^{18}F-FDG PET/CT and ultrasonogrpahy in differentiated thyroid carcinoma patients with elevated serum levels of antithyroglobulin antibody, negative Tg and whole body ^{131}I scan

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Abstract

Objective: In the follow-up of patients with differentiated thyroid cancer (DTC), several patients had elevated serum levels of antithyroglobulin antibody (TgAb), undetectable serum thyroglobulin (Tg), and negative radioiodine whole body scan (^{131}I-WBS). We describe the use of neck ultrasonography (US) and fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) imaging in these patients to investigate this clinically challenging problem and propose treating. **Subjects and Methods:** A total of 49 DTC patients (mean age, 42.7±12.9 years; range, 16-73 years; males, 6) with elevated serum levels of TgAb (>115IU/mL), undetectable Tg and negative ^{131}I-WBS were divided into two groups (positive and negative) according to the neck US findings. Differences in the rate of recurrence between the two groups were investigated. The diagnostic value of ^{18}F-FDG PET/CT in these patients was evaluated. **Results:** Among the 49 patients, the rate of recurrence of patients with positive neck US was 50%, which was significantly higher than that of patients with negative neck US (17.24%; P=0.014). The sensitivity, specificity, and positive predictive values of ^{18}F-FDG PET/CT imaging in diagnosing the clinical status of these patients were 93.33%, 70.59% and 58.33%, respectively. After the ^{18}F-FDG PET/CT scan, clinical management was changed in 14 patients. Nine patients were operated and five underwent ^{131}I ablation therapy. **Conclusion:** In the 49 DTC patients with elevated serum levels of TgAb but negative findings in serum Tg and in ^{131}I-WBS, neck US and ^{18}F-FDG PET/CT imaging supported the clinical diagnosis and suggested subsequent treatment.

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Introduction

Differentiated thyroid cancer (DTC) is the most common thyroid cancer, which includes papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). The worldwide incidence of DTC is increasing yearly. To our knowledge, the best treatment for DTC is near-total or total thyroidectomy, with subsequent iodine-131 (^{131}I) therapy (RIT) and thyroid-stimulating hormone (TSH) suppression therapy [1]. The measurement of serum thyroglobulin (Tg), neck ultrasonography (US) and ^{131}I whole body scan (^{131}I-WBS) are well-established diagnostic modalities in the follow-up of DTC patients who have undergone near-total or total thyroidectomy and subsequent iodine-131 therapy [2-3]. Serum Tg is crucial in the subsequent follow-up of patients with DTC [4]. However, the presence of serum antithyroglobulin antibody (TgAb) can influence the measurement of serum Tg. Several scholars believed that the presence of TgAb may indicate the recurrence of DTC.

Managing DTC patients who persistently show elevated serum levels of TgAb, undetectable Tg and negative ^{131}I-WBS is a clinically challenging problem. The present study aimed to investigate the recurrence in DTC patients with elevated serum levels of TgAb, undetectable Tg and negative ^{131}I-WBS by using neck US and fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scans. The values of US and ^{18}F-FDG PET/CT can be used to guide the selection of follow-up clinical treatment.

Methods

Patients and their characteristics

Forty nine DTC patients who visited the outpatients department for follow-up between September 2014 and August 2016 were enrolled in our study. Their mean age was: 42.7± 12.9 years; range: 16-73 years; males were 6. Among them, 48 patients were pathologically diagnosed with papillary carcinoma (PTC) and only one with follicular carcinoma (FTC). All patients had undergone total or near-total thyroidectomy and received consecutive high-dose RIT which achieved successful thyroid remnant ablation. Blood sampling for laboratory data, including Tg and TgAb; ^{131}I-WBS and neck US were examined every 6 or 12 months.

Measurement of serum Tg and TgAb

Serum Tg and TgAb levels were measured by electrochemiluminescence immunoassay (ECLI) using a commercial kit (Roche Cobase411, Germany). The normal range of TgAb is 0-115IU/mL. In patients who have undergone total or near-total thyroidectomy and RAI treatment, the cut-off points of Tg, which indicate disease-free status, are <0.2ng/mL during TSH suppression or <1ng/mL during TSH stimulation in the absence of interfering antibodies [5].

Neck US

All patients underwent US examination of the neck, which was performed using a color Doppler imager (Aplio XG made by TOSHIBA or IU22 made by Philips) with a 12.5MHz linear phased-array transducer. The US features suggestive of metastatic lymph nodes included: a) round shape (long axis to short axis ratio <1.5), b) absence of an echogenic hilum, c) microcalcifications, d) cystic changes and peripheral blood flow on the color Doppler image [6].

^{131}I-WBS

Patients were withdrawn from thyroxine replacement for 4-6 weeks or from triiodothyronine for 2 weeks and maintained a low-iodine diet for 2 weeks for workup 4-6 months after high-dose iodine-131 (^{131}I) therapy. Then, patients underwent anterior and posterior scanning and joint neck-chest tomography fusion imaging using the Siemens Symbia T16 single photon emission tomography/CT (SPET/CT) instrument after taking 111-185MBq of ^{131}I.

^{18}F-FDG PET/CT

The ^{18}F-FDG PET/CT scan was performed using the Siemens Biograph TruePoint 64 ring PET/CT (Germany) instrument. Patients fasted for at least 6h, and their blood glucose levels were <11.0mmol/L at the time of tracer injection. The images were obtained 60min after an intravenous injection of 3.70-4.44MBq ^{18}F-FDG/kg body weight. The metabolically active parts of the thyroid gland, which were detected by image processing of the scan, were outlined as the regions of interest and the computer software automatically calculated the highest standardized uptake value (SUVmax). All imageological examination results were interpreted by at least two experienced diagnosticians, and a final consensus was achieved for all patients. Any foci of increased uptake greater than that of surrounding normal tissue or a SUVmax of 2.5 or higher was considered as positive.

Diagnosis of tumor recurrence

When suspicious lesions were detected by imaging, ultrasound-guided fine needle biopsy cytology test or CT-guided biopsy cytology test was conducted and evaluated according to their findings.

Statistical analysis

Data were analyzed using the SPSS software, version 17.0. Pearson's χ^2 test was used to evaluate the differences in the rate of recurrence of DTC patients who had neck US positive or negative performance. The sensitivity, specificity, positive predictive (PPV) and negative predictive values (NPV) of ^{18}F-FDG PET/CT imaging and neck US for the diagnosis of recurrence or metastases of these patients were evaluated at the same period of time. A P value of <0.05 was considered statistically significant.

Results

Results of neck US

Of the 49 patients with elevated serum levels of TgAb, undetectable Tg and negative ^{131}I-WBS, 15 patients were diagnosed by pathology with recurrence and 34 patients without. Twenty patients showed positive findings in the neck US (20/49, 40.82%), with 10 patients finally diagnosed with recurrence by pathology and 10 patients without recurrence. Moreover, the other 29 patients showed negative findings in the neck US, with 5 finally diagnosed with recurrence by pathology and 24 without recurrence (Table 1). The sensitivity, specificity, PPV and NPV of neck US in the diagnosis of these patients with elevated serum levels of TgAb, undetectable Tg and negative ^{131}I-WBS were 66.67%, 70.59%, 50.00%, and 82.76%, respectively. Pearson's χ^2 test was used to evaluate the differences in the rate of recurrence of DTC patients who had neck US positive or negative performance. χ^2=5.98, P=0.014, with statistical significance.

Table 1. *Information of recurrence or metastases in patients with positive and negative neck US.*

Group	Recurrence (number)		Summation
	+	−	
Neck US (positive)	10	10	20
Neck US (negative)	5	24	29
Summation	15	34	49

Performance and results of ^{18}F-FDG PET/CT imaging

Imaging by ^{18}F-FDG PET/CT was performed in all 49 DTC patients with elevated serum levels of TgAb, undetectable Tg and negative ^{131}I-WBS. Among them, 24 patients had po-

sitive findings (24/49, 48.98%), while most of these 24 cases (18 cases) had lesions in the neck lymph nodes (Figure 1), 2 cases had in the lung lymph nodes (Figure 2), 2 cases in the neck and the supraclavicular lymph nodes, 1 case in the soft tissue behind the thyroid cartilage and 1 case had metastatic lesions in the shoulder blade (Figure 3). By contrast, the remaining 25 patients had negative findings (25/49, 51.02%). Out of the 25 patients who showed negative findings in ^{18}F-FDG PET/CT imaging, 1 case was finally diagnosed with recurrence (false negative) and 24 were true negative (Table 2). The sensitivity, specificity, PPV and NPV of ^{18}F-FDG PET/CT imaging in the diagnosis for all our patients were 93.33%, 70.59%, 58.33% and 96.00%, respectively (check the 24 cases in Table 2, 1st line)

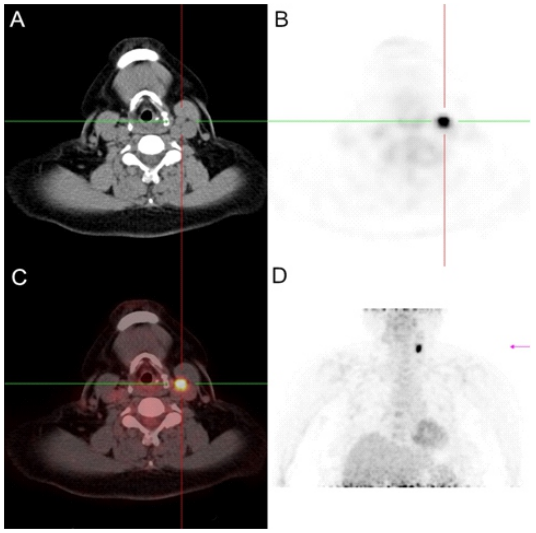

Figure 1. A 60 years old female DTC patient with elevated serum levels of TgAb, undetectable Tg and negative ^{131}I-WBS. (A) An enlarged three-field lymph node in the left neck was detected during computed tomography; (B, D) PET scan showed obvious ^{18}F-FDG uptake in the left neck; (c) PET/CT scan showed obvious ^{18}F-FDG uptake in the lesions (maximum standardized uptake value, SUVmax=31.9).

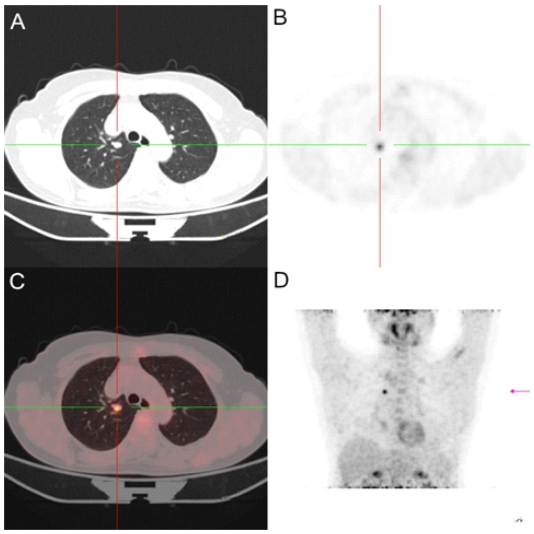

Figure 2. A 59 years old female DTC patient with elevated serum levels of TgAb, undetectable Tg and negative ^{131}I-WBS. (A) A high-density node was detected during computed tomography; (B, D) PET scan showed moderate ^{18}F-FDG uptake in the right chest; (c) PET/CT scan showed moderate ^{18}F-FDG uptake in the lesions (maximum standardized uptake value, SUVmax=7.5).

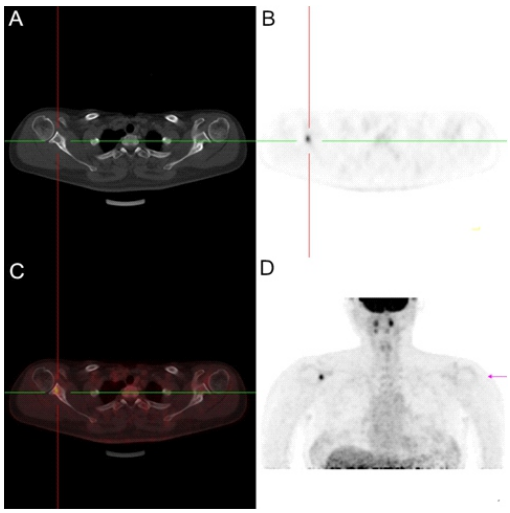

Figure 3. A 38 years old female DTC patient with elevated serum levels of TgAb, undetectable Tg and negative ^{131}I-WBS. (A) Destruction of bone in the right scapula was detected during computed tomography; (B, D) PET scan showed obvious ^{18}F-FDG uptake in the right shoulder; (c) PET/CT scan showed obvious ^{18}F-FDG uptake in the lesions (maximum standardized uptake value, SUVmax=9.1).

Table 2. *Information of recurrence or metastases in patients with positive and negative ^{18}F-FDG PET/CT.*

Group	Recurrence (number)		Summation
	+	–	
^{18}F-FDG PET/CT (positive)	14	10	24
^{18}F-FDG PET/CT (negative)	1	24	25
Summation	15	34	49

Contrast of the diagnosis of neck lymph nodes between neck US and ^{18}F-FDG PET/CT imaging

Among the 11 patients with lesions located in the neck lymph nodes, 10 patients were diagnosed by US. By contrast, ^{18}F-FDG PET/CT imaging detected all of them. The detection rates were 90.90% and 100%, respectively, but without statistical significance.

Discussion

The determination of Tg through ECLI is affected by TgAb, and the interference is concentration dependent, with Tg presenting a false negative value because of the interference of a high concentration of TgAb; moreover, TgAb in patients with DTC have a certain positive rate [7]. Other studies have shown that the incidence of chronic lymphocytic thy-

roiditis combined with thyroid cancer is 0.15% to 38% and most of them were DTC patients [8]. Meanwhile, most patients lose their TgAb positivity during the follow-up because of the disappearance of thyroid tissue and its antigenic components after thyroidectomy and RIT. Gorges et al. (2005) reported that the prevalence of demonstrable TgAb decreased to <10% after 3 years while the median serum half-life of TgAb in treated DTC patients was 10 weeks [9]. Others showed that the media disappearance time was 3 years for TgAb [10]. A previous study reported that the measurement of serum TgAb levels at 6 to 12 months after residual thyroid tissue ablation or the changes of TgAb concentration after early surgery, might predict recurrence [11]. As a result, several authors considered that the increasing serum TgAb levels might indicate the recurrence of DTC [12].

In clinical work, when serum Tg and ^{131}I-Dx-WBS of patients with DTC are negative, patients are considered without recurrence and in a stable state. Although many studies reported that an increase in serum TgAb level might be associated with the recurrence of DTC, reports of the cut-off point of serum TgAb levels are rare and not all very convincing. Dealing with DTC patients who persistently show elevated serum levels of TgAb, undetectable Tg and negative ^{131}I-WBS is problematic for clinicians.

Ultrasound test has been widely adopted because of its high sensitivity in the diagnosis of recurrence in the neck in the follow-up of patients with DTC. Many scholars assume that ^{131}I-WBS cannot be a routinely recommended method in the follow-up of patients with DTC; instead, neck US is recommended because most of the recurrent lesions usually occur in the neck [13-15]. In this work, the rate of recurrence of patients with positive neck US (10/20) was significantly higher than that of patients with negative neck US (5/29; P= 0.014).

The role of ^{18}F-FDG PET/CT in the follow-up of patients with DTC, especially if ^{131}I-WBS negative is well accepted [16-18]. The detection rates of US and ^{18}F-FDG PET/CT were better for the later with obvious difference between them. Thus, for DTC patients with uncertain metastatic lesions, ^{18}F-FDG PET/CT was sensitive and specific for the diagnosis of recurrence.

The characterization and localization of lesions is essential for subsequent treatment. A previous study reported that 10% to 57% of DTC patients opted to change their treatment plan because of ^{18}F-FDG PET/CT imaging [19]. In this study, 14 patients opted to change the treatment plan after undergoing ^{18}F-FDG PET/CT imaging; among them, nine patients underwent surgery again and five patients were subjected to high-dose RIT because of the multifocal transfer of lung or surgical contraindication.

In conclusion, our results indicate that in the follow-up of DTC patients after ablation of the remnant when serum TgAb shows persistent elevation that may indicate increased serum Tg and metastases. Neck US and ^{18}F-FDG PET/CT imaging support clinical diagnosis and the choice of treatment. More studies on this subject are warranted.

The authors declare that they have no conflicts of interest.

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