Journal of the American Society of Cytopathology (2019) 8, 34–38

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jascyto.org/

ORIGINAL ARTICLE

The usefulness of fine-needle aspirates for detection of recurrent carcinoma in the thyroid bed

Andrea Cruz Ferraz de Oliveira, MD[a], Camila Destefani, MD[a], Louise De Brot, MD, PhD[a], Débora Lacerda, MD[a], Flavio Alexandre Moreira, MD[a], Clovis Pinto, MD, PhD[a], Demian Travesso, MD[b], Mauricio Amoedo, MD, MSc[b], Luiz Paulo Kowalski, MD, PhD[c], Ricardo Pastorello, MD[a], Mauro Ajaj Saieg, MD, PhD, MIAC[a,d,e,*]

[a] *Department of Pathology, AC Camargo Cancer Center, Sao Paulo, Brazil*
[b] *Department of Radiology, AC Camargo Cancer Center, Sao Paulo, Brazil*
[c] *Department of Head and Neck Surgery and Otorhinolaryngology, AC Camargo Cancer Center, Sao Paulo, Brazil*
[d] *Department of Pathology, Santa Casa Medical School, Sao Paulo, Brazil*
[e] *Department of Pathology, Fleury Laboratories, Sao Paulo, Brazil*

Received 25 June 2018; received in revised form 22 August 2018; accepted 23 August 2018

KEYWORDS
Thyroid bed;
FNA;
Thyroglobulin;
Thyroid cancer recurrence

Introduction Locoregional recurrence of thyroid carcinoma has a negative impact on patient prognosis. In the current study, we retrospectively reviewed cases of thyroid bed lesions in the last 3 years, correlating cytologic diagnoses with clinical findings and, whenever available, final surgical diagnosis.

Materials and methods Cytologic results and needle wash thyroglobulin results from patients with fine-needle aspiration (FNA) of thyroid bed lesions were retrospectively collected from our electronic files. Additional retrieved data included sex, age at diagnosis, previous thyroidectomy diagnosis, time lapse since surgery, and corresponding surgical diagnosis (whenever available).

Results A total of 91 cases from 72 patients (54 F, 18 M) were retrieved from the electronic files, with a median age of 49 years. Average interval between surgery and thyroid bed FNA was 5 years. Thyroglobulin levels were available for 60 (65.2%) cases. The average level was 276.2 ug/mL, with a range of <0.1 to 4720 ug/mL. Information on final surgical diagnosis was available for 31 samples. Complete agreement

*Corresponding author: Mauro Ajaj Saieg, MD, PhD, MIAC, Department of Pathology, Santa Casa Medical School, Rua Cesário Mota Jr, 61, São Paulo, Brazil. Tel: (55) 11-2176-1503; Fax: (55) 11-2176-1503.
E-mail address: maurosaieg@yahoo.com (M.A. Saieg).

https://doi.org/10.1016/j.jasc.2018.08.004

between final cytologic and histologic diagnoses was achieved in 28 of 31 (90.3%) of the cases, with 1 false negative and 2 false positives. Cytology sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 95.2%, 71.4%, 90.9%, 83.3%, and 89.1%, respectively.

Conclusions Ultrasound-guided FNA is an accurate and minimally invasive diagnostic method for suspicious thyroid bed lesions, with high sensitivity and positive predictive value.

Introduction

Papillary carcinoma is the most common malignancy of the thyroid gland,[1] and it generally demonstrates an indolent behavior.[2] Its incidence has increased over the past decades,[3,4] probably due to improved imaging techniques and widespread surveillance.[4] Resection with total or subtotal thyroidectomy is the mainstay of initial therapy,[4-6] but up to 15% to 30% of patients have recurrent or persistent tumor in the postsurgical thyroid bed,[4,7,8] mostly occurring within 10 years after initial diagnosis.[4,9] Recent guidelines by the American Thyroid Association state that ultrasound evaluation of the thyroid bed should be performed 6 months after surgery, then 1 year after surgery and periodically afterwards, depending on the patient's risk.[10]

The appropriate imaging and clinical management of patients who will develop thyroid bed lesions can be challenging. Patients with thyroid bed recurrence have a 5-fold increased risk of mortality compared with those with regional nodal recurrence,[7,11] and all patients must be followed postoperatively, because about 3% of the recurrent cases occur in low-risk patients.[12] The initial diagnostic follow-up after thyroidectomy includes clinical examination of neck masses, serum thyroglobulin (TG-W) levels, and neck ultrasounds with fine-needle aspiration (FNA) of any suspicious imaging findings.[4,6,12-15] Discrimination based on imaging features alone may be difficult, however.[5,9,11] Hypoechogenicity, for example, is seen both in recurrent and benign lesions such as foreign-body granulomas.[4,9,12-14] Other suspicious features cited in the literature include microcalcification, irregular margins, and internal vasculature.[4,7,11,12] Recent studies have also shown that the addition of simultaneous TG-W testing of FNA needle wash fluid can improve sensitivity for disease detection over FNA alone,[7,15] especially in negative/indeterminate cytology cases.[15] The recent recommendations of the American Thyroid Association also reinforce the use of TG-W as a reflex test for negative lymph node aspirates.[10] Serum TG-W levels, however, may not be as reliable,[11] because sensitivity for detection of recurrence by this method is relatively low (57%)[4] and up to 10% of recurrent/metastatic tumors may not be detected by serum TG-W measurements alone.[7] There is still no validated cutoff value for discriminating TG-W levels in benign or malignant nodules[15] because there is variability in the sensitivity of TG-W levels in the detection of thyroidectomy bed recurrence, and it may also be increased in cases of thyroid remnants from an incomplete surgical removal.[7,9]

In general, as stated by a recent surveillance study with imaging and laboratory analysis, thyroid bed nodules warrant FNA cytology when they persist, increase in size and number, or exhibit suspicious ultrasound characteristics.[12]

To date, published data on the performance of ultrasound-guided FNA in detection of recurrent thyroid carcinoma in the thyroid bed is limited to relatively few reports.[4,5,11-13] The purpose of the current study was to retrospectively review all cases of thyroid bed lesions in the last 3 years that had a FNA performed at our institution, correlating cytological findings with TG-W levels and, whenever available, final surgical diagnosis.

Materials and methods

All cases of thyroid bed lesions submitted to ultrasound-guided FNA from January 2015 to March 2018 were retrospectively collected from the laboratory electronic files. Extracted data included age, sex, number of performed passes, previous thyroidectomy diagnosis, lesion size, cytologic diagnosis, and, whenever available, correspondent surgical diagnosis. TG-W levels were obtained from patient labs results.

All FNAs were performed at our institution, with the presence of the pathologist onsite, performing rapid onsite examination. In cases with no diagnostic cells, up to 3 passes were performed. Criteria for nondiagnostic (ND) samples in thyroid bed FNA have not been standardized and therefore can be somewhat subjective, as hypocellular smears could be due to fibrosis. We chose to group ND and negative reports in the same group (negative for malignant cells) for statistical purposes. All cases signed out as suspicious in cytology were considered concordant with a final diagnosis of malignancy.

For TG-W measurement, leftover material in the needle was rinsed in 1 mL of saline and then immediately sent to the processing lab. Analysis of TG-W level was performed by the same electrochemiluminometric assay routinely used for serum detection of TG levels (Roche, Basel, Switzerland).

Statistical analysis

All data evaluation was calculated using IBM SPSS Statistics. Pearson's χ^2 test was used when appropriate. Follow-up histology was used as the gold standard to determine true positive and negative cases. A P value <0.05 was considered statistically significant.

Results

A total of 106 FNAs were retrieved from the electronic files. Diagnoses from previous thyroidectomies were not available in 15 cases and these were excluded from the study. The remaining 91 biopsies belonged to 72 patients (54 F, 18 M), with a mean age of 49 years (range: 20 to 84 years). Histologic reports from previous thyroidectomies revealed papillary thyroid carcinoma (PTC) in 79 (86.8%) cases, follicular carcinoma in 6 (6.6%), medullary thyroid carcinoma (MTC) in 2 (2.2%), concomitant PTC and MTC in 1 (1.1%), paraganglioma in 1 (1.1%), and benign lesions (hyperplastic nodules) in 2 (2.2%). Number of performed passes varied from 1 to 4, with a mean of 1.5 passes/case. Thyroid bed mean lesion size was 11.1 mm (range: 3 to 56 mm). The average interval between surgery and thyroid bed FNA was 5 years (range: 4 months to 30 years).

Cytologic diagnoses were first assigned as ND in 20 cases and negative in 39 (20 compatible with inflammatory process with reactive lymphoid cells/reactive lymph node; 12 described as foreign-body type granulomatous reaction, and 7 compatible with benign remaining/re-grown thyroid tissue). These 59 (64.9%) cases were grouped together as "negative for malignant cells" in this study, for statistical and correlation purposes. Remaining cases were atypical in 4 cases (4.4%), suspicious for carcinoma in 6 (6.6%), and positive in the remaining 22 cases (24.2%). Corresponding final histologic diagnosis from the surgical removal of the thyroid bed lesion was available in 31 (34.1%) cases. A complete list of cases with cytohistologic correlation is detailed in Table 1. Excluding cases with an "atypical" diagnosis on FNA, cytology sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated at 95.2%, 71.4%, 90.9%, 83.3% and 89.1%, respectively. There were 2 false-positive cases (suspicious for PTC) with final histologic diagnoses of foreign-body reaction (Fig. 1) and paraganglioma. One case was deemed as false negative, reported as negative on FNA with a final surgical diagnosis of recurrent PTC (Table 1). Among atypical cases, 3 had surgical removal of the lesion, with finding of recurrent papillary carcinoma in three of them (75%). For the unoperated case, patient was lost to follow-up at the hospital and no clinical information could be obtained.

Among cases not submitted for surgery at our institution, clinical follow-up was available for 55 cases (91.6%). Ten patients had been operated elsewhere, with known external diagnosis: 6 cases with a positive diagnosis on cytology and confirmed PTC in the surgical specimen, 2 cases with negative cytology and a confirmed negative histology, and 2 false-negative cases, with our cytology signed out as negative and external surgical diagnosis of recurrent PTC. The remaining patients were in clinical surveillance, asymptomatic, most of them with replacement thyroid hormone therapy and no apparent signs of recurrent disease.

Table 1 Complete list of cases with cytohistologic correlation.

CASE#	FNA category	Surgical diagnosis	Agreement
01	NEG	Fibrotic tissue	Yes (TN)
02	NEG	Reactive lymph node	Yes (TN)
03	NEG	Reactive lymph node	Yes (TN)
04	NEG	Fibrotic tissue	Yes (TN)
05	NEG	Fibrotic tissue	Yes (TN)
06	NEG	Papillary carcinoma	No (FN)
07	SUSP	Foreign-body giant cell reaction	No (FP)
08	SUSP	Papillary carcinoma	Yes (TP)
09	SUSP	Paraganglioma	No (FP)
10	SUSP	Papillary carcinoma	Yes (TP)
11	SUSP	Papillary carcinoma	Yes (TP)
12	SUSP	Papillary carcinoma	Yes (TP)
13	POS	Papillary carcinoma	Yes (TP)
14	POS	Papillary carcinoma	Yes (TP)
15	POS	Papillary carcinoma	Yes (TP)
16	POS	Papillary carcinoma	Yes (TP)
17	POS	Papillary carcinoma	Yes (TP)
18	POS	Papillary carcinoma	Yes (TP)
19	POS	Papillary carcinoma	Yes (TP)
20	POS	Papillary carcinoma	Yes (TP)
21	POS	Medullary carcinoma	Yes (TP)
22	POS	Papillary carcinoma	Yes (TP)
23	POS	Papillary carcinoma	Yes (TP)
24	POS	Papillary carcinoma	Yes (TP)
25	POS	Papillary carcinoma	Yes (TP)
26	POS	Papillary carcinoma	Yes (TP)
27	POS	Papillary carcinoma	Yes (TP)
28	POS	Papillary carcinoma	Yes (TP)
29	AUS	Papillary carcinoma	Yes (TP)
30	AUS	Papillary carcinoma	Yes (TP)
31	AUS	Papillary carcinoma	Yes (TP)

Abbreviations: AUS, atypia of undeterminate significance; FN, false negative; FP, false positive; NEG, negative; POS, positive; SUSP, suspicious for malignancy; TN, true negative; TP, true positive.

TG-W levels were available for 60 (65.2%) cases. The average level was 276.2 ug/mL, with a range from <0.1 to 4720 ug/mL. The average level among true negative cases was 0.7 ug/mL (range: <0.1 to 1.2 ug/mL) and among true positive cases was 477 ug/mL (range: 0.22 to 4720 ug/mL). The limited number of cases with surgical follow-up hindered the diagnostic test evaluation of TG-W levels. TG-W levels were available for 2 of the 3 cases with discrepant cytohistologic correlation: It was aberrantly low (0.1 ug/mL) in the false-negative case and accordingly low (also 0.1 ug/mL) for the false-positive case with a final diagnosis of paraganglioma.

Discussion

FNA is the method of choice for sampling suspicious thyroid bed lesions. In the present study, we confirm its

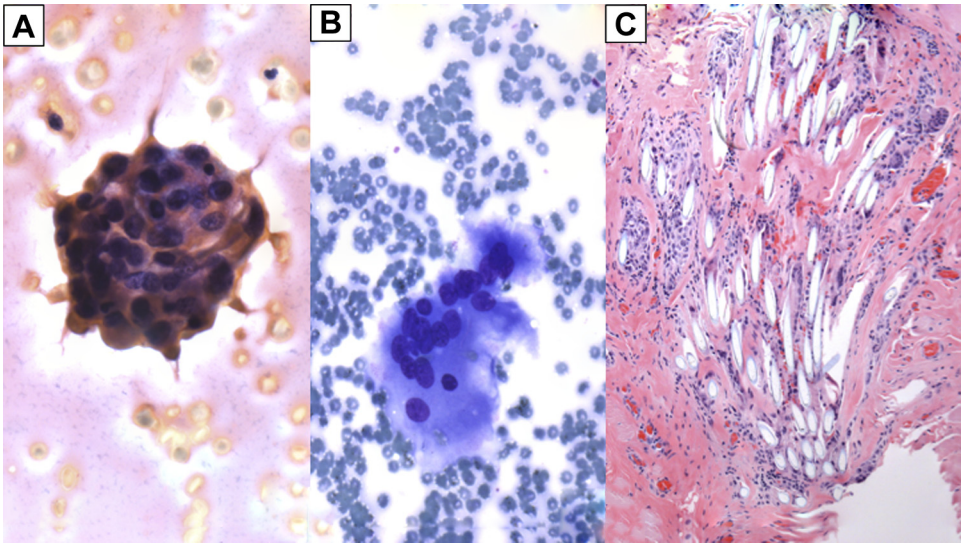

Figure 1 Example of one of the false positive cases. A and B, Cytologic aspects of the lesion, with clusters of epithelioid cells with discrete atypia and a multinucleated giant cell. C, Surgical analysis of the lesion revealed a foreign-body type granulomatous reaction with epithelioid histiocytes and giant cells surrounding suture threads remnants. (A, Papanicolaou stain, 400×; B, Diff-Quik stain, 400×; C, hematoxylin and eosin stain, 200×).

accuracy, with a high positive predictive value and good concordance to histologic findings.

One of the main limitations of FNA from thyroid bed lesions is the scant number of cells often encountered in these samples, due mainly to extensive scarring after surgery. Several studies report a high rate of ND samples.[5,6,11] One study showed that the majority of these patients with ND cytology did not present with any local progression of the thyroid bed mass over time, neither in size nor in ultrasound characteristics, which alleviates this management dilemma[11] and also prompted us to categorize ND cases in the "negative for malignant cells" group. The additional ancillary tests such as immunohistochemistry or TG-W may not aid in these instances, since the nature of the lesion precludes an ample sampling of possibly present residual neoplastic cells, if present. Our study also shows a high positive predictive value for FNA of thyroid bed lesions, similar to the previously published series.[4-6] Despite the overall success in identifying disease, many papers advocate the need to pay extra attention when dealing with those types of specimens.[4,6,16] Challenges in diagnosis are associated with post-therapy changes and difficulty in obtaining cellular specimens. Although sporadic, false-positive cases have also been reported in other previously published series.[4-6] In our series, one of the false-positive cases was revealed to be a foreign body giant cell reaction by histologic examination, with severe inflammation, which may have caused reactive atypia leading to an erroneous interpretation of malignancy by cytology. The other turned out to be a paraganglioma, a well-known mimic of papillary thyroid carcinoma.[6] We also report a false negative cytology result where surgery was performed irrespective of the FNA result, since analysis of the neck nodes had already shown suspicious recurrent disease. Possible explanations for false negative cases include potential sampling error, since many of these cases recur in scar or fibrotic tissue and FNAs of these lesions might reveal only scant material and miss the neoplastic cells. In these cases, imaging and clinical correlation should prevail over morphology alone and repeat FNA or even surgery may prove beneficial for early detection of recurrent disease. Sonographic features previously described for recurrent disease in the thyroid bed include hypoechogenicity, microcalcifications, irregular margins, and internal vascularity.[7,11,17] These features are sometimes difficult to interpret, however, because extensive fibrosis and suture granulomas can also mimic some of these findings.[13,14,18]

The use of TG-W analysis as part of the diagnostic workup is also controversial. It seems to be of little assistance in positive lesions, but of great value as a reflex test in cases with negative cytology.[15] Nevertheless, residual benign thyroid tissue in the surgical bed should also be perceived as a potential source of elevated TG-W levels in the absence of disease, and throughout correlation with morphological features must be carried out.[15] A recent meta-analysis of the published series on the use of TG-W level as an ancillary test for lymph node and thyroid bed FNA has shown that variable cutoffs have been used for determining suspicious or positive cases.[15] According to the study, authors have also used assorted approaches to define cutoffs, from receiver operator curves to +2 standard deviations of control groups.[19] This has obvious statistical implication on the studies and hampers an exact analysis of the impact of TG-W levels in determining malignancy.[15]

As already mentioned, our current study has several limitations, mainly due to its retrospective nature. TG-W

levels were not assessed for all nodules and some of the cases with positive results by cytology had not yet been operated by the time this report was produced, which may have hampered the calculation of the actual positive predictive value of our series. In addition, not all patients with a thyroid bed image were selected for FNA, and this might have led to a potential bias to our selected data. One important question that could be addressed from the presented data is whether TG-W levels of remaining/re-grown benign thyroid tissue would differ from recurrent papillary thyroid carcinoma. Out of our negative cases, only 7 (out of 39 [17.9%]) were compatible with remaining/re-grown benign thyroid tissue and only 2 had TG-W level measurement, with a value of <0.1 ug/mL for both cases, and no obvious conclusions could be therefore drawn from this limited data. A prospective study on thyroid bed lesions, with systematic collection of TG-W and meticulous preanalytical control and ultrasound features, may yield more reliable results, with the true identification of the importance of TG-W as a reflex test for negative or even ND lesions.

In conclusion, the present study confirms that ultrasound-guided FNA is an excellent method for an accurate and minimally invasive diagnosis of suspicious thyroid bed lesions, with a high positive predictive value, prompting an early and precise diagnosis of these lesions and helping patients achieve better results in their fight against recurrent thyroid cancer.

Funding sources

None.

Conflict of interest disclosures

The authors have no conflict of interest to disclose.

References

1. Dean DS, Hay ID. Prognostic indicators in differentiated thyroid carcinoma. *Cancer Control*. 2000;7:229–239.
2. Ito Y, Higashiyama T, Takamura Y, Kobayashi K, Miya A, Miyauchi A. Prognosis of patients with papillary thyroid carcinoma showing postoperative recurrence to the central neck. *World J Surg*. 2011;35:767–772.
3. Lamartina L, Grani G, Biffoni M, et al. Risk stratification of neck lesions detected sonographically during the follow-up of differentiated thyroid cancer. *J Clin Endocrinol Metab*. 2016;101:3036–3044.
4. Zhao L, Gong Y, Wang J, et al. Ultrasound-guided fine-needle aspiration biopsy of thyroid bed lesions from patients with thyroidectomy for thyroid carcinomas. *Cancer Cytopathol*. 2013;121:101–107.
5. Bishop JA, Owens CL, Shum CH, Ali SZ. Thyroid bed fine-needle aspiration: experience at a large tertiary care center. *Am J Clin Pathol*. 2010;134:335–339.
6. Webster N, Fox C, Fan F. Thyroid bed fine needle aspiration in patients after thyroidectomy—a useful follow-up tool with proposed diagnostic categories. *Ann Diagn Pathol*. 2014;18:177–180.
7. Kamaya A, Gross M, Akatsu H, Jeffrey RB. Recurrence in the thyroidectomy bed: sonographic findings. *AJR Am J Roentgenol*. 2011;196:66–70.
8. Park DS, Cho JS, Park MH, et al. Malignant thyroid bed mass after total thyroidectomy. *J Korean Surg Soc*. 2013;85:97–103.
9. Shin JH, Han BK, Ko EY, Kang SS. Sonographic findings in the surgical bed after thyroidectomy: comparison of recurrent tumors and nonrecurrent lesions. *J Ultrasound Med*. 2007;26:1359–1366.
10. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26:1–133.
11. Zini C, Thomas S, Raad R, et al. Fine-needle aspiration biopsy of thyroid bed lesions in post-thyroidectomy patients: what is the importance of nondiagnostic biopsy results? *J Ultrasound Med*. 2012;31:1973–1976.
12. Choudhary C, Wartofsky L, Tefera E, Burman KD. Evaluation of thyroid bed nodules on ultrasonography after total thyroidectomy: risk for loco-regional recurrence of thyroid cancer. *Eur Thyroid J*. 2015;4:106–114.
13. Kim JH, Lee JH, Shong YK, et al. Ultrasound features of suture granulomas in the thyroid bed after thyroidectomy for papillary thyroid carcinoma with an emphasis on their differentiation from locally recurrent thyroid carcinomas. *Ultrasound Med Biol*. 2009;35:1452–1457.
14. Langer JE, Luster E, Horii SC, Mandel SJ, Baloch ZW, Coleman BG. Chronic granulomatous lesions after thyroidectomy: imaging findings. *AJR Am J Roentgenol*. 2005;185:1350–1354.
15. Pigal A, Draganova-Tacheva R, Solomides CC, Bibbo M. Thyroglobulin wash testing in the surveillance of patients with thyroid carcinoma: proposal for a reflex test. *Acta Cytol*. 2013;57:545–549.
16. Krishnamurthy S, Bedi DG, Caraway NP. Ultrasound-guided fine-needle aspiration biopsy of the thyroid bed. *Cancer*. 2001;93:199–205.
17. Lee JH, Lee HK, Lee DH, et al. Ultrasonographic findings of a newly detected nodule on the thyroid bed in postoperative patients for thyroid carcinoma: correlation with the results of ultrasonography-guided fine-needle aspiration biopsy. *Clin Imaging*. 2007;31:109–113.
18. Chen SJ, Yu SN, Tzeng JE, et al. Characterization of the major histopathological components of thyroid nodules using sonographic textural features for clinical diagnosis and management. *Ultrasound Med Biol*. 2009;35:201–208.
19. Jeon MJ, Park JW, Han JM, et al. Serum antithyroglobulin antibodies interfere with thyroglobulin detection in fine-needle aspirates of metastatic neck nodes in papillary thyroid carcinoma. *J Clin Endocrinol Metab*. 2013;98:153–160.