REVIEW ARTICLE

Fine Needle Aspiration in the Investigation of Thyroid Nodules

Indications, Procedures and Interpretation

Joachim Feldkamp, Dagmar Führer, Markus Luster, Thomas J. Musholt, Christine Spitzweg, Matthias Schott

SUMMARY

Background: Thyroid nodules are a common finding in Germany. Most are benign; thyroid cancer is very rare. The challenge for the physician is to diagnose malignant tumors early. Fine needle aspiration is an important tool for this purpose.

Method: This review is based on pertinent articles (1980–2014) retrieved by a selective search in PubMed and on the current recommendations of guidelines issued by the specialty societies in Germany and abroad.

Results: Clinical, ultrasonographic, and scintigraphic criteria are used to identify high-risk nodules, which are then further studied by fine needle aspiration. Important ultrasonographic criteria for malignancy are low echodensity (positive predictive value [PPV]: 1.85), microcalcifications (PPV: 3.65), irregular borders (PPV: 3.76), and intense vascularization. Fine needle aspiration of the thyroid gland is an inexpensive and technically straightforward diagnostic procedure that causes little discomfort for the patient. It helps prevent unnecessary thyroid surgery and is used to determine the proper surgical strategy if malignancy is suspected. The cytological study of fine needle aspirates enables highly precise diagnosis of many tumor entities, but follicular neoplasia can only be diagnosed histologically. In the near future, molecular genetic methods will probably extend the diagnostic range of fine needle aspiration beyond what is currently achievable with classic cytology.

Conclusion: Fine needle aspiration biopsy of the thyroid gland in experienced hands is an easily performed diagnostic procedure with very little associated risk. It should be performed on ultrasonographically suspect nodules for treatment stratification and before any operation for an unclear nodular change in the thyroid gland.

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Benign thyroid nodules are common in Germany (1–3). One contributing factor is iodine deficiency, which was prevalent in the country until the beginning of the millennium, but has now been mitigated by the increased use of iodized table salt in private homes, the food industry and animal production.

Thyroid cancer is rare and accounts for less than 1% of all space-occupying lesions of the thyroid (e1). Fine needle aspiration (FNA) biopsy is considered the gold standard diagnostic tool for thyroid nodules. Benign FNA results help to prevent unnecessary thyroid surgery. If malignant cells are detected, the FNA result is a decisive factor in determining the surgical strategy (hemithyroidectomy vs. total thyroidectomy, extent of lymph node dissection).

The indication, significance, limitations, and potential risks of FNA are discussed below in detail.

Methods

The article is based on a review of pertinent articles (1980–2014) that were retrieved by a selective search in the PubMed database employing the search terms “thyroid nodules” and “biopsy”. In addition, the reference sections in the identified original articles and reviews were analyzed. Furthermore, current recommendations of national and international professional societies (European Thyroid Association, British Thyroid Association, and American Thyroid Association) were taken into consideration (4–8).

Criteria for malignancy

Thyroid cancer can already be suspected based on a patient’s clinical history and certain physical examination findings, such as a firm, rapidly growing cervical mass or, less frequently, symptoms of a space-occupying lesion. If this is the case, ultrasonography is indicated for immediate diagnostic evaluation. Should the results be conspicuous, FNA is indicated and, where required, scintigraphy. A history of neck radiation is associated with an increased risk of thyroid cancer. An analysis of pooled data calculated an excess relative risk per Gray radiation dose of 7.7, with an almost linear increase (9). While well-differentiated thyroid carcinoma is rarely hereditary, approximately 25% of medullary thyroid cancer has a genetic cause (e2). Newly developed hoarseness as well as firm palpable lymph nodes may be a sign of thyroid malignancy (e3, e4).

Clinic for General Internal Medicine, Endocrinology, Diabetology, Pneumology, and Infectiology; Bielefeld Clinical Centre, Germany: PD Dr. med. Feldkamp

Department of Endocrinology and Metabolic Disorders, Essen University Hospital, Germany: Prof. Dr. med. Führer

Department of Nuclear Medicine, Philipps University Marburg, Germany: Prof. Dr. med. Luster

Department of General, Abdominal and Transplantation Surgery, University Medical Center of the Johannes Gutenberg University Mainz, Germany: Prof. Dr. med. Musholt

Department of Internal Medicine II, Hospital of the University of Munich, Germany: Prof. Dr. med. Spitzweg
Division of Special Endocrinology, University Hospital of Düsseldorf: Prof. Dr. med. Schott

TABLE 1a

Sonographic patterns, estimated risk of malignancy, and fine needle aspiration guidance for thyroid nodules*

Sonographic pattern	Ultrasound features	Estimated risk of malignancy, %	FNA size cutoff (largest dimension)
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE.	>70–90 [†]	Recommend FNA at ≥ 1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins without microcalcifications, ETE, or taller than wide shape.	10–20	Recommend FNA at ≥ 1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or ETE, or taller than wide shape.	5–10	Recommend FNA at ≥ 1.5 cm
Very low suspicion	Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate, or high suspicion patterns.	<3	Consider FNA at ≥ 2 cm Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	<1	No biopsy [‡]

US-guided FNA is recommended for cervical lymph nodes that are sonographically suspicious for thyroid cancer

[†] The estimate is derived from high volume centers, the overall risk of malignancy may be lower given the interobserver variability in sonography.

[‡] Aspiration of the cyst may be considered for symptomatic or cosmetic drainage.

ETE, extrathyroidal extension.

*according to the American Thyroid Association, 2015 (8)

TABLE 1b

Sensitivity and specificity of ultrasound features of lymph nodes according to current recommendations*

Feature	Sensitivity (%)	Specificity (%)
Microcalcification	5–60	93–100
Cystic aspect	10–34	91–100
Peripheral vascularization	40–86	57–93
Hypoechoogenicity	30–87	43–95
Round shape	37	70

* according to the American Thyroid Association, 2015 (8)

Thyroid ultrasonography

Ultrasonography of the thyroid should be performed by an experienced sonographer, using at least a 7.5 MHz linear ultrasound transducer probe (e5). Thyroid volumetry should always be undertaken.

Description of findings

Any thyroid nodules detected should be described in detail. Documentation should include the following criteria:

- Size (diameters in 3 dimensions)
- Echogenicity (hypoechoic, normoechoic, hyperechoic, anechoic, and complex echoic)
- Cystic areas
- Microcalcifications or macrocalcifications
- Presence of a hypoechoic rim encircling a nodule (halo sign)
- Nodule margins (well-defined versus ill-defined)
- Configuration (asymmetrical, “taller than wide”)
- Vascularization.

The size of a nodule is by itself not a reliable indicator of thyroid cancer (10). A taller-than-wide configuration on transverse view is associated with a slightly increased risk of malignancy (Odds Ratio [OR], 11.1) (11).

The description of the size of a nodule should include the transverse, anteroposterior and longitudinal diameters. An almost accurate calculation of the volume of a thyroid nodule can only be achieved if the lump has an oval shape.

The following B-mode ultrasound criteria are associated with a higher risk of malignancy:

- Hypoechoogenicity
- Poorly-defined margin
- Absence of a halo
- Presence of microcalcifications
- Taller-than-wide configuration on transverse view
- Increased intranodular vascularity.

Combination of ultrasound criteria

Depending on the identified ultrasound criteria for malignancy, thyroid cancer can be predicted with various degrees of probability (10, 12, 13). Specificity varies significantly between studies, ranging from 41% to 92% for hypoechoic nodules (positive predictive value [PPV], 1.85), 44% to 95% for microcalcifications (PPV, 3.65), and 48% to 92% for ill-defined nodular margin (PPV, 3.76) (14). The available data are summarized in the current recommendations of the American Thyroid Association (Table 1a) (8). Overall, however, the significance of ultrasound criteria remains limited. The positive predictive value increases when two or more ultrasound criteria for malignancy are present (e6).

FIGURE

Diagnostic algorithm for the evaluation of a thyroid nodule detected on ultrasonography; TSH, thyroid-stimulating hormone

Lymph node detection

The number of cervical lymph nodes is subject to inter-individual variation. The lymph node hilum is visible in normal, non-pathological lymph nodes in approximately 29% to 87% of cases (e7). Hilum-lymph node blood flow can be detected using color duplex ultrasonography in approximately two thirds of normal lymph nodes. This finding largely excludes lymph node malignancy. Peripherally increased blood flow is observed in approximately 18% of benign lymph nodes. Lymph nodes that have lost their oval shape are suspicious for malignancy (Table 1b) (e8). If a suspicious lymph node is identified in adults with nodular goiter, it can be biopsied with fine needle aspiration, in the same way as a suspected primary tumor, to confirm the diagnosis. Complication rates of lymph node and thyroid FNA biopsies are comparable and in our experience rather low.

Color duplex ultrasonography

Nodules can be categorized based on blood flow levels. While an increased perfusion of the margin is indicative of a benign adenoma, increased intranodular blood flow with and without arteriovenous fistula may indicate thyroid cancer (15, 16).

Elastography

Elastography is not considered a standard technique. It measures the stiffness of thyroid nodules. Thyroid carcinomas frequently demonstrate a higher degree of tissue hardness than benign nodules (for hardness degrees 3 and 4: sensitivity 86% and specificity 87%). The value of elastography is based on its high negative predictive value for nodules assessed as soft and moderate positive predictive value for thyroid cancer in nodules with a high degree of tissue hardness in elastography (e9).

Contrast-enhanced ultrasound

Data published so far have not shown that contrast-enhanced ultrasound brings about a higher detection rate of thyroid malignancy (17). Apparently, contrast-enhanced ultrasound is not superior to the combination of conventional ultrasound and color duplex ultrasonography.

Scintigraphy

Technetium 99m (Tc-99m) pertechnetate scintigraphy can detect lesions with a diameter of ≥ 1 cm which can show either increased, identical or reduced uptake and thus are described as hot, warm or cold nodules on thyroid scans. Simple cysts showing as hypofunctional

lesions on scintigraphy can be considered benign. In the initial workup of thyroid nodules, a thyroid scan in combination with ultrasonography is well suited to identify areas of functional autonomy. These lesions should not be biopsied using fine needle aspiration techniques (18).

Role of other imaging techniques

Neither magnetic resonance imaging (MRI) nor computed tomography (CT) nor other scintigraphic techniques, such as methoxyisobutylisonitrile (MIBI) scintigraphy, are useful in the routine work-up of thyroid nodules and are not recommended by the professional societies (European Thyroid Association [ETA]).

Fine needle biopsy

Indication

The requirements of the European and the US guidelines with regard to the indication for fine needle aspiration biopsy of thyroid nodules are largely along the same lines. Since multinodular goiter is common in Germany, it is advisable to limit the indication for fine needle aspiration biopsy to non-autonomous nodular lesions >1 cm which are identified with the help of scintigraphy. In addition, ultrasound features of the lesion are taken into consideration (*Figure*).

Fine needle biopsy of a thyroid nodule is indicated in the following situations (5–7):

- Patients with clinical signs of thyroid cancer
- Nodules >1 cm with at least two ultrasound criteria for malignancy
- Nodules of any size with extracapsular extension or indeterminate cervical lymph nodes
- Nodules of any size in patients with a history of neck radiation
- History of well-differentiated thyroid carcinoma in more than two first-degree relatives
- Medullary thyroid carcinoma or multiple endocrine neoplasia (MEN) type 2
- Increased calcitonin levels.

Smoking, proton-pump inhibitors, renal failure, and chronic alcohol consumption may lead to a mild to moderate increase in calcitonin levels (check abstinence levels, where appropriate).

Fine needle aspiration biopsy should explicitly not be performed if the nodule represents an area of focal autonomy on thyroid scintigraphy and/or has no ultrasound features suspicious of malignancy. Needle biopsy of simple cysts is not advisable.

Complications

The range of complications associated with FNA biopsy is very small.

Pain: Data on pain associated with FNA are scarce. A mild pain was reported by 8.9% of patients who underwent FNA biopsy (e10).

Bleeding: Easily comparable epidemiological data on the occurrence of bleeding events during or after thyroid FNA biopsy are not available because of the retrospective design of the majority of studies and the

use of different techniques and needle sizes. The published bleeding rates range between 0.3% and 2.3% (e11, e12).

Metastatic spread: In patients with thyroid cancer, metastasis along the needle canal is extremely rare and only few individual case reports have been published (19). This is because well-differentiated thyroid carcinoma, the most common form of thyroid malignancy, is treated with radioiodine therapy which would also eliminate any cancer cells spread during the FNA. The risk of local tumor cell spread is almost always limited to the highly malignant anaplastic carcinoma.

Needle biopsy in patients with anticoagulation therapy

Needle biopsy in patients taking acetylsalicylic acid (ASA, aspirin) can be performed without an increased risk up to a dose of 100 mg ASA (20). Patients receiving higher doses of ASA should pause treatment for 10 days prior to the intervention. In patients taking phenprocoumon/coumadin, it is recommended to hold anticoagulation therapy until the INR (International Normalized Ratio) is <1.5 (bridging with heparin). The last dose of clopidogrel/ticlopidine should be taken at least 24 hours—better 36 to 48 hours—prior to the biopsy.

Fine needle aspiration biopsy can be performed on patients taking nonsteroidal anti-inflammatory drugs with inhibiting effect on platelet function, including diclofenac, ibuprofen, piroxicam, and indomethacin.

Since the experiences with the new oral anticoagulants are limited, the manufacturers' recommendations regarding the discontinuation of the drug prior to a surgical procedure should be followed. Dabigatran should be stopped 2 days prior to biopsy with normal kidney function, 3 days with impaired kidney function, up to 4 days without bridging with more severely impaired kidney function. Rivaroxaban should not be taken 24 hours prior to FNA. Apixaban should be stopped 24 hours—better 48 hours—prior to the intervention.

Contraindications

Bleeding diathesis is not the only contraindication to FNA. A fine needle aspiration biopsy should not be performed on an uncooperative patient and when the cytological result has no therapeutic consequences.

Technique of fine needle biopsy

A fine needle thyroid biopsy should be performed under ultrasound guidance, whenever possible, to be able to document that the needle was correctly placed within the target. Well-palpable nodules which can be accurately classified based on thyroid ultrasonography may be considered an exemption (*Figure*) (e13). Needle biopsy with aspiration is distinguished from a non-aspiration technique. With fine needle aspiration, aspiration of thyroid cells is effected by creating a negative pressure (needle gauges approximately 22 to 23). The use of larger-gauge needles does not improve the yield of material suitable for cytology but is associated with a slightly greater bleeding risk and a higher rate of hemorrhagic smears without thyrocytes (e14).

Aspiration is achieved by manual suction with a 10–20 mL syringe or with an aspiration aid.

With the non-aspiration technique, a very fine needle (25–27 gauge) is advanced into the nodule. The technique for needles with an obturator is to only remove the obturator when the needle has reached the target nodule in order to avoid contamination of the cell material with other tissue. As in aspiration biopsy, the needle is moved back and forth in a fan-like fashion within the nodule. Subsequently, the sampled material is spread on a slide and air-dried.

Hygiene requirements

The Commission for Hospital Hygiene and Infection Prevention (KRINKO, Kommission für Krankenhaus-hygiene und Infektionsprävention) at the Robert Koch Institute issued hygiene recommendations for needle biopsies of organ tissues in 2011 (21). According to these recommendations, needle biopsies on organs and joints should be performed under aseptic conditions, using a sterile-covered transducer probe (if this can come into contact with the skin or the biopsy needle) and a sterile drape with or without aperture and sterile surgical gloves. Alcohol-based skin disinfectant or sterile ultrasound gel can be used as an ultrasound conductive medium. Special disposal products designed as sterile covering of the transducer probe are commercially available. These recommended hygienic measures are intended to protect the patient against infection.

However, the results of the literature search showed that reports of complications related to thyroid FNA, including infection, were very rare (5 reported cases in hundreds of thousands of FNA biopsies performed worldwide) (22–26). Internationally and in also in Germany, thyroid needle biopsies have frequently been performed without sterile covering of ultrasound transducer probes and without sterile surgical drapes. The KRINKO recommendations are primarily based on reports on infections related to needle biopsies performed on other organs and on joints as well as catheterizations, including the risk of transmitting hepatitis viruses (hepatitis B and C) or an *Enterobacter cloacae* infection (e15–e19) (27–31). The question arises whether the KRINKO recommendations are useful for fine needle biopsy of the thyroid in their current form or whether they should be reviewed and revised.

However, at this point it is generally advisable to follow the KRINKO recommendations. While ignoring these recommendations does not imply disregarding the current knowledge, physicians will be required in case of litigation to prove that their approach did not cause an increased risk of infection (32). Thus, in individual cases it may be necessary to justify why a needle biopsy was performed below the standard set in the KRINKO recommendations.

Information for pathologists

By providing relevant information, clinicians can help pathologists to correctly interpret the thyroid cytology

TABLE 2

Cytological classification and corresponding recommendations according to the guidelines of the European Thyroid Association (6)

Cytological classification		Recommendation
I	Non-diagnostic	Repeat FNA within a short time frame*, except for simple cysts
II	No tumor cells detected	Clinical and ultrasound follow-ups to exclude progressive growth, repeat FNA if nodule increases in size or according to the evaluation of the clinician/pathologist
III	Follicular neoplasia of undetermined significance	Typically surgery; in individual cases, monitoring based on an interdisciplinary decision
IV	Presence of tumor cells suspected	Surgery; exemption: repeat FNA, if more sample material is required
V	Tumor cells detected	Surgery for well-differentiated carcinomas; further diagnostic work-up for anaplastic carcinomas, lymphomas, and metastatic lesions

* A repeat FNA should be performed either directly after receipt of the results or after 3 months, because otherwise the desmoplastic changes caused by the needle trauma could make it more difficult for the pathologist to interpret the findings.

findings. It is not enough to query whether the nodule is benign or malignant. The following information is relevant to the pathologist:

- Size and location of the nodule
- History: carcinomas/autoimmune disease
- Family history: carcinomas?
- Radioiodine therapy/external radiation?
- Treatment: Antithyroid drugs/thyroxine?
- Ultrasound findings; where appropriate, scintigraphy findings

Cytopathology reporting

Currently, no internationally accepted classification scheme for cytopathology reporting of thyroid fine needle aspiration is available. The European Thyroid Association (ETA) recommends the use of the following classification with 5 categories; percentages represent the proportion of thyroid FNA material reported in the original studies (33, 34):

- I: Inadequate specimen (10–15%)
- II: No tumor cells detected (60–80 %)
- III: Follicular neoplasia of undetermined significance (10–20%)
- IV: Suspicious for tumor cells (2.5–10%)
- V: Tumor cells detected (3.5–10%) (35).

FNA findings should be reliably assigned to one of the five categories, as these are linked to specific recommendations (Table 2). In case of inadequate specimen, one repeat FNA is sufficient in more than half of the cases to arrive at a useful cytological diagnosis (36).

Cytological diagnosis

In case of an inadequate specimen (at least 6 cell clusters are required, each cluster composed of at least 10 thyrocytes), the sensitivity for thyroid carcinoma

KEY MESSAGES

- Criteria for malignancy of thyroid nodules in ultrasonography include hypoechogenicity, microcalcifications, irregular margin, and increased intranodular vascularity.
- The predictive value increases when multiple ultrasound criteria of malignancy are found.
- In everyday healthcare, sensitivity and specificity of fine needle aspiration biopsy are reported lower than in the literature.
- When performed correctly, fine needle aspiration biopsy helps to avoid unnecessary thyroid surgery.
- Anticoagulants such as phenprocoumon, clopidogrel and the new oral anticoagulants must be stopped prior to the needle biopsy according to the manufacturers' recommendations.

detection is approximately 60–90% (in some cases up to 100%) and the specificity 60–100% in the hands of an experienced cytologist (37, 38).

Papillary carcinomas, with more than 80% the most common form of well-differentiated thyroid cancer, can be reliably diagnosed. In contrast, the so-called follicular neoplasia is the most difficult to interpret abnormality with regard to possible cell changes. Even with the use of complementary molecular diagnostic methods, it is currently not possible to distinguish a benign follicular adenoma (approximately 70–80% of cases) from a follicular carcinoma.

Molecular genetic testing options

So-called BRAF mutations are typical of papillary thyroid carcinoma. The most important BRAF mutation (BRAFV600E) is found in approximately 45% of papillary thyroid carcinomas. A meta-analysis showed that an FNA-verified BRAFV600E mutation is associated with a risk of 99.3% for papillary thyroid carcinoma (39). However, routine analysis of smears is currently not possible, not least because this approach would increase the costs. New molecular genetic techniques are based on the simultaneous testing of many genes in one FNA sample. These so-called gene classifiers significantly improve the diagnostic value of FNA, especially in cell specimens with follicular neoplasia. Worth noting is the high negative predictive value (exclusion of a carcinoma) of 90%–95%—depending on the method used and the prevalence of thyroid cancer in the surveyed population (40). The positive predictive value (detection of a carcinoma) is significantly lower.

The molecular genetic analysis of FNA specimens will further improve with the identification of additional genes involved in the pathogenesis of thyroid cancer and advances in sequencing technology allowing high throughput in the shortest time (next-generation sequencing). While some of these testing sets are already commercially available, currently these are not suitable for routine testing as they still lack adequate validation.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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Corresponding author
 Prof. Dr. med. Matthias Schott
 Funktionsbereich Spezielle Endokrinologie
 Universitätsklinikum Düsseldorf
 Moorenstraße 5
 40225 Düsseldorf, Germany
 matthias.schott@med.uni-duesseldorf.de

Supplementary material
 For eReferences please refer to:
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Erratum

In the original article “The Efficacy of Body-Oriented Yoga in Mental Disorders—A Systematic review and Meta-Analysis” by Rahel Klatte and colleagues in the issue of 25 March (issue 12), the numbers given in Table 2 under the heading “Treatment context” are incorrect. The correct numbers are:

TABLE 2						
Subgroup analyses of the efficacy of yoga compared with untreated control groups (primary endpoint)						
Factor of influence	Hedges' g	95-% CI	p	k	I ²	p
Treatment context						
Not receiving any treatment	1.34	0.99; 1.68	<0.001	5	24.4%	0.009
Receiving inpatient/outpatient treatment	0.52	0.01; 1.02	0.045	6	64.3%	

PTSD, post-traumatic stress disorder; k, number of comparisons; CI, confidence interval; I², measure of heterogeneity

The results are correctly reported and discussed in the text of the article.

MWR

Supplementary material to:

Fine Needle Aspiration in the Investigation of Thyroid Nodules

Indications, Procedures and Interpretation

by Joachim Feldkamp, Dagmar Führer, Markus Luster, Thomas J. Musholt, Christine Spitzweg, and Matthias Schott

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