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Thyroid Cancer Detected by Ultrasound-Guided Fine-Needle Aspiration Biopsy

Tamotsu Yokozawa, M.D.,[1] Shuji Fukata, M.D.,[1] Kanji Kuma, M.D.,[1] Fumio Matsuzuka, M.D.,[1]
Akira Kobayashi, M.D.,[1] Keisuke Hirai, M.D.,[1] Akira Miyauchi, M.D.,[2] Masahiro Sugawara, M.D.[3]

[1]Kuma Hospital, 8-2-35 Shimoyamate Dori, Chuo-ku, Kobe 650, Japan
[2]Second Department of Surgery, Kagawa Medical School, Kagawa, Japan
[3]Medical and Research Services, West Los Angeles Veterans Affairs Medical Center and University of California Los Angeles, School of Medicine, Los Angeles, California, 90073, U.S.A.

Abstract. A greater percentage of thyroid cancers can be detected by ultrasound-guided fine-needle aspiration biopsy (UG-FNAB) than by ordinary FNAB. A group of 678 patients were selected sequentially as having been diagnosed with benign nodules by the conventional FNAB method. We reexamined these patients by UG-FNAB and investigated the types of thyroid cancer that were missed by the conventional FNAB. Of the 678 patients diagnosed with benign nodules (using conventional FNAB), 571 (84.2%) demonstrated the same diagnosis when UG-FNAB was used. The remaining 107 patients (15.8%) studied were suspected of having a malignancy after UG-FNAB had been performed. Surgical specimen histology proved thyroid cancer in 99 of the 107 patients: 93 had papillary carcinoma, 4 had follicular carcinoma, 1 had medullary carcinoma and 1 had anaplastic carcinoma. Two drawbacks were noted when conventional FNAB was used: (1) cancer lesions difficult to palpate (*n* = 55) (e.g., small cancers with or without benign lesions or cancers associated with Hashimoto's thyroiditis or Graves' disease); and (2) palpable cancers with insufficient cell material for analysis (*n* = 44) (e.g., cystic carcinoma and cancers with calcified lesions. UG-FNAB is a powerful technique for detecting microcancers, cystic carcinomas, cancers associated with benign nodules, Hashimoto's thyroiditis, or coarse calcifications.

Fine-needle aspiration biopsy (FNAB) is commonly used for diagnosing thyroid nodules. In general, it is a fairly reliable method so long as thyroid nodules are palpable [1–3]. Small cancers, however, or cancers associated with benign lesions, cysts, or calcification present difficult problems, as an accurate hit to the cancer lesion is difficult by palpation. To overcome this difficulty, multiple sampling has been used as one of the standard approaches [3]. To increase the diagnostic accuracy of thyroid nodules, ultrasound-guided FNAB (UG-FNAB) has been used [4–8]; indeed, this technique is useful for diagnosing small thyroid lesions or occult lesions [7]. One of us (T.Y.) developed a simple, accurate method for diagnosing thyroid nodules using UG-FNAB [5]. We used UG-FNAB to reassess cytologic diagnoses of conventional FNAB and determined the advantages of UG-FNAB and the pitfalls of conventional FNAB, particularly for detection of thyroid cancers. Our study indicated that cytologic diagnosis for certain types of thyroid cancers requires UG-FNAB.

Correspondence to: T. Yokozawa, M.D.

Patients and Materials

Patients

We selected 678 patients sequentially who had been diagnosed as having benign thyroid nodules by ultrasonography and conventional FNAB. There were 25 men and 653 women with a mean (± SD) age of 52.2 ± 11.9 years. The mean (± SD) size of thyroid nodules on the initial evaluation was 18.1 ± 12.9 mm. There were 357 single nodules and 321 multiple nodules. At 2 to 24 months after conventional FNAB, all patients underwent UG-FNAB, after which cytologic diagnosis by conventional FNAB was compared with that of UG-FNAB.

Procedure of UG-FNAB

All steps of the procedure have been described previously [5]. The ultrasound scanner used was Aloka SSD 2000, focus type (Aloka, Tokyo, Japan) equipped with two different transducers: 10 MHz ASU-35WL-10 mechanical sector probe and 7.5 MHz UST-987-7.5 convex probe. Initially, an ASU-35-10 probe was used to obtain a clear picture of the thyroid gland, and the biopsy site was determined. Then a small probe with convex shape (UST-987-7.5) was applied to the neck. A 22 gauge needle attached to the 10 ml syringe was placed just above the UST-987-7.5 probe. By watching the tip of the needle in the monitor, the needle was inserted almost perpendicular to the neck and guided to the biopsy site. The tip of the needle was clearly visible as a bright spot in the monitor. When the needle reached the biopsy site, the probe was removed, and the syringe-needle unit was fixed with the operator's left hand. Suction was then applied by pulling the piston portion of the syringe up to the 1 to 2 ml level with the right hand. While maintaining the suction by pulling the piston portion of the syringe with the right hand, the outer part of the syringe that was connected to the needle was spun two to three times using the left thumb and index finger. This drill technique cuts thyroid tissue by the spinning needle, and abundant cell material can be obtained.

After samples were obtained, the specimens were put on a glass slide. The blood component on the glass slide was removed

Table 1. Thyroid cancers diagnosed by UG-FNAB, not by conventional FNAB

Cancers difficult to palpate (n = 55)
Solitary small cancer (n = 15, size 12 ± 3 mm)
Cancers associated with benign nodule (n = 26, size 16 ± 5 mm)
Cancers associated with chronic thyroiditis (n = 10, size 15 ± 7 mm) or Graves' disease (n = 4, size 13 ± 4 mm)
Palpable nodules but inadequate cells for cytologic diagnosis (n = 29)
Cystic carcinoma (n = 5, size 39 ± 15 mm)
Advanced calcification (n = 24, size 18 ± 4 mm)
Poor technique of FNAB (n = 15, size 30 ± 18 mm)

The size of the cancer was measured by ultrasonography and is expressed as the mean ± SD.

quickly by wiping it with soft tissue paper. The cell component was then spread with another glass slide. The slides were fixed and stained with the Papanicolaou stain.

Results

Among the 678 patients, 571 (84.2%) agreed to the initial cytologic diagnosis by conventional FNAB. However, 107 patients (15.8%) were suspected to have malignancy after UG-FNAB, so all 107 patients underwent surgery. Surgical specimen histology revealed thyroid cancer in 99 patients and benign nodules in 8. There were 93 papillary carcinomas, 4 follicular carcinomas, 1 medullary carcinoma, and 1 anaplastic carcinoma. Among the 93 patients with papillary carcinomas, there were 21 microcancers (diameter < 1 cm). The rest of the papillary carcinomas showed sizes of 21.2 ± 9.2 mm (mean ± SD). The four patients diagnosed with follicular carcinomas had lesions of 47.5 ± 13.6 mm (mean ± SD) on the surgical specimen. One anaplastic carcinoma had a longitudinal diameter of 13 mm. Eight patients who underwent surgery had no malignant lesion, as shown by surgical specimen analysis. These patients showed borderline cytology for malignancy; thus surgery was performed.

We analyzed each case in which the thyroid cancer was diagnosed by the UG-FNAB method and missed by conventional FNAB. Table 1 presents causes of inaccurate cytologic diagnosis by conventional FNAB. Nonpalpable cancer was the most common cause (55.6%) of inaccurate diagnosis by conventional FNAB. In this category, cancers associated with benign nodules were most common, followed by solitary small cancer and coexistent cancer with autoimmune thyroid diseases, particularly Hashimoto's thyroiditis. The next common problem of diagnosing thyroid cancer by the conventional FNAB method was palpable cancers with inadequate cells for cytologic diagnosis (29.3%). Cancers with advanced calcification or cystic carcinoma belonged to this category. Poor technique accounted 15.2% of causes of inaccurate diagnosis of thyroid cancer by conventional FNAB.

Representative Difficult Cases

A 36-year-old woman was found to have a micronodule on ultrasound examination in another hospital. FNAB was unsuccessful because the nodule was not palpable. The tissue specimen was obtained from a 6 mm cancer lesion by UG-FNAB. Histologic examination revealed that microcancer invaded to the recurrent laryngeal nerve (Fig. 1).

Figure 2 shows a small cancer associated with large benign lesions. In this case the benign lesion was easily palpable; thus initial FNAB was done on the benign lesion, not the cancer. A malignant lesion was strongly suspected from the ultrasound findings; the use of UG-FNAB was diagnostic in this case.

Figure 3 shows thyroid cancer associated with Hashimoto's thyroiditis. The thyroid gland of Hashimoto's thyroiditis is generally palpated as lobulated firm nodules, making the biopsy site difficult to choose. The ultrasound findings showed a hypoechoic lesion suggestive of cancer; and indeed it was seen to be a microcancer when samples were obtained by the UG-FNAB method.

Figure 4 is an example of thyroid cancer associated with advanced coarse calcification. Conventional FNAB from the calcified lesion resulted in an empty cell. Ultrasound-guided FNAB allowed us to select more invasive peripheral lesions for the biopsy site. Cell samples obtained from peripheral portions of the calcified lesion showed papillary carcinoma.

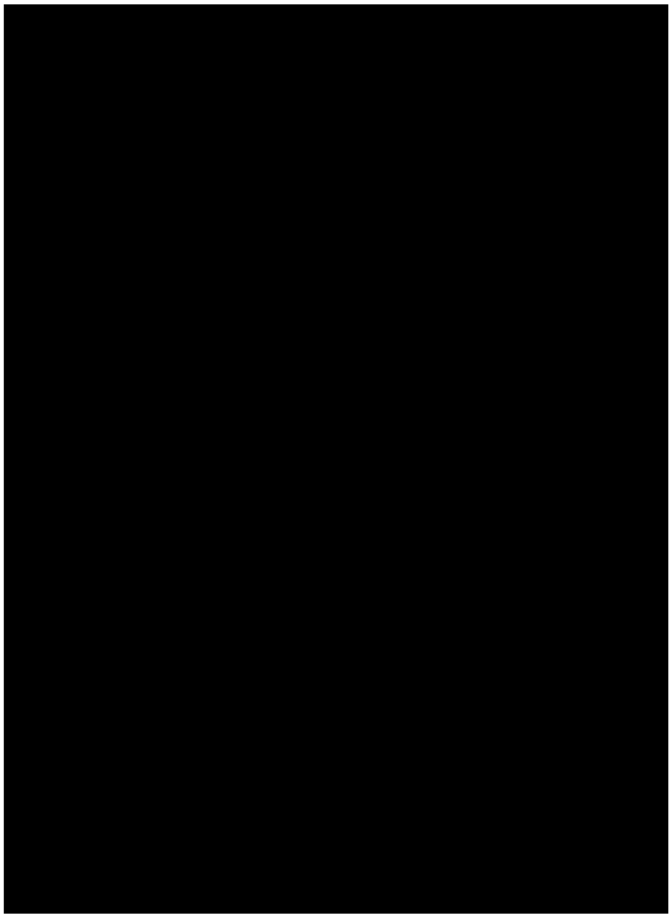
Figure 5 shows cystic carcinoma. It is almost impossible to hit a portion of the cancer lesion by conventional FNAB when cystic carcinoma is present. Again, an accurate selection of biopsy site by UG-FNAB was diagnostic in this case.

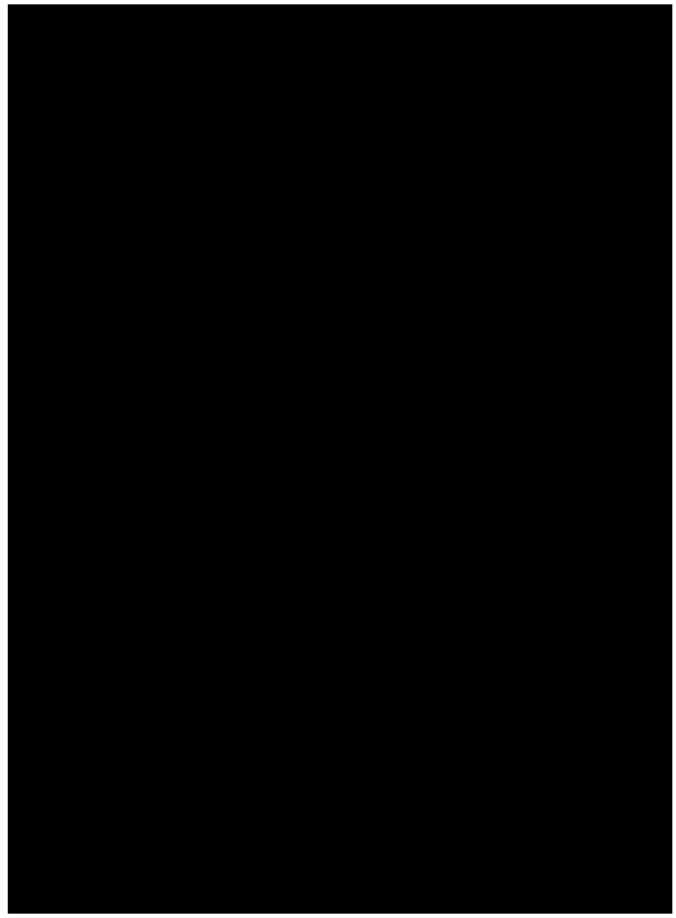
Discussion

There is no doubt that the cytologic diagnosis is improved if biopsy sites are chosen accurately. This was the idea for developing of UG-FNAB [4–8]. UG-FNAB, however, can be difficult to perform because a large probe may obstruct needle insertion. In addition, this procedure may require expensive instruments or an assistant. One of us (T.Y.) developed a much simpler method of UG-FNAB using a portable ultrasound machine and a small probe [5]. This procedure can be done at an outpatient site without assistance. We used UG-FNAB to examine what types of thyroid cancer were missed by the conventional FNAB method.

Our plan was to study patients who had been previously diagnosed to have benign thyroid nodules by conventional FNAB; the accuracy of conventional FNAB was then evaluated by UG-FNAB. Among the 678 patients with benign nodules, 107 patients (15.8%) who were suspected to have malignancy by UG-FNAB underwent surgical resection. Ninety-nine patients (14.6%) turned out to have a malignancy on histologic examination of surgical specimens. Cytologic diagnosis of thyroid nodules by UG-FNAB was made 2 to 24 months after the initial FNAB. It can be argued that new cancer lesions developed between the initial FNAB and UG-FNAB, but Kuma et al. reported that almost all benign thyroid nodules remain benign for more than 8 years, and that transformation of benign nodules into malignant nodules is rare [9]. Our impression is that cancer lesions were probably missed by conventional FNAB. This view can be supported by the findings that 47 cases of thyroid cancer were detected when UG-FNAB was performed within 3 months of the initial FNAB. The only exception was a patient with anaplastic carcinoma. Because UG-FNAB was done 1 year after the conventional FNAB, this anaplastic carcinoma may have been a newly developed cancer.

Next, we examined the characteristics of thyroid cancers detected by UG-FNAB and not by conventional FNAB. Table 2 summarizes the types of thyroid cancer that are missed by conventional FNAB. Small cancers are always difficult to detect by conventional FNAB. Köhler and Köhler reported that 59% of





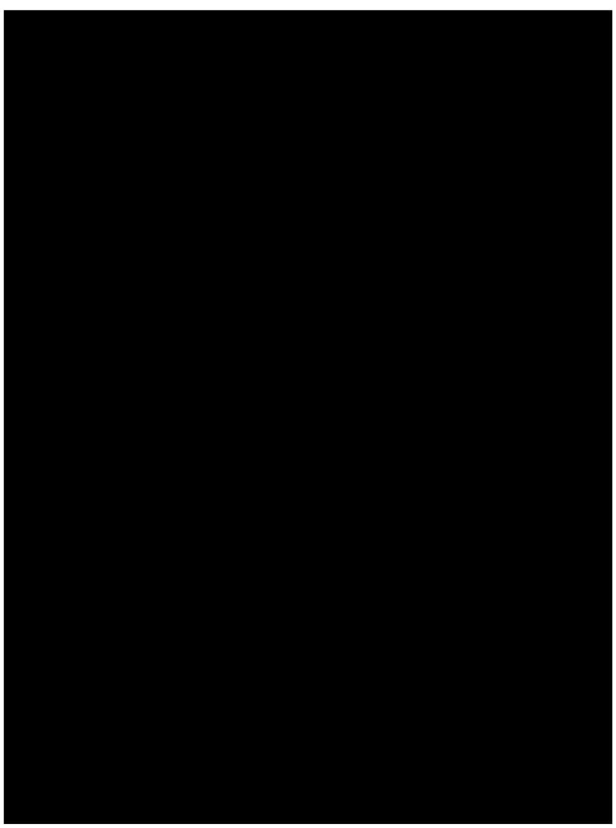


Fig. 1. Microcancer. Top: ultrasound scan; bottom: surgical specimen. Arrow (top) indicates the location of the microcancer (6 mm) invading the recurrent nerve (arrow, bottom).

Fig. 2. Thyroid cancer associated with benign nodules. Arrow indicates a benign nodule, and the arrowhead shows thyroid cancer. Histologic examination showed a 2.0 cm cancer and a 2.5 cm benign nodule.

Fig. 3. Thyroid cancer associated with chronic thyroiditis. Arrows indicate the location of the papillary carcinoma (9 mm). The rest of the thyroid gland is typical of Hashimoto's thyroiditis (arrowheads).

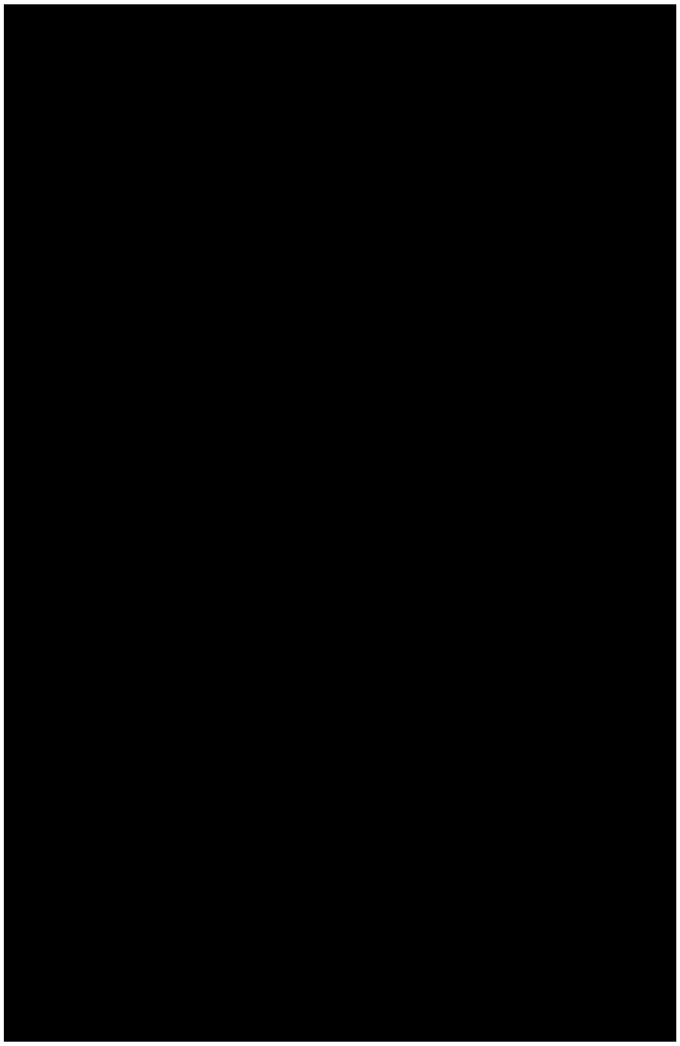


Fig. 4. Calcified cancer. Calcification (arrows) and the peripheral portion of the calcified cancer lesion (arrowheads) are shown. The biopsy from the peripheral lesion was diagnostic.

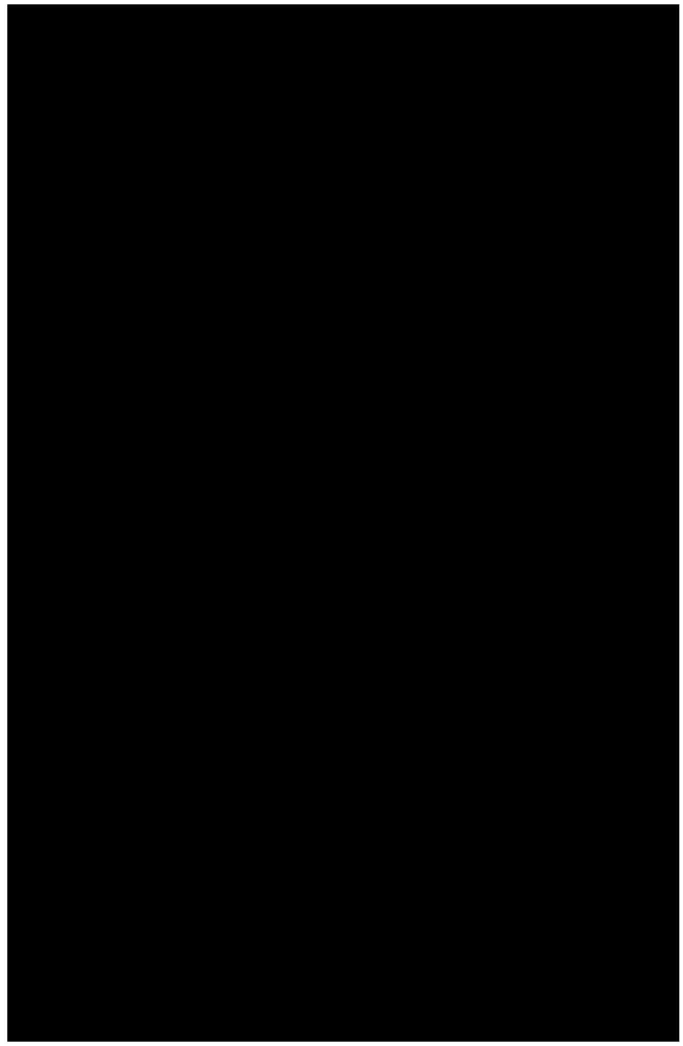


Fig. 5. Cystic carcinoma. Biopsy was obtained from the base of a cystic tumor (arrows).

thyroid cancers were missed by FNAB when they were < 1.5 cm in size [10]. In the study of Schmid et al., aspiration cytology missed 39% of cases (22 of 56 cases) of thyroid cancer when the size of the cancer was < 3 cm [11]. Fortunately, UG-FNAB is a powerful technique for detecting microcancers. As shown in Figure 1, a 6 mm papillary carcinoma was diagnosed by UG-FNAB. Based on our experience, cancer lesions as small as 5 mm can be diagnosed relatively easily by UG-FNAB. Whenever small lesions are present, one has to use a drill technique rather than multiple sampling as we described previously [5], as this technique increases the yield of cell components.

It has been reported that thyroid cancer is associated with benign single or multiple nodules at an incidence of 1.4% to 17.0% [12, 13]. In our series of 321 cases of multiple nodules, 26 patients (8%) had thyroid cancer. The coexistence of small cancers and large benign nodules always makes the diagnosis difficult (Fig. 2), as FNAB is done on benign nodules. Careful screening of thyroid nodules by ultrasonography (Table 2) and judicious choice of biopsy sites are needed; thus UG-FNAB is the most suitable method for detecting small cancers associated with benign nodules.

Another difficulty when detecting thyroid cancer by conventional FNAB is if a cancer is associated with Hashimoto's thyroiditis [14–16] because the thyroid gland can be firm and lobulated. Even with the use of ultrasound, cancer lesions are sometimes difficult to delineate. Choosing a hypoechoic area for the biopsy site in the thyroid gland of patients with Hashimoto's thyroiditis (Fig. 3) enabled us to diagnose thyroid cancer in 10 cases. Four separate instance of thyroid cancer were found in the thyroid gland of Graves' disease (4%). The prevalence of thyroid cancer in Graves' disease, at least in this series, does not reflect the overall incidence of thyroid cancer in the Graves' thyroid gland because only patients with Graves' disease, who were found to have nodules on ultrasound examination, were included in our study.

Another indication for use of UG-FNAB is cystic carcinoma. Generally, it has been thought that cystic tumors of the thyroid are benign; however, De Los Santos et al. summarized previously reported cases of cystic tumors including his own experience and

Table 2. Ultrasound classification of thyroid nodules.[a]

Class	Sonographic findings	Types of nodule
I	Round and anechoic area	Cyst Adenomatous nodule
II	Round and cystic nodule (single or multiple) or isoechoic solid nodule	Adenomatous nodule Follicular adenoma
III	Round and hypoechoic solid nodule	Follicular adenoma Adenomatous nodule Carcinoma
IV	Solid nodule with irregular border or presence of psammoma calcification	Carcinoma
V	Solid nodule with irregular border and extrathyroidal invasion	Carcinoma

[a]This classification was based on the comparison between ultrasound findings and histologic diagnoses of more than 1000 cases.

reported that 62 of the 443 patients with cystic tumor (14%) had malignancy [17]. With use of conventional FNAB it is almost impossible to hit the cancer lesions if a thyroid cyst is present; therefore, Gharib recommended repeated FNAB [2]. Some recommend surgery if a cystic tumor does not regress by repeated aspiration [17]. Hatabu et al. reported specific sonographic signs of cystic carcinoma; calcified nodules in the cyst were seen in 8 cases [18]; nevertheless, choosing the base of a cystic tumor, not the degenerative portion of the cyst, as a biopsy site should enable one to make the diagnosis of cystic carcinoma.

It is known that thyroid cancer, particularly papillary carcinoma, may have calcification within it. Kasai and Tsuya studied the nature of calcification in 68 cases of thyroid cancers and classified three types [19]: type 1, multiple, minute calcifications; type 2, mixture of minute and coarse calcification; type 3, coarse calcification. Cancers encountered in the present study were type 2 or type 3 (Kasai's classification). If a needle hits the portion of calcification, it is difficult to aspirate cancer cells. As Katz et al. reported, ultrasound is an excellent tool for delineating the peripheral portions of tumors [20]. We were able to obtain biopsy specimens from peripheral hypoechoic lesions of calcified tumors; indeed, an ultrasound-guided needle was able to reach the cancer site and enough cancer cells were obtained.

Lastly, it is important to make a good preparation for cytologic examination. Gharib described a 10 step protocol to improve aspiration cytology techniques [2]. Multiple poking of the nodule and repeated aspiration if cells are unable to be obtained are a common practice. Hamburger [3] described the same approach as outlined by Gharib [2]; however, multiple pokings can result in bloody samples, and interpretation of the aspiration cytology can be difficult. Our FNAB, under the guidance of ultrasound, uses a drill technique, which eliminates multiple poking; more importantly, enough cells for diagnosis can be obtained with little bleeding. UG-FNAB is no longer difficult to perform. This procedure should be used to improve the diagnostic accuracy of thyroid cancers.

Résumé

On détecte plus de cancers thyroïdiens par la biopsie à l'aiguille fine écho-guidée que par la biopsie à l'aiguille fine classique. Six cent soixante-dix-huit patients ayant un nodule bénin par la méthode conventionnelle ont été sélectionnés de façon consécutive. Nous avons réexaminé tous ces patients par la méthode écho-guidée et ensuite analysé les cas de cancer non vus par la méthode conventionnelle. Des 678 patients ayant eu un diagnostic de nodule bénin (en utilisant la méthode conventionnelle), 571 (84.2%) avaient le même diagnostic avec la biopsie écho-guidée. Chez les 107 autres patients (15.8%), un cancer était suspecté après l'examen par la biopsie écho-guidée. L'examen anatomopathologique de la pièce chirurgicale a détecté un cancer chez 88 des 107 patients: 93 étaient des cancers papillaires, quatre des cancers folliculaires, un, un cancer médullaire alors que le dernier était un cancer anaplasie. Deux inconvénients sont à noter en ce qui concerne la biopsie conventionnelle: 1) les lésions de cancer sont difficiles à palper (n = 55) comme par exemple les petits cancers avec ou sans lésion bénigne associée ou les cancers associés à la thyroïdite de Hashimoto ou la maladie de Basedow; et 2) les cancers peuvent être palpables sans avoir suffisamment de matériel cellulaire pour faire l'analyse (n = 44), par exemple les cancers kystiques et les cancers associés à des lésions calcifiées. La biopsie à l'aiguille fine écho-guidée est un outil puissant pour détecter les microcancers et les cancers kystiques, ainsi que les cancers associés à des nodules bénins, la thyroïdite de Hashimoto ou des calcifications.

Resumen

Un mayor porcentaje de los cánceres tiroideos puede ser detectado mediante aspiración-biopsia por aspiración con aguja fina guiada por ultrasonografía (AAF-GU) que mediante aspiración-biopsia ordinaria con aguja fina. Se seleccionaron 678 pacientes en forma secuencial en quienes se estableció el diagnóstico por el método convencional de aspiración con aguja fina. Reexaminamos tales pacientes mediante AAF-GU e investigamos los tipos de cáncer tiroideo que no habían sido detectados con la aspiración-biopsia convencional. De los 678 pacientes diagnosticados como nódulos benignos (utilizando la aspiración con aguja fina convencional), en 571 (84.2%) se hizo el mismo diagnóstico con la AAF-GU. En los restantes 107 pacientes (15.8%) estudiados, se sospechó malignidad luego de la AAF-GU. La histología del espécimen quirúrgico demostró cáncer en 99 de 107 pacientes: 93 carcinomas papilares, 4 carcinomas foliculares, 1 carcinoma medular y 1 carcinoma anaplásico. Se anotaron dos desventajas con el método de la aspiración con aguja fina convencional: 1) cuando las lesiones malignas son difíciles de palpar (n3D55); por ejemplo, los cánceres pequeños con o sin lesiones benignas asociadas o los cánceres asociados con tiroiditis de Hashimoto o enfermedad de Graves, y 2) cánceres palpables con material insuficiente para análisis (n3D44); por ejemplo, carcinoma quístico y cánceres con lesiones calcificadas. La aspiración-biopsia con aspiración guiada por ultrasonido es una excelente técnica para detectar microcánceres, carcinomas quísticos y cánceres asociados con nódulos benignos, tiroiditis de Hashimoto o calcificaciones gruesas.

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Invited Commentary

Bertil Hamberger, M.D.

Karolinska Institute, Department of Surgical Sciences, Division of Surgery, Karolinska Hospital, Stockholm, Sweden

The paper by Yokozawa et al. describes their experience of ultrasound-guided fine-needle aspiration performed 1 year after conventional fine-needle aspiration has been done without ultrasound. In their experience 15% of the patients with suspicion of malignancy were operated on, and 90% of these operated patients were found to have a thyroid carcinoma.

Several possible explanations and conclusions must be considered from the present study. Many of the small papillary cancers were probably present also at the initial fine-needle aspiration—some not possible to palpate, with others palpable but the fine-needle aspiration was not diagnostic. Some of these papillary carcinomas had probably grown slowly over the year, and so they are easier to find and aspirate. Small papillary cancers are common, and occult papillary carcinomas are usually considered not to need treatment and follow-up as manifest cancers. It may also be unnecessary to find them with ultrasound. It is probable that the patient with anaplastic carcinoma had developed this cancer during the last year, but it is reasonable to believe that most of the other cancers were present at the first diagnostic event, although smaller.

The value of using ultrasound-guided fine needle aspiration is particularly obvious in small lesions where it is important to ascertain that the needle is indeed in the lesion and for cystic lesions, after aspiration of the fluid, it is helpful.

For more than 40 years we have had a special unit for fine needle aspiration cytology. This unit has a special interest in the thyroid, and several studies have been reported on the accuracy of fine-needle aspiration [1]. In this early study about 3% false-negative cases were reported when all thyroids were operated on after fine-needle aspiration [1]. A low false-negative rate is reported from most specialist centers when fine-needle aspiration cytology is compared with surgical outcome. Many factors can influence the outcome in various regions, including experience, the size of the thyroid, the frequency of nodules, and thyroiditis. Particularly when in doubt about trying to aspirate a palpable lesion, our unit uses fine-needle aspiration with ultrasound.

Screening the thyroid with ultrasound in combination with fine-needle aspiration to detect malignancy is possible and yields many small cancers mainly of the papillary type. Most of these cancers have little biologic significance and do not affect survival. They do, however, call for numerous medical procedures, including operation, and cause great patient anxiety. The initial approach to thyroid cancer should be to find a palpable lesion; screening with ultrasound should not be encouraged. When in doubt about the fine-needle aspiration aspirate being exclusively from a lesion that may lie deep in the thyroid and be small, there is a definite need for ultrasound-guided fine-needle aspiration. The authors have clearly demonstrated the value of ultrasound-guided fine-needle aspiration and have provided a good scientific basis for its future use.

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