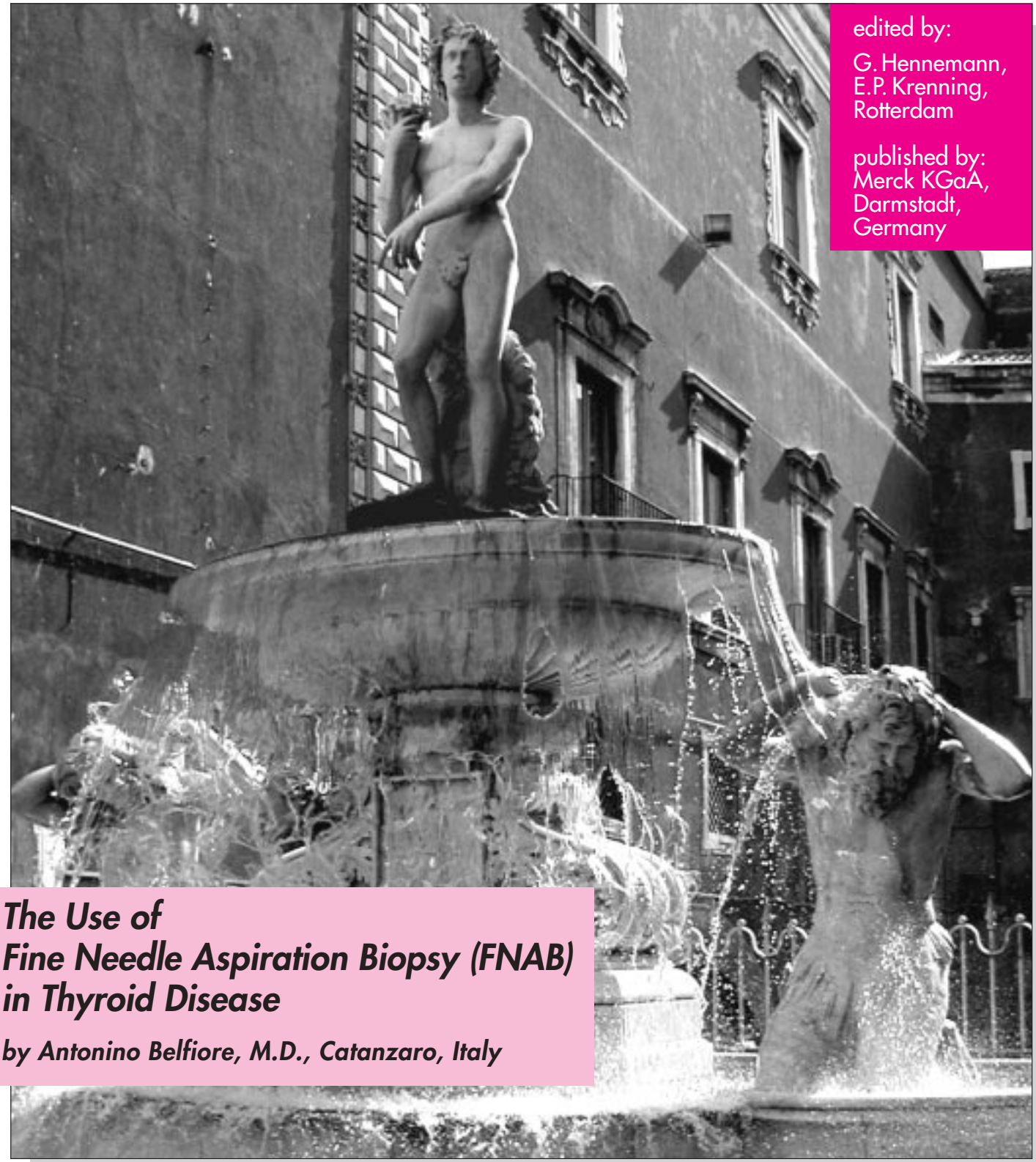
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Dr. Antonino Belfiore was born in Catania, Italy, where he graduated in Medicine and Surgery. He got a PhD in Endocrinology and Metabolism (University of Naples) and has worked at the Middlesex Medical School of London (Immunology Department, 1985-87) and at the Department of Medicine and Physiology, Mount Zion Hospital, San Francisco.



He has been assistant professor of Endocrinology at the University of Catania, Department of Endocrinology, till 1998. At present he is associate professor of Endocrinology, head of the Endocrinology Unit, and director of the post-graduate School of Endocrinology and Metabolism at the University of Catanzaro, Italy.

His research has been focused on endocrine and hormone dependent tumors with interest to both clinical and translational aspects. Major achievements have concerned specific aspects of thyroid cancer as well as the role of insulin receptor isoforms as a key component of the activation of the IGF system both in thyroid and breast cancer.

Studies in thyroid cancer have included diagnostic and clinical aspects of thyroid nodules, the association of thyroid cancer with hyperthyroidism, the role of cMet overexpression in papillary thyroid carcinomas and the identification of a new autocrine loop involving IGF-II and isoform A of the insulin receptor that is activated in thyroid cancer and is related to tumor progression.

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The Use of Fine Needle Aspiration Biopsy (FNAB) in Thyroid Disease

INTRODUCTION

Nodular thyroid disease is found in approximately 5% of the population at palpation screening and is almost ten-fold more frequent at echographic screening[1]. A higher prevalence is observed in endemic goiter areas. Thyroid nodules are rare in children and adolescents and increase almost linearly with age; females are affected 2-4-fold more frequently than males[2]. Nodular thyroid disease is a heterogeneous disorder with regard to clinical, functional or histological aspects: nodules may be single or multiple, hyper- or hypo-functioning, benign or malignant. Malignant nodules account for approximately 5% of all nodules. The large majority of them arises from the follicular epithelium and includes well-differentiated carcinomas in approximately 75% of cases and poorly differentiated or anaplastic in 15% of cases. Medullary cancer arising from calcitonin producing parafollicular cells account for approximately 10% cases.

Thyroid cancer can be a mortal disease: mortality ranges from 10% of well differentiated tumors, to 50% of poorly differentiated and medullary and to 100% of anaplastic tumors, respectively. An early diagnosis and treatment is, therefore, of utmost importance to reduce thyroid cancer mortality. However, as malignant nodules are a small minority, the choice to address all nodules to surgical treatment is impractical, cost ineffective and would expose people with benign nodules to unnecessary morbidity and mortality.

Fine-needle aspiration biopsy (FNAB) of the thyroid, first described in 1948[3] and pioneered by Scandinavian Authors in the early seventies[4], has now gained wide acceptance as the most accurate diagnostic procedure for distinguishing benign from malignant thyroid nodules[5-7]. The routine use of FNAB has changed the management of thyroid nodules by allowing to spare unnecessary operations for benign lesions and reducing costs of care. Although apparently simple, thyroid FNAB requires multidisciplinary expertise to give best results. Moreover, it gives limited information in approximately 25% of cases because of insufficient cellular yield or "indeterminate" diagnoses. This review will focus on the clinical use and limitations of FNAB in the management of thyroid nodular disease.

INDICATIONS OF THYROID FNAB

The main indication of FNAB is the preoperative selection of thyroid nodules. On clinical grounds, nodular thyroid diseases are classified as solitary nodules or multinodular goiters. The use of FNAB is well established in these two groups of clinical nodular disease. The widespread use of high-resolution echography has, however, lead to the recognition that non-palpable nodules are surprisingly frequent. The role of FNAB in this group is rather controversial. Non-nodular thyroid enlargement or enlarged cervical lymph nodes may also harbor cancer and require FNAB for diagnosis. The indications of FNAB for the detection of thyroid cancer in these different conditions will be briefly discussed.

a) Solitary thyroid nodule: when a solitary thyroid nodule is evidenced by palpation, it is important to rule out the presence of a cancer and of an autonomously functioning thyroid nodule (AFTN), which may lead to hyperthyroidism. Cancer and AFTN account for approximately 5% and 10% of all nodules, respectively. The large majority of solitary thyroid nodules are, therefore, benign and asympto-

matic. There is a general consensus that FNAB and ultrasensitive TSH are the two most accurate tools to diagnose cancer and hyperthyroidism, respectively, and should be both used as first line diagnostic tests. When serum TSH is normal, thyroid nodules are supposed to be hypofunctioning and thyroid scintigraphy is unnecessary. As no clinical or echographic feature can exclude cancer in hypofunctioning nodules, all of them should be examined by FNAB[5-7]. In contrast, when TSH is low/suppressed, an AFTN is suspected and scintigraphy should be carried out for confirmation. As AFTNs have a very low cancer risk (in the range of 0.2–0.5 %), FNAB is indicated only in selected cases with clinically suspected features (e.g. rapid growth of solid areas, hard consistency, etc.).

b) Multinodular goiter: multinodular goiters are especially common in endemic goiter areas with deficient iodine intake. They may also harbor AFTNs and/or malignant nodules. As for solitary nodules, a serum TSH determination will be important to raise the suspect of AFTN. For long time nodules in the context of a multinodular goiter have been believed to have a low cancer risk. However, it has become clear that the cancer risk in multinodular goiters is similar to that found in solitary nodules[8,9]. Therefore, all palpable nodules, except for AFTNs, discovered in the context of a multinodular goiter should be also examined by FNAB. At present, over 70 % of american physicians do use FNAB as a key diagnostic approach in multinodular goiter[10].

A fast growing multinodular goiter, involving one or both thyroid lobes, should raise the suspect of either an anaplastic thyroid cancer or a thyroid lymphoma. A prompt cytological diagnosis is crucial in determining a timely and appropriate therapy for these two aggressive malignancies.

c) Subclinical thyroid nodular disease. Non-palpable thyroid nodules are found in 25–50 % of the population by using ultrasound screening[11]. However, such a screening is not recommended at present and, therefore, these nodules may come to the clinician's attention following a neck echography carried out either for a single palpable nodule or an apparently diffuse goiter or a non-thyroid disease. Approximately one third of patients with a single palpable nodule are diagnosed additional non-palpable nodules when examined by echography.

Non-palpable nodules are a heterogeneous group: they may be either single or multiple and with variable size. Even relatively large nodules (>2 cm) located deeply or in the context of a goiter, may escape detection by physical examination[12]. The use of US-FNAB now allows examining nodules of few millimeters in size. However, cytological examination of all non-palpable nodules is considered cost ineffective and a reasonable approach is to limit FNAB to two groups of non-palpable nodules: **a)** nodules ≥ 1.5 cm[13], **b)** nodules <1.5 cm when suspected to be small aggressive cancers (e.g. history of exposure to radiations, familiarity for thyroid cancer, suspect of medullary carcinoma, presence of enlarged locoregional lymph-nodes, etc.).

The rational of these recommendations is based on the fact that, although small asymptomatic nodules may be malignant in 3–4 % of cases, the large majority of these occult carcinomas do not actually progress to a clinical disease. Several studies indicate that, while the prevalence of occult thyroid cancers is very high (on average = 36 per 1,000 people, range, 4.5–356), clinical thyroid cancers occur much less frequently (approximately 2.5 per 1,000)[14]. Therefore, diagnosing and treating these tumors would lead to unnecessary costs and morbidity.

d) Graves' and Hashimoto's disease. In Graves' patients the occurrence of thyroid nodules and cancer was considered rare. However, different lines of evidence now indicate that palpable thyroid nodules are approximately 3-fold more frequent than in the general population and carry an increased cancer risk[15]. There is also evidence that thyroid cancer associated to Graves' disease may behave more aggressively and have a poorer outcome than in euthyroid patients[16]. For these reasons, it is wise to screen Graves' patients for thyroid nodules and to examine nodules by FNAB.

Hashimoto's thyroiditis may be also associated with thyroid carcinoma or with a thyroid lymphoma[17].

Furthermore, diffuse sclerosing papillary carcinoma, a histological variant of papillary carcinoma characterized by a diffuse involvement of an entire lobe or the whole gland, may mimic chronic thyroiditis[18]. For these reasons, FNAB is a very useful tool to confirm the diagnosis of Hashimoto's disease and to exclude association with malignancies.

e) Enlarged cervical lymph-nodes. FNAB is a powerful tool to diagnose thyroid cancer metastases in patients with a thyroid nodule and enlarged cervical lymph nodes. It is also very useful to identify small metastatic lymph nodes in the post-operative follow-up of patients operated for a thyroid cancer. The identification of metastatic thyroid cancer cells in standard cytological smears is, however, complicated by the frequent occurrence of inflammatory lymphadenopaties and metastases of non-thyroid malignancies. The use of ancillary techniques (see below) has an important role when examining enlarged lymph nodes for detecting thyroid cancer.

FNAB TECHNIQUE

FNAB is preferably carried out in an outpatient setting. The patients is informed of the limitations of the diagnostic procedure (possibility of inadequate samples or "indeterminate" diagnoses) and reassured that the procedure is almost painless and free of major complications. The patient is then invited to assume a recumbent position with a pillow under the neck to relax the neck muscles. Thyroid nodules are identified by palpation and the patient is advised to swallow once or twice before inserting the needle but not during the procedure. Most authors use a 23-gauge needle attached to a 20-ml plastic syringe hold with a special pistol grip (Cameco pistol). The needle is then inserted into the nodule and moved back and forth while maintaining a slight aspiration. The aspiration is released when the aspirated material appears in the needle hub and just before withdrawing the needle, in order to avoid contaminating the sample with material coming from the needle tract. FNAB has no major complications. Subcutaneous hematoma, limited intranodular bleeding or slight local pain occasionally occur. Rarely, aspiration of a cystic lesion may favor acute inflammation. Isolated reports exist of acute thyroid swelling, transient bradycardia and transient paralysis of the vocal cord.

Variables that may affect adequacy and quality of cytologic smears

A number of variables may affect the yield of cellular material and the quality of cytological smears:

Use of real time echography. The use of ultrasounds (US) to assist or guide FNAB (US-FNAB) has been shown to be helpful in increasing cellular yield while avoiding excessive blood or cystic fluid aspiration and increasing diagnostic accuracy[19-21]. US-FNAB is used by more than 40 % European authors but only infrequently in the States. Although the use of US assistance is unnecessary for palpable nodules, it is precious for localizing difficult-to-palpate nodules and identifying solid parenchymatous areas in partially cystic or partially calcified nodules. The higher cost of US-FNAB is counterbalanced by the reduction of inadequate samples and the increase of diagnostic accuracy[19].

Clinical examination. The use of US should not lead to neglect palpation, which allows evaluation of nodule mobility and consistency. Small, mobile nodules should be carefully fixed manually whether or not US assistance is used. Furthermore, assessing nodule consistency is very useful to graduate the suction applied to the syringe and the number of needle movements. In most cases it is preferable to apply a slight suction or no suction at all. This technique, "non aspiration FNAB", will reduce blood aspiration while still yielding a cellular sample and works well except for hard- consistency/fibrotic nodules[22].

Choice of needle and syringe. A 23 gauge (0.6 mm) needle is mostly used. The use of thinner needles (27 gauge, 0.4 mm) may limit the aspiration of peripheral blood that can dilute the cellular yield. The use of larger needles (21 gauge, 0.7 mm) may

result in a more abundant cellular yield but also in excessive peripheral blood aspiration and should be reserved in selected cases (e.g. presence of very viscous colloid, fibrotic nodules). A 20 ml syringe is used when employing Cameco pistol. This has the advantage to allow the operator to fix the nodule with one hand. When examining small nodules, especially with US assistance, it may be easier to use a 5 ml syringe or a needle without a syringe.

Number of punctures per nodule. The structure of a thyroid nodule is often heterogeneous. In order to examine different areas of the same nodule and to increase the cellular yield, each nodule should be subjected to more than one aspiration. Some authors have found that the number of aspirations is directly related to the adequacy of the specimen[23,24]. In one study, the inadequate sampling rate decreased from 16 % (only one aspiration at the nodule center) to 5.3 %, 4 % or 2.6 % with increasing number of aspirations (2, 3 or 4 more aspirations in different nodule areas)[24].

Accordingly, some authors perform as many as 6–12 aspirations. We and others[25-27], however, find that 2–4 punctures per nodule result in an acceptably low inadequacy rate and are well tolerated by the patient, whereas several aspirations carried out in one setting are often poorly tolerated and increase the risk of local edema and hemorrhage.

Cystic or complex nodules. Approximately one third of all palpable thyroid nodules have a partially cystic structure (complex nodules) originating by ischemic necrosis of solid areas. In cystic nodules a progressive suction is applied in order to allow an evacuation of the cystic fluid as complete as possible. The cystic fluid is then centrifuged and the sediment smeared onto slides. However, the fluid sediment may only contain scanty follicular cells. Aspiration of solid areas in the context of complex nodules, preferably under US assistance, may result in a better cellular yield[28].

Smear preparation. Direct smear of the aspirated material onto glass slides is most commonly used. Care should be taken to avoid the sample to dry, as cells may become fragile. The aspirated material should be immediately smeared after expulsion and, preferably, in a single course. The smears are then fixed according to the staining technique.

Recently, thin layer processing of FNAB aspirates by Thin-Prep® processor has gained increasing popularity[29,30]. According to this technique, the aspirated material is collected in a buffered fixative, spun down and resuspended in a second buffer. A special device, Thin-Prep® processor, is then used to prepare a thin cell monolayer on a glass slide. Thin layer processing may be carried out with the material that remains in the needle hub after preparation of direct smears. The interpretation of thin-layer slides requires specific experience since the cytomorphology may substantially differ from direct smears[29,30]. In general, colloid appears disperse in droplets and is less evident in thin-layer preparations. Tissue fragments are less frequently observed that in direct smears, although other major architectural features (microfollicles, honeycomb arrangement and papillae) are conserved. Nuclear details may be better preserved but cytoplasm is more often disrupted as compared to direct smears. The rate of inadequate samples may increase when using thin-layers as the sole processing technique. However, Thin-Prep® processing may be a useful addition to direct smears.

Staining technique. Papanicolau and May-Grunwald-Giemsa are the two most used staining techniques. Papanicolau method is preferable, in my opinion, because it best evidences details of nuclear chromatin including the ground glass nuclei and the nuclear grooves characteristics of papillary cancer. Colloid is also better evidenced with this method. On the other hand, lymphoid cells are better recognized with May-Grunwald-Giemsa staining.

Immediate microscopic evaluation of sample adequacy. Some authors use Diff-Quick staining for rapid assessment of sample adequacy while the patient is waiting. The aspiration can be repeated if the smears are judged poor or inadequate, thus reducing to a minimum the proportion of inadequate sampling.

WHO SHOULD PERFORM FNAB

As thyroid FNAB is used as a screening procedure to select nodules to address to surgery, a major issue is to reach a high sensitivity while keeping low costs. Three steps have been shown to increase the probability to obtain a representative sample: a) clinical evaluation of the thyroid nodule(s); b) ecographic evaluation; c) rapid assessment of sample adequacy by immediate microscopic evaluation. Ideally, the aspiration would involve, therefore, a clinician (for clinical evaluation), a radiologist (to perform echography) and a cytopathologist (for rapid assessment of sample adequacy). Both in USA and Europe, the aspiration is performed by a clinician in approximately 60% of cases, by a cytopathologist in 6–8% of cases and by a radiologist in 2–3% of cases[31]. At Karolinska Intitute both the aspiration and the cytological examination are performed by a special Cytology Unit[32]. Ravetto et al.[27] have recently reported that, when a clinician and a cytopathologist jointly take part to the aspiration procedure, inadequate samples are kept at a minimum (<2%), even in the absence of rapid microscopic sample assessment, that would increase costs and procedure time. In our Institution, thyroid FNAB is centralized, and only two clinicians, with special interest in thyroid perform all steps, including clinical assessment, nodule aspiration, echographic assistance and cytological evaluation. This setting has resulted in a good accuracy and in low inadequate sampling rate and low costs[25 and unpublished data].

In any case, there is ample evidence that the rate of inadequate samples is inversely related to the operator experience with the highest inadequacy rates being found in Institutions where poorly trained clinicians perform the aspirates[33].

CYTOLOGICAL ASPECTS OF DIAGNOSTIC AND NON-DIAGNOSTIC FNAB

Thyroid FNAB smears can be classified as diagnostic or non-diagnostic. In the first group are comprised the majority of benign and malignant thyroid lesions that can be identified with high accuracy by standard cytological criteria. In the second group are comprised two subgroups: a) smears containing insufficient cellular material (inadequate samples); b) smears that cannot be reliably classified either in the benign or in the malignant group on the basis of standard cytological criteria ("indeterminate" lesions).

A detailed description of cytological features of thyroid lesions can be found elsewhere[4,34,35]. Herein we will focus on basic cytological aspects that allow identification of thyroid lesions and on the characteristics of "indeterminate" lesions, which represent a major limitation of thyroid FNAB.

Basically, the following aspects are of importance when examining a thyroid smear: a) presence of colloid; b) cell arrangement; c) nuclear and cytoplasmic features; d) additional background features.

For instance, the presence of moderate or large amount of colloid is suggestive of nodular goiter. In contrast, colloid is scanty or absent in neoplastic or inflammatory lesions. The evaluation of the cellular arrangement may give indications of the histological structure. Cytoplasmic and, especially, nuclear details may suggest a neoplastic lesion with a degree of accuracy depending on the tumor histotype. For instance, papillary carcinoma is characterized by relatively specific nuclear features that include ground glass cell nuclei, nuclear inclusions, groves[34]. Elongated "bipolar" nuclei suggest a medullary cancer[36] while highly pleomorphic spindle-shaped or giant nuclei are compatible with an anaplastic cancer[37]. The presence of additional features such as psammoma bodies, inflammatory cells, cell necrosis, is of major relevance for the diagnosis of many types of lesions.

Major cytological findings of the most common thyroid lesions are summarized in *Table 1.*

Table 1 Cytological features in common thyroid lesions.

Cytological diagnosis	Colloid	Cell arrangement	Nucleous	Cytoplasm	Miscellaneous
Nodular goiter	scanty to abundant groups, microfollicles	monolayers,	picnotic,	ill-defined common	Cystic changes
Chronic thyroiditis	absent	isolated, clusters hyperplastic changes	degenerative and/or	degenerative and/or hyperplastic changes	
Adenoma	absent or scanty	microfollicles, clusters	enlarged, with overlapping, nucleoli	scanty	Cystic changes common
Follicular carcinoma	usually absent	microfollicles, clusters	enlarged, anysonucleosis, overlapping, nucleoli, atypical	scanty	
Papillary carcinoma	scanty or absent	monolayers, papillae Microfollicles	enlarged, groves ground glass type, inclusions	ill-defined to abundant	psammomas, giant cells
Medullary carcinoma	absent	isolated, small clusters	eccentric, round or elongated, hyperchromatic	polygonal, spindle shaped azurophilic granules	amyloid
Anaplastic carcinoma	absent	isolated, clusters	giant or spindle-shaped, atypical, large nucleoli,	pleomorphic	necrosis
Hurthle cell lesion	absent	isolated, microfollicles	vescicular, anysonucleosis, prominent nucleoli	large, pleomorphic, metachromatic granules	

a) Diagnostic FNAB

Benign lesions, such as nodular goiter and chronic thyroiditis, and malignant lesions, such as papillary, medullary and anaplastic carcinomas, mostly show specific cytological aspects *(Table 1).* They can be diagnosed with high accuracy and are included in this group.

b) Non-diagnostic FNAB

Inadequate sampling

Cytological smears should contain a good number of well preserved and well stained cells with epithelial characteristics in order to be classified as benign. Aspiration of too few cells to reach a diagnosis is a major limitation of FNAB. In a recent review of seven large series, the mean inadequacy rate was 17% (range 2–21%)[34]. It is important to avoid making a diagnosis in the presence of a suboptimal sample, as this is a major cause of false negatives. In order to facilitate recognition of sample adequacy, some authors have proposed to follow quantitative criteria. Hamburger recommends that cancer cannot be excluded if the sample does not contain at least six benign follicular cell clusters, each containing 10–15 cells, in two specimens derived from two different aspirates[5]. Other authors have adopted less stringent criteria.

Variables that may affect adequacy and quality of cytologic smears have been described above.

"indeterminate" lesions

Standard thyroid FNAB is unable to reliably classify as benign or malignant a proportion of nodules ranging 15–30%. These lesions are variably indicated as "follicular" or "suspicious" or "indeterminate" and represent a heterogeneous group of lesions, either benign or malignant, that have overlapping cytomorphologic aspects:

1. *Follicular lesions:* the most common component of the "indeterminate" group is represented by well differentiated lesions with follicular structure, which account for 10–15% of all thyroid nodules.

The large majority of these nodules are benign tumors (follicular adenomas) or hyperplastic goiter nodules. However, approximately 1 out of 10–15 follicular lesions is malignant (well differentiated follicular carcinoma). These carcinomas differ from adenomas because have acquired the ability to invade the tumor capsule and/or blood vessels. On the basis of the extent of invasion follicular carcinomas are classified as minimally or widely invasive. Cytological atypias are present in widely invasive tumors but are rare in minimally invasive follicular carcinomas. This last category, therefore, can be only diagnosed at histopathology after examination of multiple sections.

2. *Papillary carcinomas:* it is increasingly recognized that, especially in areas where follicular carcinomas are rare, papillary cancer is a significant component of malignancies diagnosed as "indeterminate" at cytology. Most papillary carcinomas classified as "indeterminate" lesions belong to the follicular variant (FVPTC). In FVPTC (approximately 20% of all papillary carcinomas) a number of cytologic features characteristic of papillary cancer, such as psammoma bodies, nuclear clearing, grooves and pseudoinclusions, are poorly represented[38,39]. A small proportion of the classic variant of papillary cancer may also scarcely present these cytological characteristics[40].

3. *Hurthle cell lesions:* Hurthle cell lesions represent approximately 2–3% of all nodules and include neoplastic lesions (either benign or malignant) and non-neoplastic lesions, such as metaplastic changes observed the context of Hashimoto's thyroiditis, or nodular goiter. Hurthle cell carcinomas represent less than 1% of all nodules and cannot reliably be differentiated from either benign Hurthle cell tumors or non-neoplastic lesions.

4. *Insular carcinoma:* it is an unusual thyroid tumor, representing 4–7% of all thyroid carcinomas. This cancer is characterized by a growth pattern in nests of cells called "insulae" and by a high aggressiveness and early spread to distant sites[41]. Smears are often highly cellular and poor of colloid. However, microfollicles are rare and there is a predominance of single cells. Nuclei are predominantly round, monomorphic and with small nucleoli. Inclusion of insular carcinoma in the "indeterminate" group may result from the scarce signs of cellular atypia.

5. *Medullary carcinoma:* medullary carcinoma represents approximately 5% of all thyroid carcinomas. Aspirates are often rich of cells with characteristic cytological features *(Table 1).* Different morphologic variants, however, exist[42]. Classification in the "indeterminate" group may result from lack of experience with all the variants of this infrequent malignancy.

CLINICAL USE OF THYROID FNAB

FNAB can provide a specific diagnosis in 70–85% of thyroid nodules. This group comprises the majority of both benign and malignant lesions. When considering only diagnostic FNAB, sensitivity, specificity and accuracy are high[43]. The clinical decision may rely, therefore, mainly on FNAB results. In the remaining 15–30% of cases FNAB cannot provide a definite diagnosis. In this group, which includes inadequate samples and "indeterminate" diagnoses, FNAB data should be integrated by additional information to finalize nodule treatment. Clinical implications of FNAB results will be briefly summarized:

Benign lesions *(nodular goiter and thyroiditis)*
Nodular goiter and chronic thyroiditis represent the large majority of benign lesions, and account for approximately 70% and 5% of all nodules, respectively. Macrofollicular adenomas are often classified as nodular goiters because of many overlapping aspects.

The real cancer risk in this group is difficult to calculate because many patients are not addressed to

surgery. However, several lines of evidence indicate a cancer risk in the range of 0.5–3 %, which depends on both the "a priori" cancer risk in a given population and the accuracy reached by the FNAB operator[4,25,42].

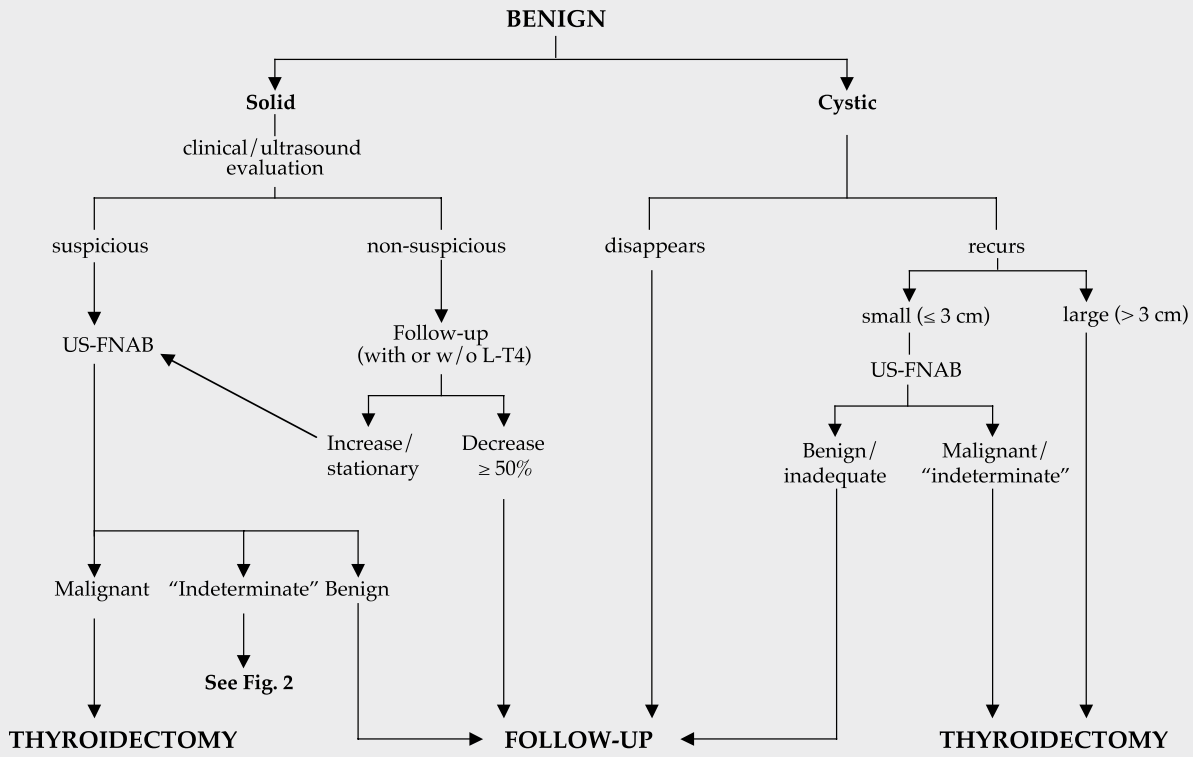
Given the slow evolution of the majority of differentiated thyroid carcinomas, the cancer mortality due to this proportion of false negatives is considered very low and clinical follow-up with echographic measurement of nodule size is appropriate. Evidences that small nodule size and presence of abundant colloid are predictive for nodule shrinkage after L-thyroxine treatment maybe useful in the decision whether or not to treat the patient with L-thyroxine[43]. Thyrodectomy can be reserved for patients with compression symptoms or esthetic problems. In patients with nodules benign at cytology but with clinical and/or echographic signs of suspect (e.g. hard consistency, rapid growth, loco-regional lymph nodes, microcalcifications, etc.) the possibility of surgery should be carefully considered and treatment individually tailored. In these patients the risk of mortality for the late discovery of a thyroid cancer should be balanced against the risk of immediate surgery.

The clinical management of multinodular goiters should be based on FNA results of all palpable nodules.

Particular attention should be paid to cystic/complex nodules because they have a cancer risk similar to that of solid nodules but a higher false negative rate (up to 17–30 %) with higher values observed in cysts larger than 3 cm[45,46]. Complete cyst disappearance after aspiration strongly suggests a benign lesion.

A proposed algorithm for the management of solid or cystic benign lesions is given in *Fig. 1.*

Figure 1 Suggested management of thyroid lesions diagnosed benign at FNAB



During the follow-up of benign nodules FNAB repetition is advised by many clinicians in order to reduce false negatives. The clinical value of rebiopsy is, however, controversial. Some authors favor the routine use of rebiopsy while others suggest that a repeated FNAB should be reserved to nodules that enlarge or show other suspicious clinical changes during the follow-up[47]. It is likely that a second FNAB can change the initial diagnosis from benign to malignant in 1–2% of cases and is, therefore, worthwhile[48,49]. More questionable is the value of a third FNAB, unless the nodule characteristics change with time.

Malignant lesions *(papillary, medullary and undifferentiated thyroid carcinomas, lymphomas, metastatic non-thyroid cancers).*
Papillary cancer is diagnosed in 3–4% of all nodules while either medullary or undifferentiated cancer is diagnosed in approximately 1% of nodules. Lymphomas and metastases of non-thyroidal tumors represent a small minority of asymptomatic thyroid nodules.

In nodules diagnosed malignant at FNAB the cancer risk ranges 97–99%. Therefore, the patient should be addressed to immediate surgery and the surgeon can plan a total or near total thyroidectomy on the basis of FNAB data. Intraoperative frozen sections are of little help in these cases[50]. Serum calcitonin is often elevated in case of medullary cancer and may be useful to confirm this diagnosis[51].

The patient should be informed of the small possibility of a false positive. False positive, however, do not represent a significant clinical problem since are mostly represented by atypical adenomas that are best treated by surgery *(Table 1)*.

"Indeterminate" thyroid lesions
Most authors advise thyroidectomy in patients with cytologically "indeterminate" thyroid lesions. However, these lesions represent a substantial proportion (15–25%) of all thyroid nodules and are malignant only in 10–20% of cases. It is obvious, therefore, that a refinement of this diagnosis would spare many unnecessary thyrodectomies. To this aim a variety of approaches have been proposed. Although no consensus is so far reached, some of these approaches are promising and appear clinically relevant.

Refining diagnosis in "indeterminate" thyroid lesions: subgrouping in classes of different cancer risk
"Indeterminate" lesions may be easily subgrouped on the basis of simple morphologic or clinical parameters. This approach, however, is clinically useful only if a subgroup can be identified with a cancer risk low enough to avoid immediate surgery.

a) morphological criteria
The presence of classical features, such as microfollicles, cell atypias, Hurthle cells and clear nuclei may be used to subgroup lesions with different cancer risk.

Some authors classify nodules in three or four categories: follicular neoplasm, Hurthle cell neoplasm, suggestive of cancer (papillary or follicular) carcinoma. A fourth category may contain miscellaneous lesions[26]. The cancer rate ranges 13–15% in the first category, 14–24% in the second and 50–60% in the third one.

We rank "indeterminate" lesions into three classes: possibly malignant (approximately 15% of all nodules and with 10% cancer risk), probably malignant (approximately 1.5% of all nodules and with 20% cancer risk), suggestive of cancer (approximately 0.5% of all nodules and with a 90% cancer risk)[25]. Patients with nodules belonging to the two high-risk subgroups are addressed to immediate surgery. In contrast, the decision to operate patients with nodules belonging to the low-risk group is taken after balancing the individual risk of surgery against the risk of cancer after considering cytological, clinical and echographic aspects.

b) clinical criteria
A number of studies indicate that the evaluation of clinical nodule features increases the accuracy of FNAB and suggest that the cytological results should always be evaluated in light of clinical features[8,52,53]. However, the use of clinical factors to stratify cancer

risk in "indeterminate" lesions is not standardized.

Statistical methods may be used to integrate clinical and cytological information. By multiple logistic regression we found that both age and gender significantly affect the "a priori" cancer risk of a thyroid nodule with the risk being higher in males and at extreme ages. Similarly, also in "indeterminate" lesions the cancer risk was higher at extreme ages[8]. Other authors have applied Bayesian analysis in a group of patients with an "indeterminate" thyroid lesion to identify clinical factors predictive of cancer. They have found that the cancer risk is higher in males than in females (43% vs.16%), in nodules >4 cm as compared with smaller ones (40% vs. 13%) and in solitary nodules as compared with nodules in a multinodular goiter (25% vs. 6%)[54].

c) use of ancillary techniques

Serum calcitonin is elevated in most medullary carcinomas and should be measured in all patients with an "indeterminate" cytological diagnosis[51].

Furthermore, a variety of molecular abnormalities have been described in thyroid tumors and appear to be relevant for tumor initiation and/or progression. On this basis, a number of studies have tried to identify molecular markers of malignancy that could be reliably evaluated in cytological aspirates.

1. *Detection of pathogenetic oncogene mutations/rearrangements*

   – *Typical of follicular cancer:* Recently, in a small series of follicular carcinomas a novel gene rearrangement has been described involving the homeobox DNA domains of the PAX-8 gene and the DNA binding, ligand binding, RXR dimerization and transactivation domains of PPAR-γ gene. The resulting fusion protein has lost the activity of wild type PPAR-γ and is suspected to have a pathogenetic role in follicular cancer[55]. No data are so far available with regard to the diagnostic value of detecting PAX-8/PPAR-γ rearrangement in FNAB aspirations.

   – *Typical of papillary cancer:* RET/PTC rearrangements are balanced inversions or translocations that involve the intron 11 of RET and result in the translation of fusion proteins with constitutive tyrosine kinase activity. Eleven types of RET/PTC rearrangements have been described, RET/PTC1 being the most frequent. The detection of RET/PTC by immunohistochemistry and/or RT-PCR has been proposed as a diagnostic tool to confirm the diagnosis of papillary cancer in uncertain cases[56]. RET/PTC is, however, present only in 20–30% papillary carcinomas. Therefore, the sensitivity of this procedure is low. Moreover, RET/PTC may be also present in Hashimoto thyroiditis, Hurthle cell neoplasms and hyalinizing trabecular tumors.

   – *Typical of medullary cancer:* Activating point mutations of the RET proto-oncogene have been identified as a genetic pathogenetic mechanism in medullary carcinomas, either occurring in the context of a MEN-2 syndrome or in the sporadic variant. The preoperative identification of RET mutations in the aspirated material allows discrimination between these two possibilities, thus influencing the therapeutic approach[57].

2) *Miscellaneous molecular markers*

This heterogeneous group comprises a variety of molecules involved in a variety of biological functions (e.g. cell transformation, proliferation, motility, resistance to apoptosis, differentiation) and that maybe abnormally expressed in cancer thyroid cells. The expression of these molecules can be evidenced by standard immunocytochemistry that could be easily included in routine thyroid FNAB process. Most of these markers are able to identify papillary cancers, including FVPTC, with good accuracy[58,67]. This ability could by itself justify their use since approximately 50% of malignancies classified "indeterminate" actually are papillary carcinomas. Widely invasive follicular carcinomas may also be positive to these markers. However, in general, these markers have a much lower accuracy in identifying minimally invasive follicular carcinomas, a diagnosis often problematic even at histologic examination. Immunostaining for calcitonin has a very good accuracy in confirming the suspect of medullary cancer. The characteristics of some of these markers are given in *Table 2*.

Table 2 **Molecular markers suggested for refining diagnosis in "indeterminate" lesions.**

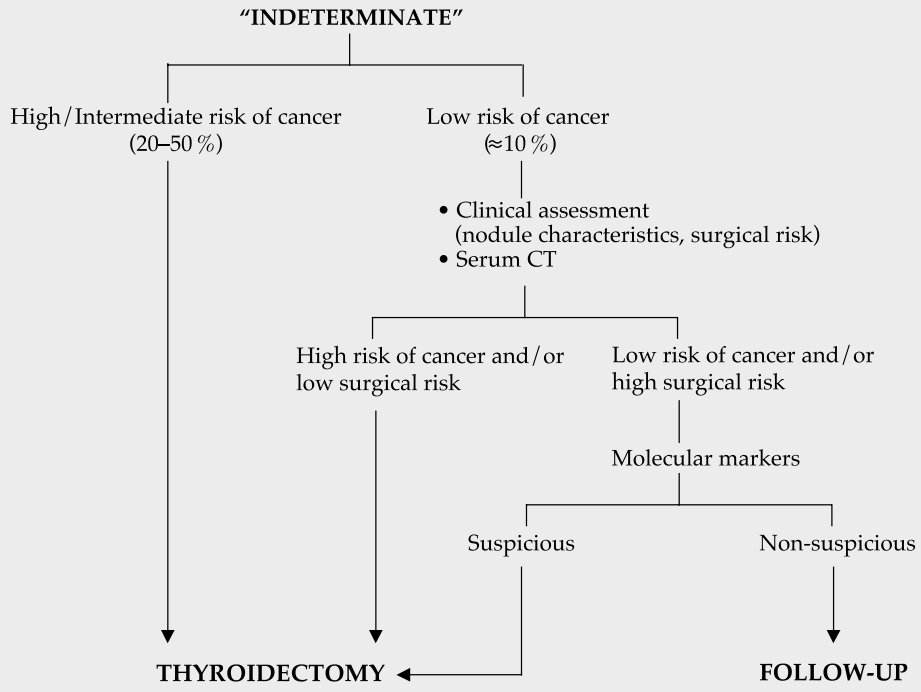
Marker	Technique	Sensitivity	Specificity	References
RET/PTC	RT-PCR	PTC: 52%		57
Calcitonin	RT-PCR/ICC	MTC: 100%		57, 58
Cytokeratin 19*	ICC	PTC: 92%	FAD: 7%	59, 60
Met/HGF receptor	ICC	PTC: 85% FVPTC: 72% FTC: 28%	At-FAD: 100%	61
Galectin-3	ICC	PTC: 98% FVPTC: FTC: 50-85%	FAD: 11%	62, 63
HMG proteins	ICC	PTC: 95% FTC: 95%	FAD: 20% NG: 5%	64
Thyroperoxidase*	ICC	PTC: 99% FVPTC: 100%	FAD: 17% HCAD: 50%	65, 66
CD26	ICC	FTC: 100%	FAD: 10% At-FAD: 50%	67

*markers that need a semi-quantitative assessment

ICC=Immunocytochemistry
PTC = papillary thyroid cancer
FVPTC = follicular variant papillary thyroid cancer
FTC = follicular thyroid cancer
MTC = medullary thyroid cancer
FAD = follicular adenoma
HCAD = Hurthle cell adenoma
At-FAD = atypical adenoma
NG = nodular goiter

Unfortunately, the sensitivities and specificities reported are calculated from small series. Prospective studies including a large number of patients are needed, therefore, to assess the clinical value of these markers in refining the diagnosis of "indeterminate" thyroid lesions and altering their management. A proposed algorithm for the management of "indeterminate" lesions is given in *Fig. 2*.

Figure 2 **Suggested management of thyroid diagnosed "indeterminate" thyroid lesions.**



In aspirations from suspected cervical lymph nodes, cells of uncertain origin can be identified as epithelial by immunocytochemistry with anti-cytokeratin antibodies and as thyroid follicular or parafollicular cells with anti-Thyroglobulin and anti-Calcitonin antibodies, respectively. In the aspirated material the presence of Thyroglobulin and/or Calcitonin can be also detected by conventional immunoradiometric methods or by RT-PCR[58,68].

Inadequate samples

In case of inadequate sampling simple rebiopsy is successful in approximately 50 % of cases. US-FNAB is recommended to avoid areas of fibrosis, calcification or cystic degeneration. Repeatedly unsuccessful FNAB does not change the "a priori" nodule cancer risk and the clinician should rely on clinical and echographic characteristics to select the nodule for surgery

CONCLUSIONS

Thyroid FNAB is a procedure that allows an accurate and cost-effective preoperative identification of malignant thyroid nodules. Its routine use leads to a reduction in the number of unnecessary thyroidectomies and, therefore, reduces surgical morbidity and mortality and costs of patient management. It also allows a prompt identification and treatment of thyroid malignancies and provides guidance for the type of surgery.

However, FNAB is a simple procedure only apparently because it requires multidisciplinary expertise. To obtain best results, the personnel involved in all FNAB steps should receive specific training, work in close cooperation and maintain an adequate workload. The two main limitations, inadequate sampling and "indeterminate" diagnoses can be reduced by experience although not eliminated. The use of ancillary techniques, such as immunohistochemistry and RT-PCR may provide help in refining the diagnosis in "indeterminate" cases, although no single marker is ideal and a standardized approach is not presently available.

In order to optimize thyroid nodule management, it is recommended that every Institution makes clinical guidelines taking into account FNAB results in conjunction with clinical data and local thyroid cancer epidemiological data.

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1. The prize is to exclusively and directly honour special scientific work in the field of the thyroid gland and serves also to recognized and encourage young scientists. DM 20,000 per year are available. In exceptional cases, the jury may decide to divide the prize.

2. Young scientists who are domiciled in Europe and have not completed their 40th year of life may apply for the prize. Employees of industrial firms are exclused. The candidates are to hand in manuscripts of (original plus nine copies) their as yet unpublished works to the President of the German Society of Endocrinology by October 31 of the year prior to the prize-giving.

3. In addition to basic research, work involved in both diagnostic as well as therapeutic problems in this specific field also may be considered for the prize. The submitted reports must not exceed 25 type-written pages à 30 lines. The number of figures and tables is to amount to no more than 1/3 of the complete report. The manuscript, in either English or German, must be drawn up according to the regulations of a scientific journal. All rights are exclusively in the control of the author. After confirmation of receipt, the author may offer his work to a journal for publication.

4. The prize project should not include more than two authors. If more authors have cooperated in a project, the team should decide on the two main authors to be named for the prize project; if necessary, the remaining authors must give their consent in writing. The curriculum vitae stating the scientific career of the author(s) must be enclosed with the prize project. The author(s) must affirm in writing that at the time of submission the manuscript had not been published or handed in for publication in a journal (exception: published abstracts).

5. A jury decides on who is to receive the prize. The jury may decide not to donate the prize if the manuscripts received are not worthy. The decision of the jury is mandatory for all participants and is not subject to judicial inquiry. If not awarded, the prize may in exceptional cases be made available in the following year for additional manuscripts which are worthy.

6. The jury comprises: The President and two members of the Board of the German Society of Endocrinology, the speaker and two members of the Thyroid Section nominated by the Board of the German Society of Endocrinology and one representative from the Pharmaceutical Section of E. Merck, Darmstadt. Other experts (without the right to vote) may be included in the assessment. The chairman of the jury is the President of the German Society of Endocrinology.

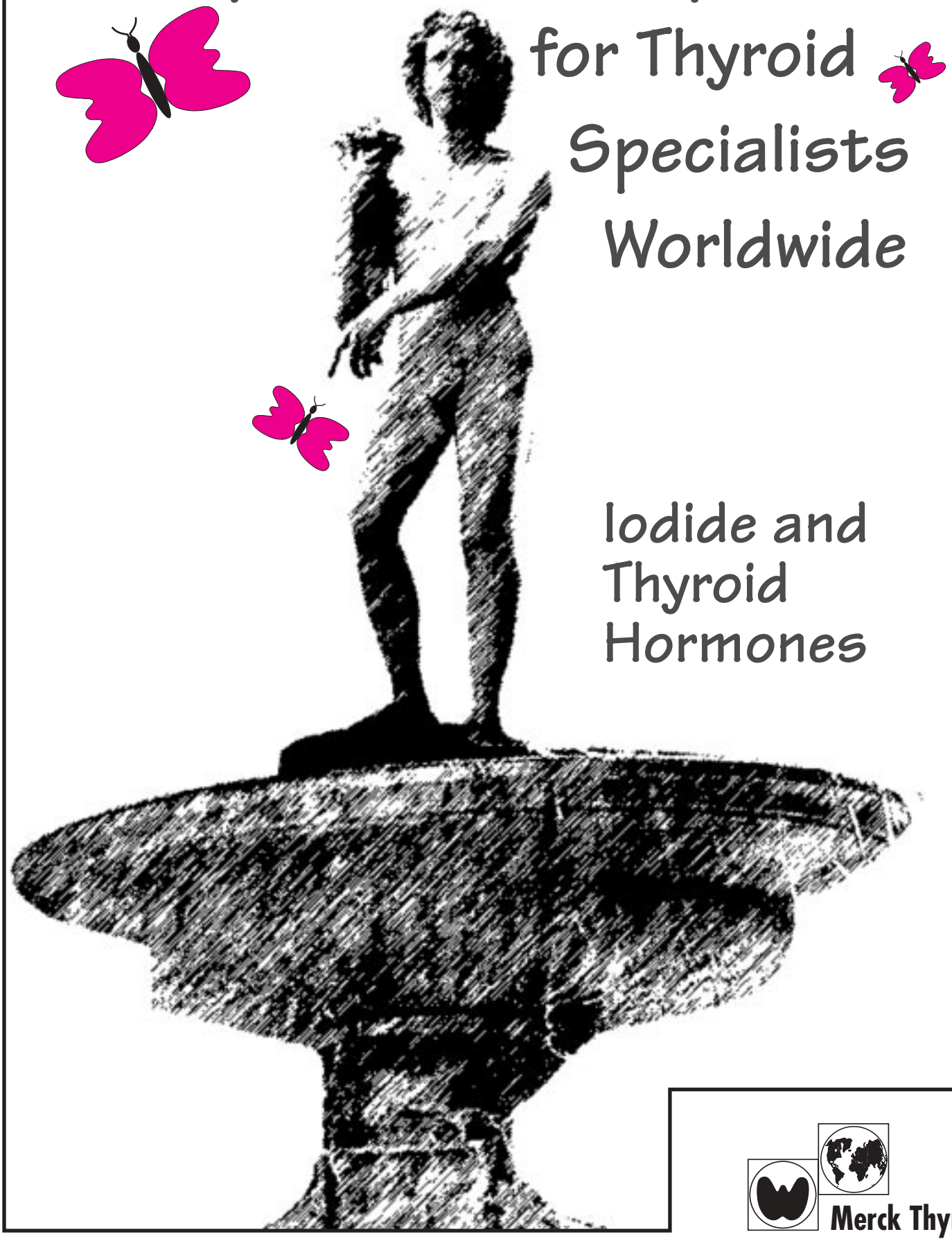
7. The jury decides with a 2/3 majority. In exceptional cases, decisions given in writing form absent jury members may be considered. A member of the jury may not take part in assessing a manuscript if it originates from his working circle. In this case, the President calls another member of the Society from the same field to the jury.

8. The prize is usually awarded once a year at the annual meeting of the German Society of Endocrinology.

9. The President of the Society will invite applications for the prize for the subsequent year at the annual meeting. The secretary and press agent of the Society will arrange announcements in several languages for the competition to be advertised in medical journals.

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