Fine-Needle Aspiration Biopsy of Benign Thyroid Nodules: An Evidence-Based Review

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Abstract

Background Since the development of fine-needle aspiration biopsy (FNAB) techniques, preoperative diagnosis and subsequent strategies for patient treatment have changed and evolved greatly. This is true also for thyroid FNAB: the vast majority of thyroid nodules are benign, and hence do not necessarily require surgical treatment.

Methods A comprehensive Medline and Cochrane Library search was performed evaluating FNAB in the thyroid. In the last decade more than 400 articles on the subject have been published. Data in relation to the experience with FNAB at the Karolinska University Hospital since its introduction were also reviewed.

Results The development of FNAB since the 1960s at the Karolinska University Hospital is described. During the period 1992–1996 the accuracy of the clinical routine was evaluated by studying the outcomes of almost 4,000 FNAs of the thyroid. The results were good, with only a few false-negative and false-positive results, but the problem of differentiating follicular adenoma from follicular carcinoma remained a significant problem. The use of immunological analysis has greatly increased the possibility of obtaining valuable information on cellular characteristics.

Conclusion A successful FNAB service rests on several factors, and the importance of clinical conferences between all specialists involved in the diagnosis and treatment of patients with thyroid disorders cannot be overemphasized. At the Karolinska University Hospital there are weekly conferences where patients are discussed both pre- and postoperatively. These conferences lead to optimal interaction between the different specialists and, most important, substantial improvement in the clinical management of patients with thyroid disorders.

Introduction

Thyroid nodules require evaluation to identify those that are cancers, although malignancies account for only approximately 5% of all thyroid nodules [1]. Although the majority of thyroid nodules are benign, an estimated 30,000 patients in United States will be diagnosed with thyroid cancer each year, and 1,500 patients are estimated to die of the disease yearly [2]. Every patient with a palpable thyroid nodule is a candidate for fine-needle aspiration biopsy (FNAB) and should undergo evaluation to determine if FNAB is warranted [3, 4].

The primary goal of the initial evaluation is to distinguish the benign nodules from those that are malignant and that require removal to limit morbidity and mortality. Thyroid nodules detected by palpation are usually at least 1.0 cm in dimension and therefore are clinically larger than those detected by ultrasound only. The proportion of thyroid nodules that are malignant is higher in children and in adult patients under the age of 30 or over the age of 60 years, and in those with a history of radiation of the head or neck.

Ultrasound guidance for FNAB of the thyroid gland is useful in the combined evaluation of the thyroid nodule as it simultaneously allows detailed examination of the

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remainder of the thyroid gland, characterization of the nodule, and accurate placement of the aspiration needle in the nodule of interest [5]. Ultrasound guidance should also be used to aspirate nodules that are not palpable. In predominantly cystic lesions ultrasound is often useful as well, especially if the prior aspiration contained insufficient cells/colloid for interpretation [6, 7].

Contraindications to thyroid FNAB are very few: specifically, hematomas can occur but will resolve in a few days. The most significant complication, although very rare, is intrathyroidal hemorrhage with acute upper airway obstruction [8].

Over recent decades FNAB has improved the preoperative assessment, mostly through its high positive and negative predictive value [1, 9]. Nevertheless, FNAB is limited by sampling difficulties that result in "nondiagnostic" aspirates and by the significant overlap in morphologic features between benign and malignant nodules, which can result in abnormal but inconclusive results [10]. The overall accuracy of FNAB exceeds 95%, and the ideal test determines if a given nodule is benign or malignant [11]. Investigators have tried to combine several immunocytochemical markers to find combinations with high accuracy; however, no marker or group of markers has yet been sufficiently validated, and measurements of molecular markers on FNAB specimens remain investigational.

In this review we discuss the evidence from the literature and from our own experience with thyroid FNAB at the Karolinska University Hospital. To secure the highest level of objectivity, we used the evidence-based approach of Sackett to analyze the literature of the last decade [12, 13].

Methods

A comprehensive Medline and Cochrane Library search was performed evaluating FNAB in the thyroid. In the last decade more than 400 articles have been published concerning FNAB of the thyroid. Data in relation to the experience with FNAB at the Karolinska University Hospital since its introduction were also reviewed.

Results

Evidence-based literature review and recommendations

Most of the published studies are retrospective or comparative studies with a level of evidence less than A (large randomized controlled trials). The few randomized controlled trials published compare FNAB with other biopsy or imaging techniques [14, 15]. A number of studies have analyzed the underlying causes for the variability in success in reaching a useful diagnosis in FNAB as applied to the thyroid gland and in general [7, 16–20].

Several issues are raised in most of the published reports: the inherent inadequacy of cytologic specimens in assessing capsular and vascular involvement of thyroid follicular lesions, difficulties with predominantly cystic lesions, and the importance of expertise in interpreting FNAB specimens. However, the root causes of most diagnostic shortcomings are poor samples or a lack of specific and meaningful diagnostic category issued by the microscopist or a combination of both. Two published reports describe successful interventions for improving FNAB nondiagnostic/inadequate sample rates of palpable lesions [21, 22]. Dramatic improvements in nondiagnostic sampling rates were achieved in both studies. Preintervention the nondiagnostic rates were 43% and 29%. Postintervention rates were 9% in both studies. In both reports preintervention FNAB samples were collected by the clinician identifying the mass and then sent for pathological processing and interpretation. The intervention in both reports consisted of establishment of a FNAB clinic, where a smaller number of physicians both collected and interpreted the samples. Another report compares FNAB nondiagnostic rates between cytopathologist-collected (12%) and non-cytopathologist-collected samples (32%) [23]. This report found no improvement in nondiagnostic rates when immediate examination for adequacy was provided to a non-cytopathologist by a cytotechnician.

Two reviews of FNAB of the thyroid gland state that procurement of the samples is not as easy as generally perceived, and they stress the importance of obtaining an adequate sample if the test is to be useful [24, 25]. The benefits of existing strategies for FNAB support adherence to recently published guidelines by the European and American Thyroid associations [3, 26].

Development of FNAB

The use of FNAB is more than 100 years old. In 1904 Greig and Gray reported that trypanosomal organisms could be detected in needle aspiration material from lymph nodes in a patient with sleeping sickness [27]. It was not until 1934 when another report described the usefulness of FNA to diagnose tumors [28]. During the late 1950s the technique was used by pioneers such as Söderström and Franzen to diagnose a wide variety of tumors [29]. During the 1960s FNAB became a standard procedure in Sweden not only for thyroid nodules but also for all palpable lumps in the body. This development contributed to the organization of specialized cytology units in Sweden, where cytopathologists performed the aspiration and evaluated

the results. The use of FNA all over the world has led to a significant reduction in the number of patients requiring surgery for thyroid nodules and has increased the yield of cancer diagnoses at thyroidectomy [30, 31].

Diagnosis of thyroid nodules

Nondiagnostic thyroid FNAB is most often caused by insufficient aspiration of material for cytologic diagnosis, generally due to inadequate numbers of follicular cells. Preventable causes of nondiagnostic FNAB include poor cell preservation from a delay in ethanol fixation, extensive hemodilution from bloody aspirates, or poorly prepared smears. Ultrasound guidance for FNAB of the thyroid has become invaluable in the precise biopsy of small, nonpalpable nodules. Repeated ultrasound-guided FNAB of previously nondiagnostic FNAB can lead to a definitive diagnosis in up to 90% of cases [11]. Nodules with persistently nondiagnostic FNAB have a 5%–9% incidence of malignancy after thyroidectomy [32]. The most common thyroid lesion is a benign colloid nodule, followed by nodular goiter, hyperplastic nodules, simple cysts, subacute thyroiditis, and lymphocytic thyroiditis. The false-negative rate for benign thyroid FNAB is low, with reported rates between 1% and 5% [1]. Benign asymptomatic thyroid nodules in patients without any risk factors for thyroid cancer can therefore be followed with clinical examinations and ultrasound. Repeat biopsy is indicated when there is evidence of growth or development of suspicious features on ultrasound.

The indeterminate categories of thyroid nodules are usually the follicular lesions, which is the most challenging diagnostic category of thyroid FNAB. These include two main groups, the first including the benign follicular lesions such as neoplastic follicular cell adenomas and Hürthle cell adenomas, and non-neoplastic follicular cell hyperplasia and Hürthle cell hyperplasia. The second group includes the malignant follicular lesions, including follicular carcinoma, Hürthle cell carcinoma, and the follicular variant of papillary thyroid carcinoma. In general, 10%–20% of follicular or Hürthle cell neoplasms are malignant. There are a few cytologic criteria that may help to differentiate benign from malignant follicular lesions, and diagnostic thyroid lobectomy with isthmusectomy is required for definitive diagnosis [21, 33].

Fine-needle aspiration biopsy is highly sensitive and specific in the diagnosis of papillary thyroid carcinoma, with an accuracy of 98% [1, 34, 35]. Medullary thyroid carcinoma (MTC), poorly differentiated thyroid carcinoma, anaplastic carcinoma, primary thyroid lymphoma, and metastases to the thyroid are also accurately diagnosed by FNAB. The cytologic appearance of MTC can mimic various other primary and metastatic lesions; however,

immunoreactivity of the tumor cells with calcitonin is essentially diagnostic of MTC. The combination of positive calcitonin and negative thyroglobulin immunostaining is helpful in differentiating MTC from other primary thyroid neoplasms [1, 36]. The diagnosis of poorly differentiated or anaplastic thyroid carcinoma is usually straightforward, as it is characterized by large irregular nuclei and frequent mitotic figures. Lymphomas might resemble lymphocytic thyroiditis, and therefore an adequate tissue sample for flow cytometry must be obtained to confirm the diagnosis.

Experience from the Karolinska University Hospital

History

In the late 1940s Dr. Sixten Franzén, then a young doctor with a special interest in the morphology of bone marrow smears, was recruited to the oncology clinic, Radiumhemmet, at Karolinska. Franzén started to make aspiration biopsies stained with Giemsa from various tumors and his diagnoses were used in the clinical management of many patients.

Franzén was extremely active in diagnosing tumors by means of FNA cytology, and he could not find time to present his astonishing achievements in scientific journals. Consequently the highly organized pathologist Joseph Zajicek was recruited to organize and document the extensive cytologic material continuously produced by Franzén. Together they wrote several scientific articles that confirmed the usefulness of the technique.

In 1967 the FNAB clinic was formally opened at the Karolinska Hospital, but it had already been operating for many years. The clinic was located in the oncology building Radiumhemmet, and mostly received patients from the oncology clinic, although patients were also referred from other departments and from doctors outside the Karolinska Hospital. Every year more than 10,000 patients were examined, underwent FNAB, and diagnosed.

The clinical impact of this activity in the management of patients with tumors was dramatic. The number of open biopsies, as well as the number of frozen sections, was reduced substantially. In many patients radical surgery was performed, and radiation therapy and chemotherapy were given based on FNAB diagnosis. At the same time, there were many opponents to the use of FNA cytology as a definitive diagnostic method. In addition to the clinical work done by the four doctors on the FNAB clinic staff—Franzén and Zajicek had been joined by Drs. Torsten Löwhagen and Pier Esposti—they happily accepted guests for training in FNA cytology. The aspiration procedure was minutely taught and the smears were examined in double-headed microscopes. Several hundred foreign doctors were thus introduced to FNA cytology over the years. As the

demand for training exceeded the capacity of the clinic, a short course was given both at the Karolinska Hospital and abroad. These courses covered all aspects at FNA cytology, and this had a great impact on spreading the technique.

Dr. Löwhagen in particular was inexhaustible in teaching the secrets of the FNAB procedure, which to an untrained eye seem deceptively simple. Today the instruction of new cytopathologists at the clinic continues to follow the principles established by Löwhagen.

Today

The FNA cytology clinic at eh Karolinska Hospital is still located in the Department of Oncology. It is organized as a "drop-in" clinic, and all patients with a physician's request for biopsy are accommodated. Approximately 10,000 patients are seen every year. Five specialists in cytopathology are engaged in the biopsy clinic and in reporting exfoliative cytology as well. Nurses and cytotechnicians assist in various activities. Computed tomography guided and ultrasonographically guided FNAB are carried out at the Department of Radiology. In collaboration with the radiologist the cytopathologist performs the actual FNA biopsy and also checks the adequacy of the material by the quick-stain technique. In addition, material is also collected for ancillary techniques.

FNAB of thyroid lesions

The thyroid is one of the most common targets for FNAB and approximately 1,500 patients are seen every year. The FNAB procedure is carried out with the patient lying supine (Fig. 1). The thyroid is examined by palpation and/or ultrasonography, and after the target has been identified the skin over it is cleansed with an alcohol preparation. Sterile draping is considered unnecessary. In most patients local anesthesia is not required. However, in pediatric

Fig. 1 The fine-needle aspiration biopsy procedure is carried out with the patient in the supine position

patients a local anesthetic ointment can facilitate the procedure.

The size of the needle to be used is determined by the examiner's clinical evaluation of the target. If the target is judged to be solid, a 27–23-gauge (0.4–0.6-mm) needle should be selected. In most cases, these needles will give an adequate cellular sample and cause very little bleeding. If the lesion is considered to be cystic a 23–22-gauge (0.6–0.7-mm) needle should be used. Unless the cystic content is too thick, it can be evacuated through needles of these sizes. A pistol grip-like holder in which the syringe is fitted is used, as originally described by Franzén [37]. A noncystic lesion is aspirated as follows: the needle is inserted into the target, continuous suction is applied, and the needle is moved with gentle up and down strokes until blood/fluid appears in the hub. The suction is then released and the needle is withdrawn. The aspirated material is expelled onto glass slides, and smears are prepared as described elsewhere [38]. At least one slide should be prepared for MGG and one for Papanicolaou staining. In many cases a gross examination of the smears is sufficient to ensure that representative material has been obtained. In questionable cases a quick stain (1 min MG and 1 min Giemsa /1:1/) should be used. This will not only reduce the number of nondiagnostic aspirates but also allow collection of material for ancillary studies. The number of passes needed obviously varies with the type of lesion aspirated as well as the experience of the operator. However, more than three passes are rarely needed for trained physicians.

Cyst fluid should be used both for direct smears and cytocentrifugation. The procedure for ultrasound-guided FNAB is almost identical to that for palpable lesions. However, it must be emphasized that ultrasound gel should not be used during the biopsy procedure, because the gel produces a precipitate on the slide which often makes microscopic evaluation impossible. Many radiologists therefore use physiologic saline as transducing material.

The microscopic diagnosis is primarily based on evaluation of MGG and Papanicolaou stained smears. However, like many other areas of tumor cytology, the introduction of immunocytochemistry has improved the diagnostic accuracy and has allowed better prediction of prognosis. Indications for immunocytochemistry are to (1) confirm the diagnosis of tumors such as MTC, poorly differentiated papillary carcinoma, lymphoma, and metastasis; (2) aid the differential diagnosis between true follicular tumors and the follicular variant of papillary carcinoma; and (3) determine the rate of cell proliferation in various tumors.

The cytology report is always descriptive and summarized in a CD (cytologic diagnosis). In general, the reports follow a four-category diagnostic scheme: (1) benign, (2) indeterminate, (3) follicular lesion, (4) malignant. Thus, in

contrast to other suggested category diagnostic schemes, we seldom report cases as unsatisfactory and suspicious for malignancy [39, 40].

In cases of an unsatisfactory FNAB, the patient will be called back within a few days for a repeat biopsy, including direct evaluation of adequacy using a quick stain procedure. The category "suspicious for malignancy" is rarely used because immunocytochemistry is stringently used to classify tumors.

Discussion

The accuracy of negative aspirates is difficult to validate because most of these patients do not undergo surgery. However, many patients have been followed for many years with clinical examination and/or sonographic examinations. Nodules with a substantial growth or worsening symptoms were considered for repeated FNAB. The results from a large series of thyroid FNAB prove that a high level of accuracy can be achieved [34]. During the period 1992–1996 the accuracy of the clinical routine in our unit at the Karolinska University Hospital was evaluated by studying the outcomes of almost 4,000 FNAs of the thyroid. The results were good, with only a few false-negative and false-positive results; but the problem of differentiating follicular adenoma from follicular carcinoma remained a significant problem [34].

In our unit the use of immunological analysis of surgical biopsy material or aspirated cells has greatly increased the possibility of obtaining valuable information on cellular characteristics such as phenotype, growth rate, and onco-gene expression. We have mainly used the technique to aid cytomorphology in the characterization of poorly differentiated epithelial tumors and lymphoid infiltrates in the thyroid [34]. It is useful with a limited panel of antibodies to cytokeratins, thyroglobulin, and calcitonin in the differential diagnosis of primary thyroid neoplasm and a metastatic deposit in the thyroid. The monoclonal antibody HMBE-1 stains most papillary carcinomas and a large proportion of follicular carcinomas, which is important in the diagnosis of malignant thyroid tumors [41].

A mixed lymphoid infiltrate composed of small immature, intermediate and large blastic lymphoid cells may be seen with lymphocytic thyroiditis and malignant lymphoma of the follicular center and malt-cell type. When the lymphoid infiltrates are massive or difficult to identify, immunocytochemistry should be used to characterize the lymphoid cells [42]. A benign lymphoid population is composed of a mixture of B and T cells; furthermore a B-cell population is diagnostic of non-Hodgkin's B-cell lymphoma. High-grade lymphomas in the thyroid can be diagnosed with cytomorphology alone, although immunocytochemistry should be used to sub-classify the lymphoma into high grade T, B, or anaplastic large cell, Ki-67-positive neoplasms a finding that is of prognostic and therapeutic importance. Using the monoclonal antibody MIB-1 to the Ki-67 antigen can be a helpful tool in diagnosing a malignant thyroid lesion [43].

Novel FNAB applications are developing. Preoperative mutation analysis of several genes can be applied to thyroid FNAB, and it may be of significance for future clinical decision making [44]. Indeed, polymerase chain reaction (PCR)-based gene expression profiles may be of great value in determining the malignant potential of, for example, follicular thyroid tumors, and it may also be of prognostic importance [45]. It will be fascinating to follow the development of molecular FNAB, and it is likely that such methods may soon become the clinical standard.

Conclusion and recommendations

A successful FNAB service rests on several factors such as trained, dedicated cytopathologists to perform the FNAB and read the smears, as well as maintain constant interaction with radiologists, endocrinologists, surgeons, and oncologists. The use of ancillary techniques is also of importance.

All cytopathologists working in the FNAB clinic at Karolinska have been trained according to the principles established by Dr. Löwhagen. Thus all doctors in training shadow a specialist in the biopsy clinic for several months before they perform their own supervised FNAB. The time to reach an acceptable level of skill is individual, but very few physicians are capable of acting independently before they have performed 500–1,000 supervised biopsies. In addition the importance of performing quick stains and immunocytochemistry is dogmatically taught.

In patients with nonpalpable thyroid lesions, aspiration biopsy is performed in collaboration with a radiologist. The cytopathologist performs the aspiration after the needle has been introduced into the target by the radiologist. The adequacy of the aspirate is immediately checked by quick stain procedure. Obviously this approach is time consuming, but it results in superior diagnostic material.

The importance of clinical conferences among all specialists involved in the diagnosis and treatment of patients with thyroid disorders cannot be overemphasized. At the Karolinska Hospital weekly conferences are held to discuss patients both pre- and postoperatively. These conferences have led to optimal interaction between the different specialists and, most important, a substantial improvement in the clinical management of patients with thyroid disorders.

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