RESEARCH ARTICLE

Diagnostic value of Thyroglobulin Measurement with Fine-needle Aspiration Biopsy for Lymph Node Metastases in Patients with a History of Differentiated Thyroid Cancer

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Abstract

Purpose: The aim of this study was to evaluate the diagnostic value of FNA-Tg for detecting lymph node metastases in patients with a history of differentiated thyroid cancer (DTC). Materials and Methods: A total of 58 patients with DTC diagnosis and evidence of single or multiple suspicious cervical lymph nodes were assessed. All underwent total or near-total thyroidectomy with (35 cases) or without (23 cases) radioiodine (RAI) ablation, followed by thyroid stimulating hormone (TSH) suppression therapy. A total of 68 lymph nodes were examined by ultrasound-guided fine needle aspiration (US-FNA) for both cytological examination and FNA-Tg measurement. Serum Tg and anti-thyroglobulin antibody (TgAb) levels were also measured. Diagnostic performance including sensitivity, specificity, accuracy, positive (PPV) and negative predictive value (NPV) of FNAC and FNA-Tg were calculated and compared. The Spearman's rank correlation coefficient was used to estimate the relationship between FNA-Tg and serum TgAb. Results: The FNA-Tg levels were significantly higher with DTC metastatic lymph nodes (median 927.7 ng/mL, interquartile range 602.9 ng/mL) than non-metastatic lymph nodes (median 0.1 ng/mL, interquartile range 0.4 ng/mL) ($p<0.01$). Considering 1.0 ng/mL as a threshold value for FNA-Tg, the sensitivity, specificity, accuracy, PPV and NPV of FNA-Tg were 95.7%, 95.5%, 95.6%, 97.8% and 91.3%, respectively. The sensitivity and accuracy of the combination of FNAC and FNA-Tg were significantly higher than that of FNAC alone ($p<0.05$). The diagnostic performance of FNA-Tg was not significantly different between cases with or without RAI ablation, and the serum TgAb levels did not interfere with FNA-Tg measurements. Conclusions: Measurement of FNA-Tg is useful. The combination of FNAC and FNA-Tg is more sensitive and accurate for detecting lymph node metastases in patients with a history of DTC than FNAC alone. Serum TgAbs appear to be irrelevant for measurement of FNA-Tg.

Keywords: Differentiated thyroid cancer-fine - needle aspiration biopsy - cervical lymph node metastases - thyroglobulin

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Introduction

Differentiated thyroid cancer (DTC), which includes papillary and follicular cancer, is responsible for 90% of all thyroid cancers (Sherma, 2003; Maseeh et al., 2013). According to the American Thyroid Association guidelines, the initial treatment for DTC consists of total or near-total thyroidectomy and cervical lymph node (LN) dissection with or without radioiodine (RAI) ablation (Cooper et al., 2009). The treatment is completed with thyroid stimulating hormone (TSH) suppression therapy using levothyroxine (Cooper et al., 2009). A minority of patients with DTC may develop recurrence many years after initial treatment, primarily in the cervical LNs, so a long-term follow-up is required (Schlumberger et al., 2004; Cooper et al., 2009).

During the follow-up, serum thyroglobulin (Tg) assays and neck ultrasonography (US) are routinely recommended for the surveillance of recurrences (Cooper et al., 2009). Tg is a high molecular weight glycoprotein produced only by normal or neoplastic thyroid follicular cells, and its tissue-specific origin predicates the clinical value of Tg measurement (Zekiye et al., 2014). Serum Tg is unreliable in patients with circulating anti-thyroglobulin antibodies (TgAbs) and it does not localize in neoplastic foci (Borel et al., 2008). Although the criteria for US to distinguish benign from metastatic LNs have been described, its specificity is not optimal (Frasoldati et al., 2004). In cases of suspicious US findings, fine needle aspiration cytology (FNAC) is generally required for excellent specificity. However, the fine needle aspiration sample may be non-diagnostic or even provide false-negative results, especially in small or cystic metastatic LNs (Frasoldati et al., 1999; Cignarelli et al., 2003;

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Bernier et al., 2005). Since its first description in 1992, Tg measurement in fine-needle aspiration biopsy (FNA-Tg) has been used to improve the diagnostic rate of FNAC (Pacini et al., 1992; Frasoldati et al., 1999; Jack Baskin H et al., 2004; Cunha N et al., 2007; Sigstad E et al., 2007; Kim MJ et al., 2009). However, research on FNA-Tg in China has not seen sufficient attention. The purpose of this study was to evaluate the diagnostic value of FNA-Tg for detecting LN metastases in patients with a history of DTC.

Materials and Methods

Patients

Between August 2010 and January 2013, a total of 58 patients (16 male and 42 female; mean ages±SD, 45.3±15.8 years) who had a previous diagnosis of DTC (55 papillary and 3 follicular) and presented US evidence of single or multiple suspicious cervical LNs were evaluated in this study. All patients underwent total or near-total thyroidectomy with (35 cases) or without (23 cases) RAI ablation, followed by TSH suppression therapy. A total of 68 LNs were examined by ultrasound-guided fine needle aspiration (US-FNA). The interval between thyroidectomy and US-FNA was 40.8±16.3 months. The ethics committee of China-Japan Union Hospital approved the study, and written informed consent was obtained from all patients.

US, US-FNA and fine-needle washout

US was performed on the cervical area using a Philips HD7 with a transducer frequency of 7-13 MHz. The US criteria for possible malignant infiltration of LNs included: a rounded rather than oval shape with a long-to-short axis ratio inferior to 1.5; irregular internal echogenicity; calcifications; loss of the fatty hilus peripheral vascularity; and cystic change ((Sherma, 2003; Schlumberger et al., 2004; Cooper et al., 2009).

US-FNA was performed on suspicious LNs by the same experienced doctor using a 21 to 25 gauge needle attached to a 10 mL syringe. Each lesion was aspirated at least twice, and all aspirates were smeared directly on glass slides for cytological examination. The same needle and syringe were rinsed with 0.5-1.0 mL of normal saline (final volume 1.0 mL), and the washout was submitted for Tg measurement.

Cytological and histological analysis

Following FNA, the aspirated material was expelled onto glass slides and smeared with a second slide to spread the material across the surface for cytological examination. Samples were then air-dried and stained with hematoxylin and eosin. Of 68 suspicious LNs labeled according to the site and side during US-FNA, 52 were surgically removed later and examined histologically. Both cytological and histological diagnoses were made by an experienced pathologist.

The cytology 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*) negative cytology: reactive lymphadenitis and absence of malignant cells; *iii*) positive cytology for DTC metastases: presence of epithelial cells with malignant cytological characteristics.

Biochemical analysis

Tg assays in the FNA washout and serum were performed using electrochemiluminescence immunoassay (ECLIA) (cobas e 601, Roche Diagnostics GmbH, Germany). Results of serum Tg and FNA-Tg were expressed in 'ng/mL' with an analytical sensitivity of 0.1 ng/mL and functional sensitivity of 1.0 ng/mL. The serum TgAb levels were assayed using the TgAb kit from Roche Diagnostics GmbH with an analytical sensitivity of 10 IU/mL and the normal values were considered <115.0 IU/mL.

Statistical analyses

Results are expressed as frequencies, mean±standard deviation (SD) or median (interquartile range). Diagnostic performance (sensitivity, specificity, accuracy, PPV and NPV) of FNAC and FNA-Tg were calculated and compared to the final diagnosis of the patients defined as follows: metastatic LNs from DTC were diagnosed by histological examination of surgically resected LNs; non-metastatic LNs were diagnosed by negative histological examination of surgically resected LNs or imaging evidence showing disappearance or absence of evolution without cytological evidence of malignancy at 12 months or more of follow-up. The McNemar's test was used to compare the sensitivity, specificity and accuracy of FNAC and FNA-Tg. The patients were divided into two groups according to the treatment of RAI ablation, and the differences between the groups were assessed using Fisher's exact test. Mann-Whitney U test was used for the comparison of FNA-Tg levels. The Spearman's rank correlation coefficient was used to estimate the relationship between FNA-Tg and serum TgAb. Statistical calculations were performed using SPSS 17.0 for Windows. Statistical significance was defined as $p<0.05$.

Results

Among the 68 suspicious LNs assessed for postoperative recurrences by FNAC and FNA-Tg, 46 (67.6%) nodes were positive for DTC metastasis and the remaining 22 (32.4%) nodes were negative, respectively, in the final diagnosis. The 46 positive LNs and 6 negative LNs were diagnosed based on histological diagnosis. The remaining 16 negative LNs were followed up for 12 months or more and no DTC recurrence was detected (follow-up: mean 23 months, range 13-31 months).

Diagnostic performance of FNAC, FNA-Tg and the combination of FNAC and FNA-Tg

As shown in Table 1, FNAC indicated positive cytology for DTC metastases in 35 LNs (51.5%), negative in 21 LNs (30.9%) and was considered inadequate or non-diagnostic in the remaining 12 LN aspirates (17.6%). Compared to the final diagnosis, the sensitivity, specificity, accuracy, PPV and NPV of FNAC were 76.1%, 86.4%, 79.4%, 92.1% and 63.3%, respectively.

The FNA-Tg levels were significantly higher in DTC metastatic LNs (median 927.7 ng/mL, interquartile range

602.9 ng/mL) than non-metastatic LNs (median 0.1 ng/mL, interquartile range 0.4 ng/mL) ($p<0.01$). In our study, the FNA-Tg levels in the non-metastatic LNs were <1.0 ng/mL (range <0.1- 0.9 ng/mL) except in 1 case (FNA-Tg: 1000 ng/mL), leaving no doubt in distinguishing positive and negative cases. We considered the FNA-Tg positive with any Tg concentration above the functional sensitivity of the assay (1.0 ng/mL). Compared to the final diagnosis, the sensitivity, specificity, accuracy, PPV and NPV of FNA-Tg were 95.7%, 95.5%, 95.6%, 97.8% and 91.3%, respectively.

The FNA-Tg levels in 12 cytologically inadequate LNs ranged from 0.1 ng/mL to 1000 ng/mL. Among them, 3 cases were finally confirmed as non-metastatic LNs with FNA-Tg levels of <1.0 ng/mL, and 8 cases were finally confirmed metastatic LNs with elevated FNA-Tg. Using 1.0 ng/mL as a cutoff value for FNA-Tg correctly classified those LNs that did not have a definitive FNAC diagnosis except in one case where a FNA-Tg level of 0.5 ng/mL demonstrated a metastatic LN in the final diagnosis.

To assess the diagnostic performance of combined FNAC and FNA-Tg, metastatic LNs were deemed present when either FNAC or FNA-Tg was positive. The sensitivity and accuracy of the FNA-Tg and FNAC with FNA-Tg were significantly higher than that of FNAC alone ($p<0.05$), whereas the specificity was comparable among them ($p>0.05$) (Table 2).

Impact of RAI ablation and serum TgAb on the diagnosis from FNA-Tg

The patients were divided into two groups. Group A consisting of 35 patients (39 LNs) had been treated by RAI ablation (administered activity ranging from 2.96 to 5.55 GBq) subsequent to thyroidectomy. Group B with 23 patients (29 LNs) had not been treated by RAI ablation. Tables 3 and 4 demonstrate the results and diagnostic performance of FNA-Tg in group A and group B, respectively.

In group A, there were no false-positive cases and only one false-negative case (FNA-Tg: 0.5 ng/mL), which had an inadequate result in FNAC examination. In the false-negative result, the serum Tg concentration was 3.6 ng/mL; whereas, serum TgAb concentration was 30.5 IU/mL. Histological examination confirmed metastasis from papillary thyroid carcinoma (PTC). In group B, there were one false-positive case and one false-negative case. The false-positive case (FNA-Tg: 1000 ng/mL) was labeled as 'neck LN at level 6' and was subsequently confirmed to have been taken from the thyroid bed. The false-negative case (FNA-Tg: <0.1 ng/mL) had a positive result in FNAC examination. The serum Tg concentration was 3.3 ng/mL; whereas, TgAb concentration was undetectable (<10 IU/mL). Histological examination displayed metastasis from poorly differentiated PTC with Tg undetectable by immunohistochemistry.

The FNA-Tg level of metastatic LNs was significantly higher than non-metastatic LNs in both Group A and Group B ($p<0.05$). No statistical difference was detected in FNA-Tg levels between Group A and Group B ($p>0.05$) (Table 3). The diagnostic performance of FNA-Tg was

Table 1. Diagnostic Performance of FNAC as Compared to Final Diagnosis

FNAC	Final diagnosis	
	Metastatic LNs (n = 46)	Non-metastatic LNs (n = 22)
Positive	35	0
Negative	2	19
Inadequate	9	3

FNAC= fine needle aspiration cytology; LNs=lymph nodes

Table 2. Diagnostic Performance of FNAC, FNA-Tg and FNAC+FNA-Tg

	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
FNAC	76.1 (35/46)	86.4 (19/22)	79.4 (54/68)	92.1 (35/38)	63.3 (19/30)
FNA-Tg	95.7* (44/46)	95.5 (21/22)	95.6* (65/68)	97.8 (44/45)	91.3 (21/23)
FNAC+ FNA-Tg	97.8* (45/46)	95.5 (21/22)	97.1* (66/68)	97.8 (45/46)	95.5 (21/22)

*$p<0.05$ compared with FNAC, derived from a McNemar test; FNAC=fine needle aspiration cytology; FNA-Tg=thyroglobulin measurements in fine-needle aspiration biopsy; PPV=positive predictive value; NPV=negative predictive value; FNAC+FNA-Tg=combination of FNAC and FNA-Tg

Table 3. FNA-Tg Results in Patients with (Group A) or without (Group B) RAI Ablationcompared with the Final Diagnosis

	Group A		Group B	
FNA-Tg	Metastatic (n= 27)	Non-metastatic (n = 12)	Metastatic (n = 19)	Non-metastatic (n = 10)
Positive	26	0	18	1
Negative	1	12	1	9
FNA-Tg, ng/mL	946.8 (603.7)*	0.1 (0.3)	908.6 (510.3)*	0.1 (0.5)

*Date are expressed as median (interquartile range); *$p<0.05$ compared with Metastatic LNs derived from a Mann-Whitney U test

Table 4. Diagnostic Performance of FNA-Tg Compared with Final Diagnosis

	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
Group A	96.3 (26/27)	100 (12/12)	97.4 (38/39)	100 (26/26)	92.3 (12/13)
Group B	94.7 (18/19)	90.0 (9 /10)	93.1 (27/29)	94.7 (18/19)	90.0 (9 /10)

*FNAC=fine needle aspiration cytology; FNA-Tg=thyroglobulin measurements in fine-needle aspiration biopsy; PPV=positive predictive value; NPV=negative predictive value

comparable and not significantly different between Group A and Group B ($p>0.05$) (Table 4).

Of the 46 patients who had metastatic LNs based on histological diagnosis, 19 (41.3%) patients had serum TgAb >115.0 IU/mL, and of the 12 patients who had non-metastatic LNs, 8 (66.7%) patients had serum TgAb >115.0 IU/mL ($p>0.05$). The association of FNA-Tg with serum TgAb was investigated using Spearman's rank correlation coefficient. We found that serum TgAb was not correlated with FNA-Tg ($\varrho=0.053$; $p>0.05$).

Discussion

For the past few years, the FNA-Tg measurement has been proposed to be a useful diagnostic method in detecting metastatic LNs of DTC patients. Several studies have reported FNA-Tg to be more sensitive than FNAC for detecting metastasis, and the accuracy of FNAC is improved when combined with FNA-Tg (Pacini et al., 1992a; 1992b; Frasoldati et al., 1999; Jack et al., 2004; Cunha N et al., 2007; Sigstad et al., 2007; Kim et al., 2009; Li et al., 2013). The results of this study are consistent with these reports.

However, the cutoff value of FNA-Tg remains controversial on account of differences in sample treatments and thyroglobulin assays. In prior studies, various diagnostic FNA-Tg threshold values have been reported including: mean+2SD of the FNA-Tg measured in patients without LN metastasis; highest Tg concentration measured in patients with reactive LNs; FNA-Tg more than serum Tg level; or fixed Tg values. Several studies compared FNA-Tg results in cases with or without a history of thyroidectomy and found that FNA-Tg levels might be affected by the presence of the thyroid (Frasoldati et al., 1999; Kim et al., 2009; Moon et al., 2013). The accuracy of the FNA-Tg measurement seemed to be superior in patients previously treated by thyroidectomy than those awaiting thyroid surgery (Kim et al., 2012; Sohn et al., 2012). Therefore, the presence or absence of the thyroid should be considered when evaluating the diagnostic performance of FNA-Tg and selecting the threshold values.

In this study, only patients who had a history of thyroidectomy with or without RAI ablation were enrolled. Using a cutoff value at the functional sensitivity of the Tg assay (1.0 ng/mL) for detecting DTC metastatic LNs resulted in a sensitivity of 95.7% and a specificity of 95.5%. Of the 12 cases without a definitive FNAC diagnosis, FNA-Tg correctly classified them except for one case with a FNA-Tg level of 0.5 ng/mL that demonstrated a PTC metastatic LN in the final diagnosis. The reason for the low level of FNA-Tg in this case might be due to the small amount of cells (unsatisfactory sample). The other false-negative case was poorly differentiated PTC metastasis (Tg was undetectable by immunohistochemistry) with a FNA-Tg level <0.1 ng/mL.

The diagnostic performance of FNA-Tg was not significantly different between cases with or without RAI ablation. However, there was one false-positive case found in a patient without RAI ablation having a FNA-Tg level of 1000 ng/mL. The sample was labeled as 'neck LN at level 6'; but after reassessment by US and FNAC, this false-positive case was confirmed to be normal thyroid tissue which has been taken from the thyroid bed. Therefore, cautious interpretation is necessary for high FNA-Tg levels of LNs at level 6 in patients with remnant thyroid tissue.

The presence of serum TgAb, which can occur in up to 25-30% of patients, can seriously affect serum Tg measurements resulting in either false positive or false negative results (BAYER MF et al., 1979; BAYER MF et al., 1979). Whether circulating TgAb affect the FNA-Tg is still a matter of debate. Several authors have reported that FNA-Tg measurements are unaffected by positive serum TgAb (Jack et al., 2004; Boi et al., 2006; Bournaud et al., 2010). Recently, a report by Jeon MJ, et al. has shown that high-serum TgAb levels could interfere with FNA-Tg measurements and thereby result in falsely low FNA-Tg levels (Jeon et al., 2012). In our current study, serum TgAb was not correlated with FNA-Tg, and no high serum TgAb level was found in false-negative cases.

Several limitations of this study should be considered. First, the 16 negative LNs without positive FNAC results were not diagnosed based on histological diagnosis. Second, the number of patients enrolled was relatively small. Third, the TgAb assays in the FNA washout were not performed in this study, and further investigation should be carried.

In conclusion, this study showed that the combination of FNAC and FNA-Tg is more sensitive and accurate for detecting LN metastases in patients with a history of DTC than FNAC alone. The diagnostic performance of FNA-Tg was not significantly different between cases with or without RAI ablation. Serum TgAb levels do not interfere with FNA-Tg measurements.

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