include thyroid carcinomas that were not biopsied due to sampling errors in multinodular goitre

Reasons for sampling errrors and pitfalls using US-FNAB	
Multinodular goiter, thyroid carcinoma in a non-biopsied nodule (group 6)	10
Thyroid carcinoma smaller than 5 mm in diameter	1
Minimally invasive thyroid carcinoma	4
Cystic or regressive nodule with thyroid carcinoma	2
Immunthyroiditis Hashimoto with thyroid carcinoma	1
Large thyroid nodule, biopsy of wrong nodule area	1
Inadequate biopsy	3

nodules, as visual control allowed the biopsy needle to be placed in the most suspicious area of the nodule.

As a result of sonographic guidance during all phases of the biopsy procedure, no major complications occurred during the study period. Only a few patients (n=17; 2.36%) reported local pain within 24 h after the biopsy.

Re-biopsies were performed in 61 cases of the 718 patients who underwent surgery. In most cases the cytolocical results did not change the initial US-FNAB results. Five cases with inadequate biopsy material during the first US-FNAB and an adequate biopsy result in the re-biopsy were the exceptions. In another two cases microfollicular proliferation was initially found and in the re-biopsy oxyphilic cells were found in addition. However, all seven cases had a benign final histology.

Discussion

Ultrasonography is already widely used to obtain the initial morphological information on the thyroid gland [6]. The consequence is the detection of a great number of occult thyroid nodules [2, 5] with only a small number of them being malignant. The clinician is thus faced with a dilemma in managing thyroid nodules, and the detection of thyroid carcinomas is especially like searching for a needle in the haystack.

Against this background, the use of US-FNAB in our study presented a promising result for this method: On the one hand, in our study the rate of biopsies with inadequate material was very low with 4.73%. This rate is comparable to other studies using ultrasound guidance for FNAB [10, 21], and it is much lower than with C-FNAB [5]. Ultrasound guidance may thus reduce the need for repeated FNABs in the future, as prior to the introduction of US-FNAB repeated biopsies of one nodule were the only way to decrease sampling errors, false-negative or inadequate cytological preparations obtained by C-FNAB [5, 9, 22, 23].

On the other hand, US-FNAB even detected biopsy nodules as small as 5 mm in diameter, providing representative cytological results. Therefore, the method often even detects tumours in early stages (Table 2) [10]. The most important factor in these results seems to be the visual control of the needle location during all phases of the biopsy

[13] (Figs. 1, 2). Thus, in malignant nodules, the surgery strategy could be already planned in advance and in suspicious nodules, the additional use of an intraoperative section could be included in the intraoperative management.

Finally, most of the 4518 US-FNABs performed during the study period showed a benign cytology, with the consequence that these patients were not referred to surgery. Re-biopsies in this study and re-evaluations of thyroid nodules [24, 25] in other studies presented no changes of the cytologies in most cases [9,25]. Consequently, because of these facts and the very high NPV of 98.13% for US-FNAB in this study, patients with non-suspicious cytologies (group 1) could be followed up safely by sonography as long as the thyroid nodules remain constant in size [24].

Therefore, out of the great number of patients with thyroid nodules referred to our thyroid ward for further investigations, US-FNAB allowed very good selection of the nodules that needed to undergo surgery, a fact already demonstrated by other authors [5, 26, 27] and the use of US-FNAB should therefore decrease the number of operations [5, 6].

However, sonographic guidance for biopsy of thyroid nodules has not been common in the past. Three recent studies [4, 10, 27] compared US-FNAB versus C-FNAB. The studies showed a global improvement of diagnostic accuracy in the preoperative selection of patients [10]. Our own results presented an accuracy of 79.53%. This accuracy is in accordance with other studies [14, 20, 21, 26] supporting the importance of US-FNAB in the preoperative management of thyroid nodules [20, 21, 26, 27]. Gharib [9] even reported a 95% accuracy after a review of several studies. The lower accuracy in our study may have been due to the fact that: (1) in most cases only one US-FNAB was performed, (2) many patients had multinodular goitre and (3) many patients had very small thyroid nodules. Last but not least, the difference may be also due to another very important fact: (4) the method of data analysis regarding microfollicular proliferations and occult carcinomas. In our survey the indeterminate cytological pattern of a monomorphic microfollicular lesion (suspicion of a follicular neoplasm; group 3) was grouped together with malignant cases in the statistical evaluation. In most cases these nodules turned out to be microfollicular benign adenomas and were interpreted as false-positives. Moreover, papillary carcinomas smaller than 10 mm in diameter (occult carcinomas), not diagnosed by US-FNAB, were also called false-negative results.

Because of this last fact, an extensive work-up of thyroid nodules may lead to the situation where occult papillary thyroid carcinoma is frequently identified. Depending on the methodology and accuracy of the histological examination [28] and differences between geographic regions [29], incidences up to 35% (Finland 35.6%; Japan 30.7%; Hawaiian Japanese 24.2%) by autopsies [30], surgery [29, 31, 32] or ultrasonography [2] have been found, whereas investigations from other regions, including Austria and Germany [33], have reported mainly incidences between 5% and 10% [29]. In general, this means a tenfold increase of thyroid nodules versus palpation [1]. Therefore, extensive diagnostic work-up of all asymtomatic patients with thyroid nodules smaller than 10 mm in diameter is still controversial [4]. However, the different arguments for an extensive investigation of thyroid nodules favouring US-FNAB as opposed to C-FNAB have to be considered.

In their study Yokozawa et al. [13] reported 15.9% extrathyroidal invasion of all carcinomas smaller than 1 cm. In our investigation, 9 patients out of 27 (33.33%) with a tumour size smaller than 10 mm had extrathyroidal invasion. This amounted to 26.47% of all tumours (34 cases) of stage IV (pTNM classification). Because stage IV tumours have the worst outcome [34], based on our results, we even recommend biopsy of thyroid nodules smaller than 10 mm in diameter. A biopsy of such small structures can only be performed reliably with ultrasonographic guidance [4, 10, 13, 14, 20].

Besides the advantages of US-FNAB over C-FNAB for very small thyroid nodules [10], US-FNAB also shows advantages in the biopsy of large, sonographically inhomogeneous or cystic nodules [4, 13], as visual control allows the biopsy needle to be placed in the most suspicious area of the nodule [4, 13].

Another argument for the use of ultrasonographic guidance of FNAB is that thyroid nodules are located close to the margins of the thyroid gland (Fig. 2) and close to other neck structures (e.g. trachea, oesophagus, carotid artery). Visual control by ultrasonography decreases the possibility of injury of these structures (Fig. 3). For this reason, no major complications of US-FNAB were observed during the study period.

Besides the arguments favouring the use of US-FNAB in the diagnostic work-up of thyroid nodules, one should be aware of the limitations of the method for different reasons (Table 3) [11, 13]. Firstly, certain cytological results are inconclusive and cannot exclude malignancy [5, 22, 23]. This is especially true for cytology of follicular proliferation, follicular neoplasm and oncocytic lesions. In our study the groups with non-malignant follicular proliferation (group 2) and malignancy not to be ruled out (group 3; including cases with follicular neoplasm) were rather large. The reason why so many aspirates were diagnosed as follicular proliferations may be due to the fact that Austria is an endemic goitre area. Hall et al. [11] demonstrated that nodular goitre may be a source of error when the diagnosis of follicular proliferation is made. Moreover, different cytological findings may lead to interpretation errors [23] with overdiagnosing benign lesions as potentially malignant or crossover diagnosis between follicular and papillary lesions.

Furthermore, there is a minimal nodule size that can be biopsied to achieve representative cytological specimens [13]. Although nodules as small as 2 mm can be biopsied [13], cytological preparations of nodules small-

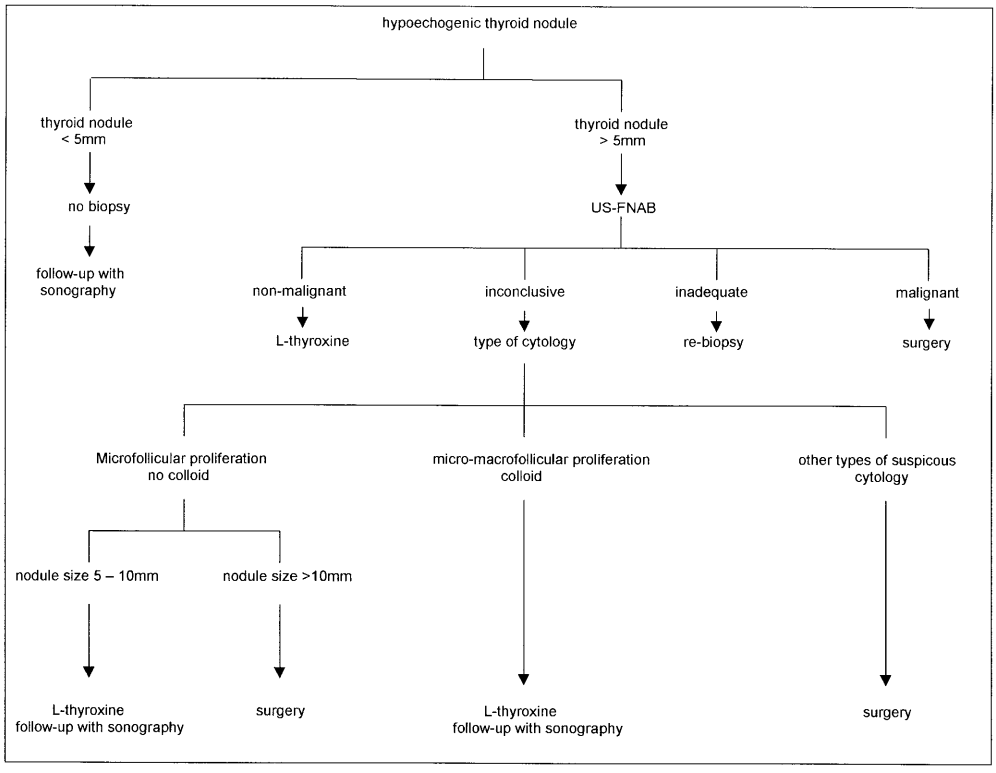

Fig. 4. Algorithm for the management of hypoechogenic thyroid nodules

er than 5 mm in diameter were rarely representative in our survey. Moreover, the biopsy of such small lesions includes the risk of aspirating perinodular thyroid tissue, which would then simulate a benign lesion [22]. Therefore, we suggest a follow-up approach of 6- to 12-month intervals for these very small lesions, as already proposed by others [9, 35].

Another limitation is multinodular goitres. The problem for the investigator is to select nodules for biopsy. As Austria is an endemic goitre area, the authors of this study were frequently confronted with this problem, especially in elderly patients where biopsies of all nodules are not possible. Although different criteria for selecting thyroid nodules for US-FNAB were applied (see materials and methods), incorrect selection occurred in ten patients with papillary thyroid carcinomas (group 6). Nine of these carcinomas were smaller than 10 mm in diameter and even if several thyroid nodules were biopsied, these thyroid carcinomas would probably be overlooked. Only one papillary carcinoma pT2 (13 mm in diameter) of a 72-year-old woman was not biopsied because a second nodule of this patient showed a significant increase in size in comparison to previous investigations. The nodule with the thyroid carcinoma presented no increase in size over the prior investigations and was therefore unsuspicious for the investigator.

Finally, we must mention that the results of US-FNAB also depend greatly on the operator's ability to perform US-FNAB [6, 7, 11, 23] and on the cytopathologist's experience in thyroid cytodiagnostics [11]. Frequent performance and interpretation of US-FNAB improve the outcome of the investigation [9, 11].

To summarize the advantages, disadvantages and limitations of US-FNAB, the clinician may now ask the question of how the diagnosis of thyroid nodules, especially hypoechogenic nodules, should be managed and whether it can be optimized. Moreover, which diagnostic methods should be initially performed and do we have to re-evaluate the role of conventional planar thyroid scintigraphy?

The use of ultrasound and ultrasound-guided biopsies can allow detection of small thyroid nodules and evaluation of whether they are malignant, with the consequence that the clinician can even manage safely small thyroid nodules and detect early cancer stages. Our results indicate that the use of US-FNAB allows us to biopsy thyroid nodules as small as 5 mm in diameter safely and accurately. Based on these results concerning nodular size and the different possibilities of US-FNAB results, an algorithm to manage hypoechogenic thyroid nodules is presented in Fig. 4. Nodules smaller than 5 mm in diameter are not biopsied and are always followed up sonographically. Nodules larger than 5 mm in diameter are biopsied, and the two endpoints for the clinician are either surgery or follow-up controls with ultrasound. In follow-up controls, an initial sonographic control is performed after 6 months and if there is no nodular growth, further controls follow at yearly intervals in our department (Table 4).

The use of conventional planar scintigraphy for the evaluation of whether the nodules are malignant or not

has to be reconsidered. In thyroid carcinomas smaller than 10 mm in diameter, in some cases even 20 mm, Kresnik et al. [36] demonstrated that conventional planar thyroid scintigraphy presents either no decrease in tracer accumulation or only an insignificant amount. The explanation for a "normal scintigraphic uptake pattern" in such small thyroid carcinomas may be different: (a) the normal thyroid tissue anterior and posterior of the thyroid carcinoma is projected to the same region in the planar image with the consequence that the normal tracer accumulation of the benign thyroid tissue overlaps with the possible hypofunctional small thyroid carcinoma; (b) the size of the thyroid nodule is below the maximal resolution of the gamma camera. Because of the limitations of conventional planar scintigraphy, different studies [37–40] have tried to evaluate the use and possible benefits of other tracers (technetium-99m-methoxyisobuthylisonitrile, Tc-99m-tetrofosmin, thallium-201) for the preoperative evaluation of thyroid nodules; however, only a very limited value for the preoperative diagnostic workup of thyroid nodules was found for these tracers as well [37–40]. Consequently, as recently concluded by Lind [41], for thyroid nodules smaller than 15 mm in diameter, not only the use of conventional planar scintigraphy, but also scintigraphy with other tracers seems to be of very limited or no value for evaluating the nodule's function and consequently whether it is malignant. Thus, patients with such small thyroid nodules should not undergo scintigraphy [41], whereas for nodules larger than 15 mm in diameter and for multinodular goitres, the use of conventional planar thyroid scintigraphies can still be of value for the clinician in terms of (a) evaluation of the nodule's function and, (b) selection of the nodule that should be biopsied. Only in patients where a surgical approach is difficult or should be avoided (e.g. limited operability of the patient), an additional multitracer imaging approach (Tc-99m-MIBI, Tc-99m-tetrofosmin, Tl-201) may be of some benefit [41].

In conclusion, US-FNAB improves the quality of diagnosis in the preoperative assessment of thyroid nodules to select patients for surgery [10, 12, 14, 20, 27] even in an endemic goitre area. Thus, intra-operative procedures can be planned in advance in cases with malignant cytology, or intra-operative frozen sections may be included in cases with suspicious cytological results. Nodules with non-suspicious cytological findings can be safely followed up with ultrasonography [9, 35]. Altogether, US-FNAB should reduce the number of surgical interventions [1, 5, 12] and may avoid a two-step surgery approach in cases of thyroid carcinomas. Consequently, US-FNAB can be highly recommended for clinicians working in the field of the thyroid [9, 10, 13, 21], and it has to be regarded as the key investigation for assessing the malignity of thyroid nodules. Optimized results can be obtained when US-FNAB is performed and evaluated by experienced operators [1] and cytopathologists [9,11].

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References

1. Mazzaferri EL. Management of a solitary thyroid nodule. *N Engl J Med* 1993; 328: 553–559.
2. Brander A, Viikinkoski P, Nickels J, Kivisaari L. Thyroid gland: US screening in a random adult population. *Radiology* 1991; 181: 683–687.
3. Mortensen JD, Wooler LB, Bennett WA. Cross and microscopic findings in clinicallly normal thyroid glands. *J Clin Endocrinol Metab* 1955; 15: 1270–1280.
4. Khurana KK, Richards VI, Chopra PS, Izquierdo R, Rubens D, Mesonero C. The role of ultrasonography-guided fine-needle aspiration biopsy in the management of nonpalpable and palpaple thyroid nodules. *Thyroid* 1998; 8: 511–515.
5. Caruso D, Mazzaferri EL. Fine needle aspiration biopsy in the management of thyroid nodules. *Endocrinologist* 1991; 194–202.
6. Hegedüs L, Karstrup S. Ultrasonography in the evaluation of cold thyroid nodules. *Eur J Endocrinol* 1998; 138: 30–31.
7. MacDonald L, Yazdi HM. Nondiagnostic fine needle aspiration biopsy of the thyroid gland: a diagnostic dilemma. *Acta Cytol* 1996; 40: 423–428.
8. Belfiore A, La Rosa GL, La Porta GA, Giuffrida D, Milazzo G, Lupo L, Regalbuto C, Vigneri R. Cancer risk in patients with cold thyroid nodules: relevance of iodine intake, sex, age, and multinodularity. *Am J Med* 1992; 93: 363–369.
9. Gharib H. Fine-needle aspiration biopsy of thyroid nodules: advantages, limitations and effect. *Mayo Clin Proc* 1994; 69: 44–49.
10. Danese D, Sciacchitano S, Farsetti A, Andreoli M, Pontecorvi A. Diagnostic accuracy of conventional versus sonography-guided fine-needle aspiration biopsy of thyroid nodules. *Thyroid* 1998; 8: 15–21.
11. Hall TL, Layfield LJ, Philippe A, Rosenthal DL. Sources of diagnostic error in fine needle aspiration of the thyroid. *Cancer* 1989; 63: 718–725.
12. Garcia-Mayor RV, Perez Mendez LF, Paramo C, Luna Cano R, Rego Iraeta A, Regal M, Sierra JM, Fluiters E. Fine-needle aspiration biopsy of thyroid nodules: impact on clinical practice. *J Endocrinol Invest* 1997; 20: 482–487.
13. Yokozawa T, Miyauchi A, Kuma K, Sugawara M. Accurate and simple method of diagnosing thyroid nodules by modified technique of ultrasound-guided fine needle aspiration biopsy. *Thyroid* 1995; 5: 141–145.
14. Carmeci C, Jeffrey RB, McDougall IR, Nowels KW, Weigel RJ. Ultrasound-guided fine-neele aspiration biopsy of thyroid masses. *Thyroid* 1998; 8: 283–289.
15. Gallowitsch HJ, Mikosch P, Kresnik E, Gomez I, Plöb J, Pipam W, Lind P. Schilddrüsenvolumina und Jodversorgung 6- bis 17jähriger Schüler (Thyroid volumes and iodine supply of 6 to 17 year old pupils). *Nuklearmedizin* 1994; 33: 235–238.
16. Bacher-Stier C, Riccabona G, Totsch M, Kemmler G, Oberaigner W, Moncayo R. Incidence and clinical characteristics of thyroid carcinoma after iodine prophylaxis in an endemic goiter country. *Thyroid* 1997; 7: 733–741.

17. DeMay RM. *The art and science of cytopathology*. Chicago: ASCP Press; 1996: 704–778.
18. Beahrs OH, Henson DE, Hutter RUP, et al. *Manual for staging of cancer*. American Joint Commission on Cancer, ed 3. Philadelphia, JB Lippincott, 1988.
19. Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: an appraisal. *Ann Int Med* 1993; 118: 282–289.
20. Rosen IB, Azadian A, Walfish PG, Salem S, Lansdown E, Bedard YC. Ultrasound-guided fine-needle aspiration biopsy in the management of thyroid disease. *Am J Surg* 1993; 166: 346–349.
21. Cochand-Priollet B, Guillausseau PJ, Chagon S, Hoang C, Guillausseau-Scholer C, Chanson P, Dahan H, Warnet A, Tran Ba Huy P, Valleur P. The diagnostic value of fine-needle aspiration biopsy under ultrasonography in nonfunctional thyroid nodules: a prospective study comparing cytologic and histologic findings. *Am J Med* 1994; 97: 152–157.
22. Hamburger JI. Diagnosis of thyroid nodules by fine needle biopsy: use and abuse. *J Clin Endocrinol Metab* 1994; 79: 335–339.
23. Oertel YC. A pathologist´s comments on diagnosis of thyroid nodules by fine needle aspiration (letter). *J Clin Endocrinol Metab* 1995; 80: 1467–1468.
24. Kuma K, Matsuzuka F, Yokozawa T, Miyauchi A, Sugawara M. Fate of untreated benign thyroid nodules: results of long-term follow-up. *World J Surg* 1994; 18: 495–499.
25. Lucas A, Llatjos M, Salinaas I, Reverter J, Pizarro E, Sanmarti A. Fine-needle aspiration cytology of benign nodular thyroid disease. Value of re-aspiration. *Eur J Endocrinol* 1995; 132: 677–680.
26. Takashima S, Fukada H, Kobayashi T. Thyroid nodules: clinical effect of ultrasound-guided fine-needle aspiration biopsy. *J Clin Ultrasound* 1994; 22: 535–542.
27. Hatada T, Okada K, Ishii H, Ichii S, Utsunomiya J. Evaluation of ultrasound-guided fine-needle aspiration biopsy for thyroid nodules. *Am J Surg* 1998; 175: 133–136.
28. Martinez-Tello FJ, Martinez-Cabruja R, Fernandez-Martin J, Lasso-Oria C, Ballestin-Carcavilla C. Occult carcinoma of the thyroid. A systematic autopsy study from Spain of two series performed with two different methods. *Cancer* 1993; 71: 4022–4029.
29. Fukunaga FH, Yatani R. Geographic pathology of occult thyroid carcinomas. *Cancer* 1975; 36: 1095–1099.
30. Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A “normal” finding in Finland. A systematic autopsy study. *Cancer* 1985; 56: 531–538.
31. Yamashita H, Noguchi S, Watanabe S, Uchino S, Kawamoto H, Toda M, Murakami N, Nakayama I, Yamashita H. Thyroid cancer associated with adenomatous goiter. An analysis of the incidence and clinical factors. *Surg Today* 1997; 27: 495–499.
32. Pelizzo MR, Piotto A, Rubello D, Casara D, Fassima A, Busnardo B. High prevalence of occult papillary thyroid carcinoma in a surgical series for benign thyroid disease. *Tumori* 1990; 76: 255–257.
33. Lang W, Borrusch H, Bauer L. Occult carcinomas of the thyroid. Evaluation of 1.020 sequential autopsies. *Am J Clin Pathol* 1988; 90: 72–76.
34. Loh KC, Greenspan FS, Gee L, Miller TR, Yeo PP. Pathological tumor-node-metastasis (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. *J Clin Endocrinol Metab* 1997; 82: 3553–3562.
35. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. *Ann Intern Med* 1997; 126: 226–231.
36. Kresnik E, Gallowitsch HJ, Mikosch P, Molnar M, Unterweger O, Gomez I, Lind P. Scintigraphic pattern in small thyroid nodules (abstract). *Eur J Nucl Med* 1998; 25: 925.
37. Kresnik E, Gallowitsch HJ, Mikosch P, Gomez I, Lind P. Technetium-99m-MIBI scintigraphy of thyroid nodules in an endemic goiter area. *J Nucl Med* 1997; 38: 62–65.
38. Kresnik E, Gallowitsch HJ, Mikosch P, Molnar M, Pipam W, Gomez I, Lind P. Evaluation of thyroid nodules with technetium-99m tetrofosmin dual-phase scintigraphy. *Eur J Nucl Med* 1997; 24: 716–721.
39. Lind P, Langsteger W, Költringer P, Klima G, Eber O. Value of thallium-201 in the preoperative and postoperative thyroid scintigraphy. *Radiobiol Radiother* 1988; 29: 248–252.
40. Mezosi E, Bajnok I, Gyory F, et al. The role of Tc-99 m methoxyisobuthyl-isonitrile (MIBI) scintigraphy in the differential diagnosis of cold thyroid nodules. *Eur J Nucl Med* 1999; 26: 798–803.
41. Lind P. Multi tracer imaging of thyroid nodules: is there a role in the preoperative assessment of nodular goiter? *Eur J Nucl Med* 1999; 26: 795–797.