CLINICAL STUDY

Thyroglobulin detection in fine-needle aspirates of cervical lymph nodes: a technique for the diagnosis of metastatic differentiated thyroid cancer

Nuno Cunha, Fernando Rodrigues¹, Fátima Curado, Olga Ilhéu², Carlos Cruz³, Plamen Naidenov¹, Maria João Rascão⁴, João Ganho³, Idílio Gomes⁴, Henriques Pereira³, Odete Real², Paulo Figueiredo⁵, Beatriz Campos¹ and Frederico Valido

Serviço de Patologia Clínica, Instituto Português de Oncologia de Coimbra Francisco Gentil, EPE, Av. Bissaya Barreto, 98, 3000 Coimbra, Portugal,

¹Serviço de Endocrinologia, ²Serviço de Citopatologia, ³Serviço de Cirurgia de Cabeça e Pescoço, ⁴Serviço de Imagiologia and ⁵Serviço de Anatomia Patológica, Instituto Português de Oncologia de Coimbra Francisco Gentil, EPE, Coimbra, Portugal

(Correspondence should be addressed to N Cunha; Email: nfcunha@gmail.com)

Abstract

Background: Fine-needle aspiration cytology is frequently used for differential diagnosis of neck masses of unknown origin. Inconclusive and even false-negative results are not uncommon.

Aim: To evaluate the utility of thyroglobulin (Tg) measurement in fine-needle aspirates (FNA-Tg) for detecting cervical lymph node (CLNs) metastases from differentiated thyroid carcinomas.

Methods: An ultrasound-guided fine-needle aspiration was done in 67 patients with 83 suspicious enlarged CLNs to obtain material for cytology and Tg measurement in the needle washout, using an immunometric chemiluminescent assay. Measurement of anti-Tg antibodies (FNA-TgAb) was also carried out in half of all the aspirates. Subjects were divided into two groups: one of 16 patients awaiting thyroidectomy and the other of 51 patients in follow-up after surgery.

Results: The first group of patients had positive FNA biopsy (FNAB-Tg) in 14 out of the 18 studied CLNs with a range of 3.2–43 352 ng/ml, while FNAB-cytology indicated metastasis in only 8 out of the 14 CLNs with positive histology. A total of 65 CLNs were studied in the follow-up group. Lymphadenectomy was performed in 23 patients and 28 aspirated CLNs were removed. Histology confirmed the diagnosis of metastasis suggested by FNAB-Tg in 20 CLNs and of reactive lymphadenitis in the remaining 8 CLNs. FNAB-cytology was positive in only 11 CLNs. Sensitivity of FNAB-Tg was not affected by the studied FNAB-TgAb.

Conclusions: The FNAB-Tg achieved a sensitivity of 100% in both groups. FNAB-Tg is an easy and inexpensive technique which proved to increase the diagnostic of cytology in the early diagnosis of papillary carcinoma recurrence to CLN even in the presence of serum TgAb.

European Journal of Endocrinology 157 101–107

Introduction

Thyroid carcinoma is the most common endocrine malignancy. Papillary carcinoma (PTC) comprises the majority (75–85%) of all thyroid cancers. The prognosis of patients with appropriate treatment for PTC is usually favourable. Although long-term survival is common, patients are at risk of tumour recurrence. About 5–20% of patients develop local or regional recurrences and 10–15% have distant metastases, after initial surgery (1–3).

Occult thyroid carcinoma with cervical metastasis at the time of presentation has been reported to occur in nearly one-fifth of all thyroid carcinoma cases (4). Even when a primary thyroid cancer is diagnosed, the demonstration of cervical lymph node (CLN) metastasis before surgery is clinically relevant, since it usually requires neck dissection in addition to total thyroidectomy.

Recurrent disease generally occurs primarily in the neck. Ultrasonography (US) is highly sensitive in the detection of cervical metastases, however, it has a low specificity (37%) because benign lymphadenopathies are extremely frequent (5, 6). The addition of fine-needle aspiration biopsy (FNAB)-cytology to the US improves the specificity, but 5–10% are non-diagnostic (7) and 6–8% rate of false-negative results (8).

A cystic mass caused by well-differentiated thyroid carcinoma (DTC) metastatic to a CLN has been shown not uncommonly to be the only presenting symptom in patients with an occult PTC (4, 6, 9, 10).

In addition, cystic changes in metastatic lymph nodes can cause diagnostic problems to the cytologist, which may cause a delay in the identification of the primary thyroid cancer or treatment of recurrent disease.

In order to improve the early detection of CLN metastases from PTC, we evaluated our experience and usefulness of detecting thyroglobulin (Tg) in fine-needle aspirate fluid (FNAB-Tg).

Patients and methods

Patients

During a 2-year period (2004–2006), we studied a total of 67 patients with enlarged neck lymph nodes (47 females and 20 males; mean ages $\pm$ s.d., 52.88 ± 14.64 years).

A total number of 83 lymph nodes aspirates were analysed. In all these, 12 patients were aspirated more than once, including both aspirations from different sites and subsequent aspirations of the same node. In the design of this study, each aspirate was considered separately.

Patients were then subdivided into two groups. One group of 16 patients (7 females and 9 males; mean ages $\pm$ s.d., 49.88 ± 18.33 years) presented with recently diagnosed lymphadenopathy or suspicious thyroid nodules with neck lymph node enlargement. These patients were referred to our Institution by their physicians in order to exclude metastatic thyroid cancer. A total number of 18 lymph nodes were examined.

A second group of 51 patients (53.86 ± 13.30 years) had previous diagnosis of DTC (48 papillary and 3 follicular) and had been treated with either total or near total thyroidectomy, followed by ^{131}I ablation therapy. All patients presented US evidence of neck lymph node enlargement and a total number of 65 lymph nodes were examined by US-FNAB.

All patients underwent physical examination and neck US.

Methods

Non-palpable lymph nodes were considered suspicious for PTC recurrence by one or more US findings, described in several reports (11–15). All biopsies were performed freehand under continuous real-time US guidance with high resolution 7.5–10.0 MHz linear-array transducers (Power Vision Toshiba, Tokyo, Japan). The presence, location and features of lymph node abnormalities were reported and the US-guided FNAB was performed on suspicious non-palpable lymph nodes using a 22 or 25 gauge needle attached to a 10 ml syringe.

Several drops of the aspirated material were placed and smeared onto glass slides for cytological examination. Samples were then air-dried and stained with May-Grünwald stain. The aspirates were reported by an experienced cytologist. The results were subdivided into three diagnostic categories: i) inadequate or non-diagnostic: presence of blood cells without lymphocytes,

plasma cells, histiocytes and epithelial cells; ii) reactive lymphadenitis (negative cytology); presence of lymphocytes and occasional plasma cells without malignant epithelial cells; and iii) positive cytology for DTC metastases: presence of epithelial cells with malignant cytological characteristics.

The same syringe was then flushed with 1 ml normal saline solution. The needle washout was centrifuged (1500 g, 2 min) (8, 9, 16) and Tg levels were immediately measured by using a immunometric chemiluminescent assay (IMMULITE 2000, Euro/DPC Ltd, Gwynedd, UK), calibrated to the CRM 457 standard with a functional sensitivity of 0.9 ng/ml and an intra-assay coefficient of variation (CV) of 4.8 and 6.8% at a mean dose level of 10 and 279 ng/ml respectively (the minimum detectable Tg was 0.5 ng/ml until August 2005 and subsequently 0.2 ng/ml). Measurement of anti-Tg antibodies (FNA-TgAb) was carried out in half of all patients' aspirates using a solid-phase, enzyme-labelled, chemiluminescent sequential immunometric assay (IMMULITE 2000, Euro/DPC Ltd), calibrated to the World Health Organization 1st International Reference Preparation 65/93 standard.

Data analysis

The sensitivity and specificity for the correct identification of lymphatic metastasis from thyroid cancer were calculated by the Galen & Gambino formula (17).

Results

Different concentrations of Tg may be detected in the FNAB washout fluid of reactive lymph nodes according to the presence or absence of the thyroid gland. Consequently, Frasoldati *et al.* and Boi *et al.* (8, 18) established a value for FNAB-Tg above which the test result was considered suspicious for DTC metastases. In the manner described by Pacini *et al.* (16), the positive Tg washout concentration cut-off value was established as equal to the mean + 2 s.d. of the FNAB-Tg in patients with negative cytology, excluding the patients with false-negative or inadequate cytological results.

In our work, the FNAB-Tg was mostly undetectable in the study group (range, 0.2–0.7 ng/ml), leaving no doubt in distinguishing positive and negative cases. We considered as positive FNAB-Tg any Tg concentration above the functional sensitivity of the assay (0.9 ng/ml; Fig. 1).

Patients awaiting thyroidectomy

Sixteen patients ($n=18$ lymph nodes) with US suspicious thyroid nodules (TNs) and concomitant nodal enlargement, cervical cystic masses or solely lymph node enlargement (US longitudinal diameter > 10 mm) were evaluated by FNAB-cytology and FNAB-Tg for

Figure 1 Individual thyroglobulin concentrations in the fine-needle aspirate fluid from enlarged cervical lymph nodes from all the patients in the two considered groups (patients awaiting surgery and thyroidectomised patients under follow-up) according to the results from FNAB-cytology. Solid lines (—), mean; (◆), Lymph node aspirates; Double lines (==), FNAB-Tg cut-off.

potential metastatic cervical lymphadenopathy from DTC.

FNAB-cytology indicated metastasis of PTC in eight lymph nodes ($n=7$ patients, 44.6%), benign reactive lymphadenitis in five lymph nodes ($n=4$ patients, 27.7%) and was considered inadequate or unsatisfactory for diagnosis in the remaining five lymph node aspirates ($n=5$ patients, 27.7%). Cytology also reported one lymph node with cystic transformation due to metastatic PTC.

The FNAB-Tg values were above the considered cut-off in 14 out of the 18 studied lymph nodes with a range of 3.2–43 352 ng/ml and a mean $\pm$ s.d. of $9642 \pm 13\,362$ ng/ml. The remaining four lymph nodes had

FNAB-Tg values within a negative range of <0.2–0.5 ng/ml.

Total thyroidectomy with lymph node dissection was performed in 14 patients and 16 previously biopsied lymph nodes were identified and excised for histological examination. The results are summarized in Table 1.

Two patients ($n=2$ lymph nodes) with palpable cervical masses, demonstrated to be of cystic nature by computed tomography (CT) and/or US, had inadequate/non-diagnostic FNAB-cytology and positive FNAB-Tg (range, 2000–3831 ng/ml). No thyroid nodules were palpable and no abnormalities were demonstrated by CT or US studies of the thyroid gland. The patients underwent thyroidectomy with modified

Table 1 Summary of results obtained for the two groups of patients.

Lymph nodes	FNAB-cytology	FNAB-Tg; range (ng/ml)	Histology
16 patients awaiting thyroidectomy (18 lymph nodes)			
7	Metastatic PTC	72–18 727	Metastatic PTC
1	Cystic metastatic PTC	15 542	Cystic metastatic PTC
2	Reactive	<0.2	Reactive
1	Reactive	32 000	Cystic metastatic PTC
2	Reactive	<0.2	—
4	Inadequate	2000–43 352	Cystic metastatic PTC
1	Inadequate	3.2	Metastatic PTC
51 thyroidectomised patients under follow-up (65 lymph nodes)			
4	Reactive lymphadenitis	<0.2–0.5	Reactive
2	Reactive lymphadenitis	4–1459	Metastatic PTC
30	Reactive lymphadenitis	<0.2–0.7	—
11	Metastatic PTC	2.3–55 000	Metastatic PTC
4	Inadequate	<0.2–0.5	Reactive
7	Inadequate	224–43 168	Metastatic PTC
7	Inadequate	<0.2	—

radical neck dissection followed by radioactive iodine therapy, and the histological study demonstrated an occult unifocal microcarcinoma (range 3–8 mm in diameter). These patients, whose aspirates were serous fluid, had simultaneous measurement of Tg in aspirated fluid without dilution and in the needle washout. The Tg measured values were consistently higher in the total aspirated fluid (range, 52 000–98 452 ng/ml).

Eleven patients with reported thyroid nodule cytology of PTC and positive nodal FNAB-cytology and/or positive FNAB-Tg underwent lymph node dissection (*n* = 12 lymph nodes) during thyroid surgery.

One patient (*n* = 2 lymph nodes) with an US report of normal thyroid and nodules with cystic changes, in whom both nodal FNAB-cytology and FNAB-Tg were negative for thyroid cancer, underwent surgical removal of the enlarged CLN for histological evaluation.

The remaining two subjects (*n* = 2 lymph nodes), both with nodal FNAB-cytology and FNAB-Tg indicative of a benign condition were assigned for monitoring with US and showed regression of lymph node swelling within 1 year.

We divided the histological report in two categories: i) metastases of PTC (*n* = 8 lymph nodes) and ii) cystic metastases of PTC (*n* = 6 lymph nodes), a total 14 lymph nodes had a histological diagnosis of metastatic PTC.

For the purpose of calculating the sensitivity of the proposed histological categories, we considered as false-negative any inadequate/non-diagnostic FNAB-cytology or negative FNAB-Tg in histologically proven metastatic lymph nodes (8, 18, 19). As shown in Table 2, the FNAB-Tg sensitivity in metastatic lymph nodes and in cystic metastatic lymph nodes was 100% in both. In sum, all the 14 metastatic lymph nodes were positive by FNAB-Tg, an overall sensitivity of 100% and a positive predictive value of 100%.

If we considered FNAB-cytology, only one of the six metastatic lymph nodes with cystic component was positive (sensitivity of 16.7%), four out of six cases were judged inadequate/non-diagnostic and one case was judged reactive.

Altogether, FNAB-cytology was positive in 8 out of the 14 diagnosed metastatic lymph nodes (sensitivity of 57%).

Unfortunately, in this study, it was not possible to evaluate the specificity or negative predictive value because of the small number of patients (*n* = 3) with negative lymph nodes by FNAB-Tg and FNAB-cytology (*n* = 4 lymph nodes) and only one patient (*n* = 2 lymph nodes) undergoing node dissection. The excised lymph nodes had a histological diagnosis of granulomatous chronic lymphadenitis with positive toxoplasmosis serology.

Thyroidectomised patients under follow-up

A total of 65 lymph nodes were examined by US-FNAB.

In the patients (*n* = 51) undergoing total or near total thyroidectomy follow-up, 11 out of 65 aspirated lymph nodes (16.9%) had a positive FNAB, 18 were considered inadequate or non-diagnostic specimens (27.7%) and 36 displayed a pattern of reactive lymphadenitis (55.4%). FNAB-Tg concentrations were above the considered cut-off in 17 patients (20 out of 65 aspirated lymph nodes) with a range of 2.3–55 000 ng/ml and a mean $\pm$ s.d. of 11 969 $\pm$ 17 570 ng/ml. The remaining 45 lymph nodes had FNAB-Tg values within a negative range of 0.2–0.7 ng/ml. Only one patient showed a positive concentration of anti-Tg antibodies (TgAb; 32 IU/ml) in FNAB washout fluid (FNAB-TgAb), all the other 28 were undetectable (<20 IU/ml) even when serum TgAb was detectable.

Lymphadenectomy was performed in 23 patients with enlarged lymph nodes and one or more US suspicious findings, positive cytology and/or FNAB-Tg concentrations above the considered cut-off. A total of 28 aspirated lymph nodes were removed and examined by histopathology.

Histological examination found metastases of PTC in 17 patients (*n* = 20 lymph nodes). Four patients (*n* = 4 lymph nodes), with both reactive cytology and undetectable FNAB-Tg, were submitted to lymphadenectomy on the basis of suspicious clinical features. Two patients (*n* = 2 lymph nodes) had false negative FNAB-cytologic diagnosis of reactive lymphadenitis, which were found to be metastases of PTC at histologic examination, confirming the positive values of FNAB-Tg (range, 4–1459 ng/ml).

Twenty-eight patients (*n* = 37 lymph nodes) with undetectable FNAB-Tg were not treated surgically. Of these, 24 patients (*n* = 30 lymph nodes) with undetectable FNAB-Tg and reactive cytology and four patients (*n* = 7 lymph nodes) with undetectable FNAB-Tg and non-diagnostic cytology, were followed by periodical US, cytology and/or FNAB-Tg from the same lymph nodes for further evaluation over 13.15 $\pm$ 8 months (mean $\pm$ s.d.). During that time, they did not evidence lymph node metastasis and showed regression of the enlarged lymph nodes evidenced by previous US examination.

Table 2 Comparison of the histological report from the group of patients awaiting thyroidectomy and the previous fine-needle aspiration biopsy (FNAB)-cytology and FNAB-thyroglobulin (Tg) results.

Histologic categories	No. of lymph nodes	Positive cytology	Positive FNAB-Tg; mean $\pm$ s.d.
Metastatic PTC	8	7/8 (87.5%)	8/8 (100%) 3739 $\pm$ 6293
Cystic metastatic PTC	6	1/6 (16.7%)	6/6 (100%) 17 512 $\pm$ 16 693
Total meta-static PTC	14	8/14 (57%)	14/14 (100%) 9642 $\pm$ 13 362

With the results presented in Table 1, it was possible to compare FNAB-cytology and FNAB-Tg with the histological report (gold standard) and also to determine the sensitivity and specificity of the tests. On this basis, we considered true positive any suspicious FNAB-cytology or positive FNAB-Tg and false-negative any inadequate/non-diagnostic FNAB-cytology (8, 18, 19) or negative FNAB-Tg in histologically proven metastatic lymph nodes.

Histological examination of 20 lymph nodes confirmed the diagnosis of metastatic lymphadenopathies initially suggested by positive FNAB-Tg (100% sensitivity). Histological findings of reactive lymphadenitis in eight lymph nodes confirmed the undetectable FNAB-Tg values (<0.2 ng/ml). These results were used to calculate the FNAB-Tg specificity (100%). No changes were observed in FNAB-Tg sensitivity in four patients with positive serum TgAb (range: 100–432 IU/ml), even though two of them had been tested for FNAB-TgAb (range: <20 –32 IU/ml).

Seven lymph nodes were inadequate/non-diagnostic and two had reactive cytology in spite of a histological report of PTC metastasis.

The sensitivity and specificity of FNAB-cytology was 55 and 100% respectively. The positive predictive value of cytology for the diagnosis of PTC was 11 out of 11 (100%), while the negative predictive value was 8 out of 17 (47.1%).

A total of 28 lymph nodes were histologically examined. Combining the FNAB-cytology and FNAB-Tg, we attained a specificity and sensitivity of 100% with a diagnostic accuracy of 100%.

One of the recurrent patients had simultaneously detectable serum-TgAb (100 IU/ml) and high serum-Tg (12 ng/ml) but the FNAB-TgAb was undetectable (<20 IU/ml) and the FNAB-Tg was 173 ng/ml, indicating lower or no assay interference.

Discussion

In up to 20% of patients with thyroid carcinoma, the first and sole initial finding is an abnormal CLN (6, 20, 21). Solitary cervical cystic lymph node is not an unusual presenting symptom of an occult PTC (9).

Cystic metastasis comprise most of the inadequate/non-diagnostic FNAB-cytology cases and could be misinterpreted as a benign cervical cystic mass or branchial cleft cysts and could therefore delay the correct diagnosis and a further radical neck lymphadenectomy. Consequently, a positive FNAB-Tg in cystic CLNs may be a trigger for further clinical investigation of an occult PTC (9, 21, 22). It should be considered that cystic metastasis could also be encountered in tumours such head and neck and squamous cell carcinomas (9, 23).

All lymph nodes with cystic components were positive by FNAB-Tg. Our results indicate that FNAB-Tg is

specific for the detection of loco-regional metastases of DTC, even in cystic metastases of PTC.

Urunu *et al.* (1) reported a FNAB-Tg and FNAB-cytology sensitivity of 81.4 and 78.0% respectively in patients awaiting surgery. They reported a sensitivity of 100% in detecting cystic metastases of PTC. Our results are in accordance with those of previous studies (1, 9). FNAB-Tg achieved a sensitivity and a specificity of 100% in solid and cystic lymph nodes respectively.

Approximately two-thirds of DTC recurrences occur in the cervical region, most of them in the loco-regional lymph nodes. Thus, US-guided FNAB-cytology has been proposed by several authors to be the best available technique for diagnosing metastatic lymph nodes from thyroid cancer (6, 12, 20, 22).

Suspicious criteria from US investigations are difficult to evaluate in the case of small lymph nodes. Thus, false-positive sonography findings are unavoidable and many FNAB-cytology will only show lymphoid cells. In addition, cytology may be inadequate or even false negative in lymph node with small metastases or partial involvement (16, 24). We reported in this group 27.7% of inadequate FNAB-cytology due to poor cellular material and aspirates containing only blood with absence of colloid. We also found that 6 out of 51 patients with inadequate FNAB-cytology had metastatic PTC in the final histopathological interpretation. This highlights the importance of FNAB-Tg in these unsatisfactory cytological reports; these patients were followed-up by US and had new aspirates performed with the same unsatisfactory results.

The measurement of Tg in the washout of the FNAB had been initially proposed in 1992 by Pacini *et al.* (16) for early detection of neck lymph node metastases in patients with DTC. He reported that Tg assayed in the aspirate increases the reliability and specificity of fine-needle biopsy. He reported that FNAB-Tg had 100% sensitivity, whereas cytology produced 85% sensitivity. In agreement with others, in the study reported here, no FNAB-Tg false-positive results were observed in post-operative patients (8, 9, 11).

In two studies, Frasoldati *et al.* reported that for 69 lymph nodes examined, FNAB-Tg sensitivity and specificity were 84 and 95.4% respectively (8) and, in another paper, some years later (11) they performed FNAB-cytology and FNAB-Tg in 46 out of 51 patients and obtained cytological results indicating malignancy in 39 out of 46 patients (84.8%), whereas the combination of FNAB-cytology and FNAB-Tg was positive in 44 out of 46 patients (95.6%). Our study also found FNAB-Tg to be more sensitive than FNAB-cytology, because only 8 out of 17 recurrent patients would have been detected if we consider only the cytological report. When combining the FNAB-cytology and FNAB-Tg, we attained a specificity and sensitivity of 100% with a diagnostic accuracy of 100% in the assessment of metastatic lymph nodes in thyroidectomized patients. A recent study also refers that US-guided

FNAB is not sensitive enough to detect all metastatic lymph nodes in contrast with FNAB-Tg that achieved 100% sensitivity (25).

The interference of serum-TgAb is the most serious technical problem that currently compromises the use of serum-Tg as a marker for DTC. With that in mind, several studies did not include patients with positive serum-TgAb (1, 8, 11). It has been reported that the presence of serum-TgAb even in low concentrations may interfere in the measurement of serum-Tg assayed by IRMA and therefore invalidating serum-Tg use for routinely monitoring DTC recurrences (5, 26).

Boi *et al.* and even Baskin (5, 18) suggested that FNAB-Tg is not affected by the presence of TgAb either due to blood contamination or active lymph-node synthesis. This situation proved to be correct in four recurrent patients with positive serum-TgAb (range, 100–432 IU/ml) and in two patients awaiting thyroidectomy (range, 244–253 IU/ml). The Tg assayed in the needle washout fluid (range 11.1–41 190 ng/ml) did not appear to be affected by the presence of serum-TgAb, however, it is quite possible that the patient with FNAB-Tg of 11.1 ng/ml may have suffered some degree of underestimation, with no diagnostic consequence. Three of these studied patients also had parallel measurement of FNAB-TgAb, with only one patient showing a detectable value of 32 IU/ml, conferring no interference in the FNAB-Tg measurement (41 190 ng/ml).

Quite recently, Boi *et al.* (18) proposed that a probable explanation for these cases was that an exceedingly elevated FNAB-Tg concentration was able to saturate all the FNAB-TgAb binding sites.

Among several groups that reported on FNAB-Tg (7–9, 16, 18), none presented false-positive results in patients under follow-up surveillance. Our results are in agreement with their work.

We had no anaplastic thyroid tumours or undifferentiated PTC, which are reported by Boi *et al.* (18) to be the only source of FNAB-Tg bias. Their group considered that poorly differentiated PTC metastases were the cause of false-negative FNAB-Tg which was due to their incapacity of synthesising/secretion quantifiable amounts of Tg; however, in contrast to these results, Cignarella *et al.* (9) found low FNAB-Tg levels, but still high enough to be differentiated from non-thyroidal CLN diseases.

Conclusions

The FNAB-Tg achieved a sensitivity of 100% in detecting metastatic lymphadenopathies in both designated groups. Unfortunately, 100% specific US-guided FNAB-cytology is not sensitive enough to diagnose PTC recurrence in CLNs.

FNAB-Tg is an easy and inexpensive technique which proved to increase the diagnostic accuracy of cytology in the early diagnosis of PTC recurrence to CLNs in

thyroidectomised patients under follow-up, even in the presence of serum Tg antibodies.

This technique proved to be very reliable in the differential diagnosis of lymph node metastasis from an occult PTC in patients with solitary lateral cervical cyst.

We conclude that US-guided FNAB-Tg should always be performed as an adjunct to FNAB-cytology in patients with suspicious CLNs.

References

- 1 Urano T, Miyauchi A, Shimizu K, Tomoda C, Takamura Y, Ito Y, Miya A, Kobayashi K, Matsuzuka F, Amino N & Kuma K. Usefulness of thyroglobulin measurement in fine-needle aspiration biopsy specimens for diagnosing cervical lymph node metastasis in patients with papillary thyroid cancer. *World Journal of Surgery* 2005 **29** 483–485.
- 2 Schlumberger MJ. Papillary and follicular thyroid carcinoma. *New England Journal of Medicine* 1998 **338** 297–306.
- 3 Mazzaferri EL. An overview of the management of papillary and follicular thyroid carcinoma. *Thyroid* 1999 **9** 421–427.
- 4 Monchik JM, De Petris G & De Crea C. Occult papillary carcinoma of the thyroid presenting as a cervical cyst. *Surgery* 2001 **129** 429–432.
- 5 Baskin H. Detection of recurrent papillary thyroid carcinoma by thyroglobulin assessment in the needle washout after fine-needle aspiration of suspicious lymph nodes. *Thyroid* 2004 **14** 959–963.
- 6 Kessler A, Rappaport Y, Blank A, Marmor S, Weiss J & Graif M. Cystic appearance of cervical lymph nodes is characteristic of metastatic papillary thyroid carcinoma. *Journal of Clinical Ultrasound* 2003 **31** 21–25.
- 7 Frasoldati A & Valcavi R. Challenges in neck ultrasonography: lymphadenopathy and parathyroid glands. *Endocrine Practice* 2004 **10** 261–268.
- 8 Frasoldati A, Toschi E, Zini M, Flora M, Caroggio A, Dotti C & Valcavi R. Role of thyroglobulin measurement in fine-needle aspiration biopsies of cervical lymph nodes in patients with differentiated thyroid cancer. *Thyroid* 1999 **9** 105–111.
- 9 Cignarella M, Ambrosi A, Marino A, Lamacchia O, Campo M & Picca G. Diagnostic utility of thyroglobulin detection in fine-needle aspiration of cervical cystic metastatic lymph nodes from papillary thyroid cancer with negative cytology. *Thyroid* 2003 **13** 1163–1167.
- 10 Seven H, Gurkan A, Cinar U, Vural C & Turgut S. Incidence of occult thyroid carcinoma metastases in lateral cervical cysts. *American Journal of Otolaryngology* 2004 **25** 11–17.
- 11 Frasoldati A, Pesenti M, Gallo M, Caroggio A, Salvo D & Valcavi R. Diagnosis of neck recurrences in patients with differential thyroid carcinoma. *Cancer* 2003 **97** 90–96.
- 12 Torlontano M, Attard M, Crocetti U, Tumino S, Bruno R, Costante G, D'Azzo G, Meringolo D, Sacco R, Arturi F & Filetti S. Follow-up of low risk patients with papillary thyroid cancer: role of neck ultrasonography in detecting lymph node metastases. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 3402–3407.
- 13 Boland GW, Lee MJ, Mueller PR, Mayo-Smith W, Dawson SL & Simeone JF. Efficacy of sonographically guided biopsy of thyroid and cervical lymph nodes. *American Journal of Roentgenology* 1993 **161** 1053–1056.
- 14 Robbins KT, Medina JE, Wolf GT, Levine PA, Sessions RB & Pruet CW. Standardizing neck dissection terminology. *Archives of Otolaryngology – Head and Neck Surgery* 1991 **117** 601–605.
- 15 Frasoldati A & Valcavi R. Challenges in neck ultrasonography: lymphadenopathy and parathyroid glands. *Endocrine Practice* 2004 **10** 261–268.
- 16 Pacini F, Fugazzola I, Lippi F, Ceccarelli C, Centoni R., Miccoli P, Elisei R & Pinchera A. Detection of thyroglobulin in the needle

- aspirates of nonthyroidal neck masses: a clue to the diagnosis of metastatic differentiated thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* 1992 **74** 1401–1404.
- 17 Galen RS & Gambino SR. *Beyond Normality: The Predictive Value and Efficiency of Medical Diagnoses* New York: Wiley, 1995.
 - 18 Boi F, Baghino G, Atzeni F, Lai ML, Faa G & Mariotti S. The diagnostic value for differentiated thyroid carcinoma metastases of thyroglobulin (Tg) measurement in washout fluid from fine-needle aspiration biopsy of neck lymph nodes is maintained in the presence of circulating anti-Tg antibodies. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 1364–1369.
 - 19 Knappe M, Louw M & Gregor RT. Ultrasonography-guided fine-needle aspiration for the assessment of cervical metastases. *Archives of Otolaryngology – Head and Neck Surgery* 2000 **126** 1091–1096.
 - 20 Wunderbaldinger P, Harisinghani M, Hahn P, Daniels G, Turetschek K, Simeone J, O'Neill MJ & Mueller PR. Cystic lymph node metastases in papillary thyroid carcinoma. *American Journal of Roentgenology* 2002 **178** 693–697.
 - 21 Verge J, Guixá J, Alejo M, Basas C, Quer X & De Castro J. Cervical cystic lymph node metastasis as first manifestation of occult papillary thyroid carcinoma: report of seven cases. *Head and Neck* 1999 **21** 370–374.
 - 22 Rosário S, de Faria S, Bicalho L, Alves MF, Borges M, Purisch S, Padrao EL, Rezende LL & Barroso AL. Ultrasonographic differentiation between metastatic and benign lymph nodes in patients with papillary thyroid carcinoma. *Journal of Ultrasound in Medicine* 2005 **24** 1385–1389.
 - 23 Ustun M, Risberg B, Davidson B & Berner A. Cystic change in metastatic lymph nodes: a common diagnostic pitfall in fine-needle aspiration cytology. *Diagnostic Cytopathology* 2002 **27** 387–392.
 - 24 Schlumberger M, Pacini F, Wiersinga WM, Toft A, Smit JWA, Franco FS, *et al.* Follow-up and management of differentiated thyroid carcinoma: a European perspective in clinical practice. *European Journal of Endocrinology* 2004 **151** 539–548.
 - 25 Mikosiński S, Pomorski L, Oszukowska L, Makarewicz J, Adamczewski Z, Sporny S & Lewinski A. The diagnostic value of thyroglobulin concentration in fine-needle aspiration of the cervical lymph nodes in patients with differentiated thyroid cancer. *Endokrynologia Polska* 2006 **57** 392–395.
 - 26 Spencer CA. Challenges of serum thyroglobulin (Tg) measurement in presence of Tg autoantibodies. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 3702–3704.

Received 11 February 2007

Accepted 23 April 2007