Management of Cystic of Predominantly Cystic Thyroid Nodules: The Role of Ultrasound-Guided Fine-Needle Aspiration Biopsy

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Abstract and Introduction

Abstract

Objective: Conventional fine-needle aspiration biopsy (FNAB) for cystic thyroid nodules (CTNs) has a high rate of nondiagnostic and false-negative results. Ultrasound-guided FNAB (UG-FNAB) permits direct sampling of the wall and/or the solid portion of CTNs, increasing the possibility of a representative sample. In this study we evaluated the role of UG-FNAB in CTNs management.
Methods: Five-hundred-seventy-five UG-FNAB of CTNs were performed. Thyroidectomy was carried out in 119 of these cases. The medical records of these 119 patients were reviewed and form the basis of this report.
Results: The nondiagnostic smear rate was 9.2%. Cytological diagnosis was benign nodule in 42 cases, predominantly follicular lesion in 50 cases, and suspicious or malignant lesion in 16 cases. The final pathology revealed a benign nodule in 98 cases (82.4%) and a carcinoma in 21 (17.6%). The overall accuracy of UG-FNAB was 88.0%. No significant differences were found in age, sex, lesion size, or echographic pattern (p = NS) comparing patients with benign CTNs to patients with malignant CTNs.
Conclusion: UG-FNAB has a low rate of nondiagnostic smears and a high overall accuracy in CTNs. All CTNs should undergo UG-FNAB to select patients for surgery, since the malignancy rate is not negligible and no clinical parameter can reliably predict it.

Introduction

Cystic Thyroid Nodules (CTN) represent 15 to 37 percent of all surgical excised thyroid nodules.[1–5] CTNs include true or simple thyroid cysts, with an epithelial lining, and mixed nodules with a predominantly fluid component.

The management of such nodules is still debated. Indeed, in the past, thyroid cysts were considered as benign lesions that could be managed conservatively.[6,7] More recently several reports have demonstrated that the incidence of thyroid carcinoma in cytologically benign CTNs is similar to, or even higher than, that of solid nodules.[1–5] Large cyst size (>3–3.5 cm), bloody cystic fluid, incomplete cyst resolution or recurrence after repeated aspirations, or previous neck irradiation have been all considered indications for surgery.[1,8–10] However, no criteria can reliably distinguish between benign and malignant CTNs.[11]

Even though fine-needle aspiration biopsy can give important information for their management,[1] cytological diagnosis in case of CTN may be difficult, because of insufficient or unrepresentative material. To improve the results of cytology, ultrasound guidance for FNAB has been proposed.[9,12,13] Ultrasound guided FNAB (UG-FNAB) permits direct sampling of the wall and/or the solid portion of CTNs. Thus it can reduce the possibility of a geographic miss and the number of false-negative results of cytology.[1,9,12,13]

The aim of this retrospective study was to evaluate the role of UG-FNAB in the management of CTNs.

Materials and Methods

Between January 1998 and June 2001, 2080 UG-FNAB of thyroid nodules were carried out at our department. Among these, 575 (27.6%) were performed for CTN in 534 patients, 117 male and 417 female, mean age of 47.1 ± 14.4 years (range, 10–85). Thyroid nodules were classified as CTN if the fluid portion represented more than 50% of the volume of the lesion,[13,14] which was calculated by using the formula for a rotational ellipsoid.[15] In 45 patients the procedure was repeated twice because of inadequate specimens or refilling of the cyst after aspiration; in three patients it was repeated three times. The rate of persistently nondiagnostic samples was 4.9% (26 cases out of 534).

One hundred-nineteen of these patients underwent thyroidectomy because of suspicious or malignant cytology (16 cases), persistently nondiagnostic cytology (11 patients), cytology consistent with predominantly follicular lesion (14 cases), incomplete cyst resolution and/or refilling after aspiration (20 cases), compressive symptoms and/or large nodule size (>3 cm) (58 cases) and were included in this study.

The medical records of these patients were reviewed. The following parameters were registered: age, gender, echographic pattern (simple cyst or predominantly cystic lesion) and size of the lesion, cytological diagnosis, and final histology.

UG-FNAB Technique

The procedure was carried out by one of the surgeons of the team (CPL, MR, CDC, ET), with optimal experience in thyroid ultrasonography and UG-FNAB. The patient was placed in a supine position, with the neck slightly hyperextended. A pillow was routinely placed under the shoulders to facilitate the procedure. A 10 MHz linear probe was used for ultrasound (US) examination. After adequate US examination, UG-FNAB was performed. A disposable syringe pistol (Sterylab S.P.A., Milano, Italy) with a 23- to 27-gauge needle is used to carry out the aspiration biopsy. The needle is introduced next to the medial edge of the transducer, allowing visualization of the tip while it was guided to the biopsy site. Aspiration is started once the needle is inside the lesion. The needle is then moved inside the lesion, under US vision to facilitate aspiration of material. In the case of CTN the needle is oriented toward the solid portion of the lesion or the cyst wall. Two separate aspirations are performed for each patient.

Once the needle is withdrawn from the lesion, the aspirated material is placed on a glass microscope slide and rubbed against a second slide to produce two smears. For each aspiration at least four glass microscope slides are made. The smears are fixed in 95% ethyl alcohol and stained with Papanicolau stain. Since March 2000 we have been processing aspirated material with both the traditional fixation and staining methods and by means of liquid preservation and thin layer cytology (Thin Prep 2000™, Cytyc, Marlborough, MA, USA).[16] The conventional smears are fixed in 95% ethanol and stained with Papanicolaou, as described above. The remnant material is then rinsed in the hemolytic and preservative solution Cytolit™ and centrifuged. The supernatant is processed according to the Thin Prep 2000 method and the resulting slide, fixed in 95% ethyl alcohol, is stained with Papanicolaou. The leftover material is stored for eventual additional examinations (immunocytochemistry, molecular biology), in Preservcyt™ solution.

In case of aspiration of a discrete amount of cyst fluid (>3 cc), the aspirate material is centrifuged (2500 rpm). The cell pellet is then resuspended in Shandon Cytospin collection fluid (Shandon Inc., Pittsburgh, PA, USA). The alcohol-fixed specimens are then centrifuged in the Shandon Cytospin 3 centrifuge at 1000 rpm. The slides obtained are stained with Papanicolau.

Cytologic Examination

The cytological examinations of the smears were performed by the same cytopathologist (GF). FNAB smear diagnoses were classified on the basis of a previously published cyto-morphological classification.[17,18] Specimens that do not contain a sufficient amount of thyreocytes (at least 6 groups of 10 or more well-preserved follicular epithelial cells) or have a large amount of blood or fibrin aggregates are considered inadequate for a diagnosis. In our center follicular (indeterminate) lesions are classified on the basis of morphologic criteria as follows: thyreocytic hyperplasia without nuclear atypia (THWNA), predominantly follicular lesions (PFL), and follicular lesions with nuclear pleomorphism (FLWNP).[17,18] Benign categories include colloid nodules, THWNA,[18] and thyroiditis. PFL are associated with a low rate of thyroid carcinoma (about 10%).[18] PFL and THWNA represent two groups of lesions that should be considered low-risk thyreocytic hyperplasias, separate from the "true," high-risk, suspicious proliferations (FLWNP).[17] However, in our current clinical practice, patients with PFL are usually referred to surgery because malignancy cannot be excluded, even if the risk is minimal. Patients are informed that in most cases these lesions are revealed to be benign (nodular hyperplasia, about 61% of cases; follicular adenoma, about 39% of cases), but since there is a 10% risk of malignancy, surgery is advisable, for a more precise diagnosis and consequent treatment. For statistical purposes (cyto-histological correlation) PFL is usually considered as benign, because it represents low-risk, usually benign, lesions.[17,18] Our choice could face some criticism, since patients are referred to surgery, as for suspicious lesions. For this reason in this paper we calculate sensitivity, specificity, and overall accuracy, by categorizing PFLs both as benign and suspicious lesions. In case of FLWNP the rate of malignancy is relatively high (about 60%).[16] Thus FLWNPs are considered as suspicious and patients referred to surgery. The malignant category includes aspirates with unequivocal diagnosis of malignancy (papillary, medullary, and anaplastic carcinoma).

Pathologic Examination

The surgical specimens were fixed in 10% buffered formaldehyde, adequately sampled, embedded in paraffin, and cut into sections 5 µm thick. The sections were then stained with hematoxylin-eosin.

Statistical Analysis

Sensitivity, specificity, and overall accuracy of UG-FNAB were calculated. For the cyto-histological correlation inadequate specimens were excluded. Microscopic carcinomas incidentally found at final pathologic examination separate from the lesion were excluded and the statistical analysis was performed considering the histology of the sampled lesion.

Patients with benign and malignant lesions were compared for demographic and clinical parameters (age, sex, lesion size, echographic pattern). Statistical analysis was performed using a commercially available statistic software package (Statistica 2.0 for Windows, Statsoft, Tulsa, OK, USA). The χ^2 test was used for sex and echographic pattern; the *t*-test for age and mean lesion size. A p value < 0.05 was considered as significant.

Results

There were 31 males and 88 females with a mean age (±SD) of 46.6 ± 12.8 years (range, 10–74). The echographic pattern of the lesions was predominantly cystic lesion in 110 cases (92.4%) and simple cystic lesion in 9 cases (7.6%). Mean nodule size (±SD) was 29.1 ± 10.7 mm (range, 10–60). Cytology showed a benign lesion (colloid nodule, thyroiditis, THWNP) in 42 cases (35.3%), PFL in 50 cases (42.0%), a suspicious lesion in 12 cases (10.1%), and a papillary carcinoma in 4 cases (3.4%). The rate of nondiagnostic smears was 9.2% (11 cases).

The final pathology revealed the CTN to be a benign nodule in 98 cases (82.4%) and a carcinoma in the remaining 21 (17.6%) (Table 1). In 17 patients (14.3%) an incidental microscopic papillary carcinoma, separate from the CTN, was identified.

UG-FNAB correctly identified malignancy in 11 cases: in 4 cases the cytological diagnosis was papillary carcinoma and FLWNP in 7 cases. In a further 10 cases, cytological diagnosis was PFL in 5, inadequate smears in 2, and benign (colloid, THWNA) lesion in 3 patients (table 1). In all 10 cases final histology showed a follicular variant of papillary thyroid carcinoma.[19] Since, in cases of PFL or persistent non-diagnostic cytology, surgery is recommended, cytological diagnosis was really false-negative in only 3 cases (2.5%). In these cases cytology showed benign (colloid) lesions. All three lesions were larger than 35 mm.

Sensitivity was 57.9%, specificity 94.4%, and overall accuracy 88.0%, when considering PFL benign. Sensitivity was 84.2%, specificity 43.8%, and overall accuracy 50.9%, if PFL are considered suspicious lesions.

No significant differences were found between patients with benign and malignant CTN concerning age, sex, lesion size, or echographic pattern (cystic or predominantly cystic lesion) (p = NS) (Table 2).

Discussion

Although CTN has been traditionally interpreted as a favorable finding because of the low risk of malignancy,[20,21] in recent years it has been reported that the incidence of carcinoma in case of CTN is similar to solid nodules, or even higher (up to 29%).[1,4,11] This is not surprising since most CTNs represent the result of a degenerative process arising in an underlying lesion[1,13,20] and true epithelial cysts are an uncommon occurrence.[21] Since the risk of malignancy it is not negligible, several attempts have been made to define which patients should undergo

surgery.[1,4,5,8] Malignancy rates seem to be higher in cases of large cyst size (>3–3.5 cm), bloody cystic fluid, incomplete cyst resolution, or recurrence after repeated aspirations and previous neck irradiation.[1,3,11] This is the reason why all these characteristics have been considered an indication for surgery. On the other hand it should be pointed out that no clinical criteria can reliably and definitively distinguish between benign and malignant lesions.[1,11,22]

Fine-needle aspiration biopsy (FNAB) represents the most reliable diagnostic tool in selecting patients for surgery in current clinical practice.[18,23] However, FNAB has important limitations in cases of CTN, because of the high rate of inadequate smears[1] and false-negative results.[11]

Nondiagnostic smears have been reported with a frequency up to 50%.[1,7] The high incidence of inadequate smears in CTN may reflect the lack of follicular cells in the cyst fluid and the difficulty in obtaining an adequate specimen from the solid portion or the wall of CTN. False-negative results have been reported in up to 50% of CTN,[2,5,11] especially in cases of large nodule size (>3 cm).[11] In cases of cytologically benign simple cysts that recurred after aspiration, malignancy rates have been reported to be as high as in solid and mixed (solid/cystic) nodules.[8] Sampling errors, rather than interpretative mistakes, are the reason for this high rate of false-negative results. Since a false-negative result implies a missed malignant lesion, this possibility is of particular concern when dealing with CTNs.

Thus, UG has been proposed to improve the results of FNAB,[9,12,13] since it allows direct sampling of the solid portion of the lesion, or even a thin cyst wall, with the tip of the needle under vision during each step of the procedure. UG-FNAB has been demonstrated to be effective in reducing the number of inadequate specimens and to improve the diagnostic accuracy of conventional FNAB in thyroid nodules.[24–26] However, its specific role in the management of CTNs has not yet been completely clarified.

Braga et al.[13] recently reported on 124 UG-FNAB performed for CTN in 113 patients. In their hands, UG-FNAB proved to be effective in reducing the rate of inadequate smears in cases of CTN, with unsatisfactory specimens in 7 of 124 (5.6%) of the cases.[13] Moreover, UG-FNAB was demonstrated to be very useful for the re-evaluation of nodules with a previously nondiagnostic conventional FNAB.[13] However, in that series only a small subset of patients (14 of 113) was referred for surgery and had a verification of cytological findings on surgical pathology.

The results of our study confirm that UG may improve the results of FNAB. The rate of inadequate smears in this series was 9.2% (11 cases of 119). This rate is lower than that reported in a recent series for CTN[1] and similar to that reported for solid nodules.[17,18] This is of particular relevance since adequacy criteria (more than 6 groups of 10 well-preserved follicular cells) are strictly followed in the cytological diagnosis. Moreover, it should be pointed out that this is a surgical series and, since persistently nondiagnostic smears are an indication for surgery, the rate of inadequate specimens may be overestimated. Indeed, the overall rate of nondiagnostic smears in the entire group of patients who underwent UG-FNAB for CTN was about 4.9% (26 of 534 patients).

Specificity was 94.4%, sensitivity 57.9% and overall accuracy 88.0%, when categorizing PFLs as benign lesions. Although these results could appear not completely satisfying, it should be considered that overall accuracy is comparable to that reported for solid nodules in recent papers[11,12,27,28] and higher than that reported for CTNs in previous reports.[8,11,13] Regarding false-negative results, since in our current practice persistently nondiagnostic smears and PFLs are considered an indication for surgery, we could speculate that a "true" false-negative result was obtained in only 3 patients (2.5%), in whom preoperative cytology showed benign (colloid) lesions, in spite of malignancy found at final histology. All 3 patients underwent thyroidectomy because of large nodule size (>35 mm). False-negative result in these patients may also be due to the large nodule size, and the consequent impossibility to sample the entire lesion, even under UG. Large nodules are confirmed to be the most important source of false-negative results.

In the other 7 cases in which malignancy was not preoperatively diagnosed, cytology showed PFL in 5 cases, or was persistently nondiagnostic in 2 cases. Thus in these patients the cytological results should not be considered completely false-negative. Indeed persistently non-diagnostic FNAB is considered an indication for surgery. Similarly, in our current practice, patients with PFL are usually referred to surgery because malignancy cannot be excluded, despite its relatively low incidence (about 10%).[18]

In all 10 cases in which cytology failed to reveal a malignancy, final histology showed a follicular variant of papillary thyroid carcinoma. It is well known that FNAB has a low sensitivity (less than 30%) in the diagnosis of this variant of papillary carcinoma.[19]

In addition, in 17 patients (14.3%) an incidental microscopic papillary carcinoma, separate from the CTN, was identified. Since microscopic foci of papillary carcinoma represent an incidental finding, we did not consider these cases as false-negative results.

In this series, no significant differences were found between patients with benign and those with malignant lesions, regarding age, gender, mean lesion size, or echographic pattern. No demographic or lesion characteristics can reliably distinguish between benign and malignant CTNs. This result is in agreement with previous reports that failed to find completely reliable clinical parameters predictive of thyroid malignancy.[1,9,11,22] Thus UG-FNAB is demonstrated to be the most important diagnostic tool in managing and selecting for surgery patients with CTNs. Perhaps in the future the evaluation of markers of malignancy, in particular HBME-1, galectin-3, and Ret proto-oncogene, even in a small thyrocyte population, may further improve the diagnostic accuracy of FNAB in CTNs.[29,30]

In conclusion, all CTNs should undergo FNAB, because the rate of malignancy is not negligible and no clinical parameter can reliably predict it. UG-FNAB may reduce the number of inadequate and false-negative smears. Thus, recommendations for thyroidectomy should be based on UG-FNAB results, especially in small and asymptomatic CTNs that could otherwise be observed and managed conservatively.

This paper is based on a work presented in part as a communication at the Meeting of the British Association of Endocrine Surgeons, Pisa, Italy, May 10–11, 2002.

Tables

Table 1. Cyto-Histological Correlation in 119 Patients with CTN who Underwent UG-FNAB

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Final histology/cytology	*Benign*	*THWNA*	*PFL*	*Suspicious (FLWNP)*	*Carcinoma*	*Nondiagnostic*

Benign	28	11	45	5	0	9
Colloid goiter	28	6	21	1	—	6
Thyroiditis	—	—	2	—	—	—
Follicular adenoma	—	5	22	4	—	3
Malignant	2	1	5	7	4	2
PTC	—	—	—	3	4	—
FV-PTC	2	1	5	4	—	2

THWNA, thyreocytic hyperplasia without nuclear atypia; PFL, predominantly follicular lesion; FLWNP, follicular lesion with nuclear pleomorphism; PTC, papillary thyroid carcinoma; FV-PTC, follicular variant of papillary thyroid carcinoma.

Table 2. Characteristics and Comparison of Patients with Benign and Malignant CTN

Parameter	*Benign CTN*	*Malignant CTN*	*P value*
Age (± SD)	46.9 ± 12.6	45.6 ± 14.2	NS (0.68)
Sex (males/females)	25/73	6/15	NS (0.99)
Echographic pattern (mixed/purely cystic)	90/8	20/1	NS (0.94)
Nodule size (± SD) (mm)	29.6 ± 10.5	26.7 ± 11.8	NS (0.26)

SD, standard deviation; NS, not significant.

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