Utility of ^{18}F-FDG PET/CT in Well Differentiated Thyroid Carcinoma with High Serum Antithyroglobulin Antibody

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Objective: *Evaluate the utility of ^{18}F-FDG PET/CT in the follow-up of differentiated thyroid cancer (DTC) patients with high serum antithyroglobulin antibody (TgAb) but negative serum thyroglobulin (Tg) measurements and negative ^{131}I whole-body scans (WBS).*

Material and Method: *The present study included 22 consecutive patients with high serum TgAb levels. They had negative serum Tg measurements and negative ^{131}I WBS. PET/CT was performed 60 min after intravenous injection of 227.55-455.47 MBq (6.15-12.31 mCi) of ^{18}F-FDG using a combined PET/CT scanner. Co-registered CT images were used to differentiate physiologic from pathologic tracer uptake. Findings on ^{18}F-FDG PET/CT were correlated with tissue pathology, follow-up imaging or clinical follow-up served as a reference.*

Results: *Twenty-two well differentiated thyroid cancer patients participated. Twelve had positive findings on ^{18}F-FDG PET/CT; six were true positives and six were false-positives. ^{18}F-FDG PET/CT results were true negative in 10 patients and the authors found no false-negative patients in the present study. The overall sensitivity, specificity and accuracy of ^{18}F-FDG PET/CT were 100%, 62.5% and 72.7%, respectively. TgAb levels, which are appropriated for sending DTC patient who are ^{131}I WBS negative but have elevated serum TgAb levels to undergo ^{18}F-FDG PET/CT scan, should be more than or equal to 414.6 IU/ml. Results should be highly consider positive if maxSUV value is equal or greater than 4.5.*

Conclusion: *^{18}F-FDG PET/CT is a useful tool for localizing recurrent or metastatic DTC patients, who have negative ^{131}I WBS but elevated serum TgAb levels. The authors recommend its use in clinical management of selected cases regardless of the TgAb level being more than or equal to 415 IU/ml.*

Keywords: *Differentiated thyroid carcinoma, Antithyroglobulin antibody, ^{18}F-FDG PET/CT*

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In patients with well differentiated thyroid carcinoma (DTC) the following follow-up procedures are recommended serum thyroglobulin (Tg), serum antithyroglobulin antibody (TgAb) and ^{131}I whole body scan (^{131}I WBS)[1,2]. Serum Tg measurement is the most sensitive modality for detection of recurrence or persistent disease[3,4]. However, the presence of TgAb could also indicate presence of recurrent disease. Tg-immunoradiometric assay (IRMA) methods are prone to TgAb interference and can under estimate serum Tg concentration, while Tg-radioimmunoassay (RIA) methods are less prone to TgAb interference, but some may over estimate serum Tg concentrations[5-7].

When patients had residual thyroid tissue or metastases of thyroid carcinoma, raising TgAb levels correlated with the inability to detect Tg in 4, 30 and 73% of the patients, when initial TgAbs were < 6, 6-50 or > 50 U/ml respectively[8,9]. Radioiodine whole body scan (WBS) using ^{131}I allows localization of recurrence or distance metastases. However, radioiodine WBS shows negative findings in some patients with detectable serum Tg levels.

In these cases, ^{18}F-FDG PET/CT scan could help to localize metastases sites with high accuracy[10-13] ^{18}F-FDG PET/CT has not yet been reported in the patients with high serum TgAb and ^{131}I WBS scan negative.

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The purpose of the present study was to evaluate the utility of ^{18}F-FDG PET/CT in DTC with negative radioiodine WBS but high serum TgAb level.

Material and Method

Patient

Twenty-two consecutive patients with well differentiated thyroid cancer (DTC) who had undergone a previous total thyroidectomy followed by ^{131}I ablation of residual thyroid tissue were studied. All patients had serum Tg measurement negative (< 10 ng/mL) under endogenous thyrotrophin stimulation after thyroid hormone withdrawal. They had high serum TgAb levels (> 200 IU/mL) and negative ^{131}I WBS scan during follow-up. ^{18}F-FDG PET/CT scans were performed in all patients at the department of nuclear medicine, King Chulalongkorn Memorial Hospital. The patient demographics are shown in Table 1.

Table 1. Patient demographics (n = 22)

Characteristic	Value
Sex	
Female (n)	22
Male (n)	0
Age (years)	
Average	45 ± 8
Range	30-62
Histologic type	
Papillary (n)	21
Mix papillary/follicular (n)	1
TgAb (IU/ml)	
Average	1,758 ± 1,517
Range	208.1-4,000
Reference standard	
Histopathology (n)	10
Follow-up (n)	12
Average (months)	13 ± 4
Range (months)	8-19

Thyroglobulin and antithyroglobulin antibody measurement

The serum Tg was measured by electro-chemiluminescence immunoassay on Elecys 2010 (ROCHE) machine. Within-and between assay variation coefficients were 1.5% and 2.5%, respectively. Serum Tg level below 10 ng/ml on TSH stimulation (> 30 mIU/L) was considered negative.

The serum TgAb was measured by electroche miluminescence immunoassay on Elecys 2010 (ROCHE) machine. Within-and between assay variation coefficients were 5.6% and 6.7%, respectively. Serum TgAb levels were considered abnormal when higher than 200 IU/mL.

^{131}I whole-body scan

Diagnostic ^{131}I whole-body scans were performed approximately 72 hours after oral administration of ^{131}I 111 MBq (3 mCi), under endogenous thyrotrophin stimulation (TSH > 30 mIU/L). Scintigraphy acquisition was done with a large field-of -view gamma camera equipped with a medium-energy parallel-hole collimator with a 20% symmetric window centered at 364 keV. Anterior images of the neck, chest, and abdomen were obtained each accumulating 100 Kcount.

^{18}F-FDG PET/CT imaging

^{18}F-FDG PET/CT scans were performed by using a BIOGRAPH 16 Hi-Rez (Siemens). This PET/CT system combines a 16 slices helical CT scanner, Somatom Sensation 16, with high resolution PET, Hi-Rez, coupled to detection electronics, PICO-3D. The PET/CT scans were performed under thyroxine suppressive therapy after fast for at least 4 to 6 hour before examination. The blood glucose level was measured before ^{18}F-FDG intravenous injection. The blood glucose levels of all patients were less than 150 mg/dL (mean, 104 ± 17 mg/dL). ^{18}F-FDG was injected with calculated dose of 0.14 mCi/kg. Each patient received 227.55-455.47 MBq (6.15-12.31 mCi) of ^{18}F-FDG administration intravenously. After tracer injection, the patients rested on the bed in an isolated room. PET/CT whole-body emission scans were obtained 60 minutes after injection of the ^{18}F-FDG. CT was performed before acquisition of the PET data in a single step with the patient supine. The scanning protocol for whole-body CT craniocaudal scanning was 120 keV, effective 120 mAs, 5-mm collimation and pitch of 0.75. Then, a dual-slice lutetium oxyorthosilicate PET scanner was used to acquire 3-dimensional PET data included 6 to 8 bed positions, (3 minutes per bed position) over the same axial extent. The helical CT scan was reconstructed by filtered back projection to match the PET scan.

CT images were used to produce attenuation correction values for the PET images. PET images were reconstructed using four iterative and eight subiteric reconstructions.

^{18}F-FDG PET/CT analysis

^{18}F-FDG PET/CT images were visually interpreted by experienced nuclear medicine physicians in conjunction with radiologists. The ^{18}F-FDG PET images and CT images of PET/CT were jointly interpreted using image fusion workstation and a final consensus was reached for all patients. Abnormal uptake was defined as any focus of increased uptake greater than surrounding normal tissue or maximum of standardized uptake value (maxSUV) was $\geq$ 3.0. ^{18}F-FDG uptake was compared with the anatomic findings on CT. Area of physiologic increased ^{18}F-FDG uptake corresponding to normal structures were not recorded. Abnormally increased ^{18}F-FDG uptake corresponding to a CT abnormality were interpreted as positive. In addition, focally abnormal increased ^{18}F-FDG that did not correspond to structural finding was defined as positive. Suggestive abnormal findings on CT without abnormal increased ^{18}F-FDG uptake were defined as negative.

The ^{18}F-FDG PET/CT results were correlated with patient follow-up information, which included the results from histologic examination of surgical specimens, subsequent imaging modalities such as neck ultrasound, CT of neck and chest and TgAb levels. The findings were classified as follow.

True-positive lesions: if positive findings on ^{18}F-FDG PET/CT were confirmed by the presence of thyroid carcinoma on histologic examination or were confirmed by persistent abnormal or increasing antithyroglobulin levels corresponding with abnormal in other imaging modality.

False-positive lesions: if biopsy sample of suggestive lesions were negative for carcinoma on histologic examination or the other images modality showed stable status or resolved on subsequent follow-up.

True-negative lesions: if negative ^{18}F-FDG PET/CT results and patients had decreased TgAb levels without any treatment with other imaging modalities such as CT chest, neck, and bone scan show negative results.

False-negative lesions: if negative ^{18}F-FDG PET/CT results but patients had metastatic thyroid cancer on pathologic examination or progression was seen on other imaging modalities with persistent abnormal TgAb.

Statistical analysis

Sensitivity, specificity, accuracy were calculated for ^{18}F-FDG PET/CT for all patients. Additional receiver operating characteristic (ROC) analyses were performed to evaluate the cut off point for serum TgAb that caused true positive result analyses on ^{18}F-FDG PET/CT and cut off SUV (standard uptake value) that represent recurrent or metastasis thyroid carcinoma. All statistical were calculated with SPSS version 17.0.

Ethics review

The present study protocol was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Results

In 22 patients, findings of ^{18}F-FDG PET/CT were positive in 12 patients (54.5%) and negative in 10 patients (45.5%). ^{18}F-FDG PET/CT findings were true-positive in six of 12 patients. All of true-positive patients were confirmed by histologic examination of surgical biopsy specimens. In the true positive group, six patients had local recurrences or lymph node metastases at the neck and two of them had both local and distant metastasis (Fig. 1).

The findings of ^{18}F-FDG PET/CT were false-positive in six patients. Two patients were histologicaly confirmed as negative for malignancy and one patient had an inconclusive pathological report but follow-up imaging ultrasound and CT of neck showed no progression of disease. The remaining three patients showed decreased serum TgAb and no progression of disease on follow-up imaging.

The finding of ^{18}F-FDG PET/CT were true-negative in all 10 patients with negative PET/CT findings. Two patients were pathologically confirmed as negative for malignancy. On follow-up, six patients had negative imaging such as ultrasound, CT, bone scan and two patients had decreasing or negative levels of TgAb during follow-up. No false-negative patient was demonstrable on the present study.

Discussion

^{18}F-FDG PET/CT is considered in DTC patients who have elevated serum thyroglobulin but ^{131}I WBS showed negative results. The presence of TgAb, even in low concentration may cause Tg underestimation[8]. Persistently elevated TgAb levels appear to serve as a useful marker for recurrent or persistent DTC in patients with undetectable serum Tg results[9]. In the present study, the authors would like to explore the utility of ^{18}F-FDG PET/CT for detecting and localizing recurrent or metastatic lesions in DTC

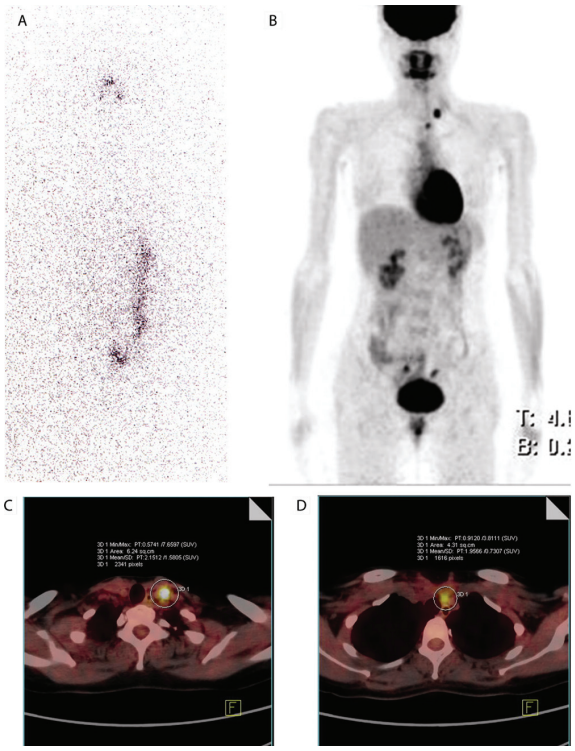

Fig. 1 A 47-years-old woman with history of papillary thyroid carcinoma presented with thyroglobulin level of < 0.1 ng/ml (TSH suppressed), antithyroglobulin level of 462.3 IU/ml and negative findings on ^{131}I WBS (A). ^{18}F-FDG PET/CT (B) demonstrated two hypermetabolic nodes at the left supraclavicular (C) and high mediastinum (D). The histology of these two hypermetabolic nodes were subsequently proven to be metastatic nodes from thyroid cancer

patients who had negative ^{131}I WBS scan, negative Tg levels but elevated TgAb levels. The overall sensitivity, specificity, and accuracy were 100%, 62.5%, and 72.7%, respectively.

The sensitivity in the present study may be over estimated due to the small population. No false negatives were detected. A future large population study should be carried out for sensitivity.

Specificity of the present study was lower than the median in literature review reported in DTC patients who had elevated serum thyroglobulin but ^{131}I WBS showed negative results (median specificity 78%)[13]. The low specificity may be related to ability of Tg levels to represent persistent or recurrent DTC at higher specificity than TgAb level.

Receiver operating characteristic (ROC) analyses were performed to evaluate the appropriated cut off point of TgAb levels for sending the patient to perform ^{18}F-FDG PET/CT imaging (prefer true positive result).

The ROC analysis (Fig. 2 and Table 2) shows TgAb levels, which are appropriated for sending DTC patients with ^{131}I WBS negatives, negative Tg measurements but presenting with high serum TgAb level to perform ^{18}F-FDG PET/CT imaging should be more than or equal to 414.6 IU/ml. In additionally, the authors searched for optimal maxSUV cut off at region of interest (ROI) which is highest sensitivity to detect recurrent or metastasis DTC.

From the ROC analysis (Fig. 3, Table 3) shows, ^{18}F-FDG PET/CT is an excellent test for separating

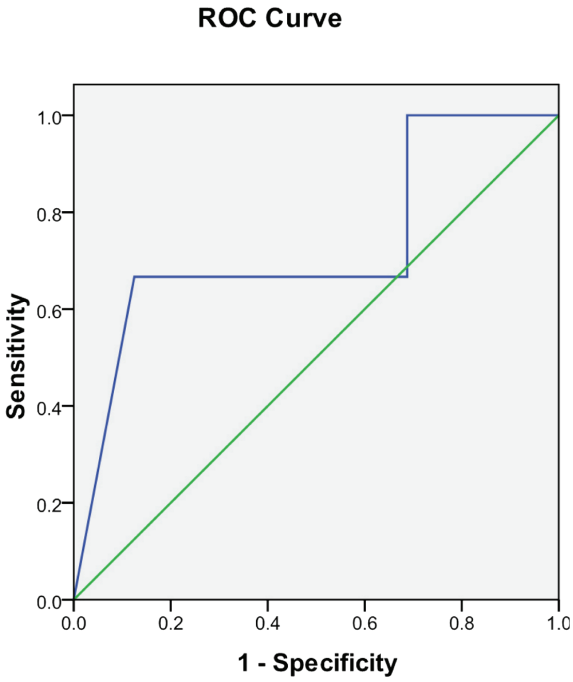

Fig. 2 ROC curve of TgAb and true-positive result from ^{18}F-FDG PET/CT

Table 2. Coordinates of the curve

Positive if greater than or equal to (IU/ml)	Sensitivity	1-Specificity
352.900	1.000	0.750
414.600	1.000	0.688
461.150	0.833	0.688
541.050	0.677	0.688

Test result variable(s): TgAb

disease (area under ROC curve 0.953) with optimal maxSUV cut off is equal or greater than 4.5, which is high sensitivity (100%) and specificity (87.5%).

Conclusion

The authors' result showed that ^{18}F-FDG PET/CT can be used to detect recurrent or metastases in DTC patients, who had negative ^{131}I WBS and Tg measurement but elevated serum TgAb levels. The authors recommend its use in cases where serum TgAb level is equal or higher than 414.6 IU/ml. It should be considered positive if maxSUV value is equal or greater than 4.5.

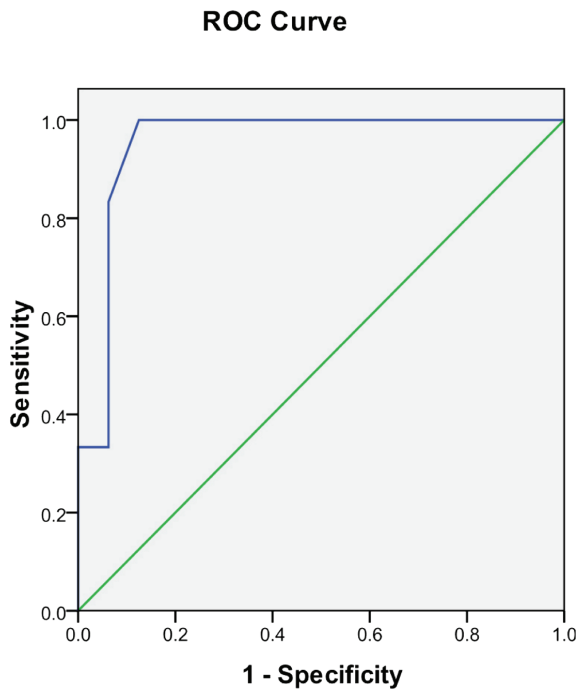

Fig. 3 ROC curve of SUV and true-positive result from ^{18}F-FDG PET/CT

Table 3. Coordinates of the curve

Positive if greater than or equal to (IU/ml)	Sensitivity	1-Specificity
4.150	1.000	0.188
4.500	1.000	0.125
4.650	0.833	0.063
4.900	0.677	0.063

Test result variable(s): max SUV
SUV = standard uptake value

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Potential conflicts of interest

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การศึกษาประโยชน์ของการตรวจแพท/ซีที (^{18}F-FDG PET/CT) ในผู้ป่วยมะเร็งไทรอยด์ชนิด well differentiated ที่มีระดับ antithyroglobulin antibody ในเลือดสูงผิดปกติ

คนึงนิจ กิ่งเพชร, รัชพงษ์ พิพัฒรัตนะ, สุภัทรพร เทพมงคล, ศศิธร ศิริสาลิโภชน์, ธวัชชัย ชัยวัฒนรัตน์

วัตถุประสงค์: *เพื่อศึกษาถึงประโยชน์ของ ^{18}F-FDG PET/CT ในการติดตามการรักษาผู้ป่วยมะเร็งไทรอยด์ชนิด well differentiated ที่มีผลการสแกนทั่วร่างกายด้วยสารเภสัชรังสีไอโอดีน-131 และระดับ thyroglobulin ในเลือดปกติ แต่มีระดับ antithyroglobulin antibody ในเลือดสูงผิดปกติ ซึ่งเป็นปัญหาที่พบได้บ่อยและมีความสำคัญในการตัดสินใจให้การรักษา*

วัสดุและวิธีการ: *การศึกษานี้ได้กระทำในผู้ป่วยมะเร็งไทรอยด์ชนิด well differentiated จำนวน 22 ราย ที่มีผลการสแกนทั่วร่างกายด้วยสารเภสัชรังสีไอโอดีน-131 และระดับ thyroglobulin ในเลือดปกติแต่มีระดับ antithyroglobulin antibody ในเลือดสูงผิดปกติ (คือมีระดับสูงมากกว่า 200 IU/ml) ผู้ป่วยจะได้รับการตรวจ PET/CT ซึ่งทำโดยฉีดสารเภสัชรังสี ^{18}F-FDG (0.14 mCi/kg) เข้าทางหลอดเลือดดำหลังจากนั้น 60 นาที ผู้ป่วยจะได้รับการถ่ายภาพด้วยเครื่อง PET/CT โดยภาพจาก CT จะช่วยบอกตำแหน่งของพยาธิสภาพได้ถูกต้องแม่นยำขึ้น ผลการตรวจที่ได้จะถูกนำไปเปรียบเทียบเพื่อหาความถูกต้องกับผลชิ้นเนื้อ หรือ การติดตามการรักษาด้วยการตรวจทางรังสีวินิจฉัยและอาการแสดงของผู้ป่วย*

ผลการศึกษา: *ผู้ป่วยมะเร็งไทรอยด์ชนิด well differentiated จำนวน 22 ราย ผลการศึกษาพบว่ามีผู้ป่วยจำนวน 12 ราย ที่ผลการตรวจ ^{18}F-FDG PET/CT ให้ผลบวก (พบความผิดปกติ) โดยในผู้ป่วยกลุ่มนี้มีจำนวน 6 ราย ที่เป็นผลบวกจริง และอีก 6 ราย เป็นผลบวกเท็จ ส่วนกลุ่มผู้ป่วยที่ผลการตรวจ ^{18}F-FDG PET/CT ให้ผลลบ (ไม่พบความผิดปกติ) จำนวน 10 ราย พบว่าทั้งหมดเป็นผลลบจริงโดยไม่พบผลลบลวงในงานวิจัยนี้ ความไว ความจำเพาะ และความแม่นยำ ของการตรวจ ^{18}F-FDG PET/CT ในงานวิจัยนี้คือ ร้อยละ 100, ร้อยละ 62.5 และร้อยละ 72.7 ตามลำดับ จากการวิเคราะห์ด้วยกราฟ ROC พบว่า ระดับ antithyroglobulin antibody ที่เหมาะสมในการพิจารณาส่งผู้ป่วยเข้ารับการตรวจ ^{18}F-FDG PET/CT คือ มากกว่าหรือเท่ากับ 414.6 IU/ml และพบว่าตำแหน่งที่มีค่า max SUV มากกว่าหรือเท่ากับ 4.5 จะมีโอกาสสูงที่จะเป็นตำแหน่งของความผิดปกติที่มีการกลับเป็นซ้ำ หรือ การกระจายของมะเร็งไทรอยด์ชนิด well differentiated*

สรุป: *การตรวจ ^{18}F-FDG PET/CT นั้นมีประโยชน์ในผู้ป่วยมะเร็งไทรอยด์ชนิด well differentiated ที่มีผลการสแกนทั่วร่างกายด้วยสารเภสัชรังสีไอโอดีนและระดับ thyroglobulin ในเลือดปกติแต่มีระดับ antithyroglobulin antibody ในเลือดสูงผิดปกติ ทั้งในการหาตำแหน่งการกลับเป็นซ้ำหรือการกระจายของโรค โดยระดับ antithyroglobulin antibody ในเลือดที่เหมาะสมในการพิจารณาส่งผู้ป่วยมารับการตรวจ ^{18}F-FDG PET/CT คือมากกว่าหรือเท่ากับ 414.6 IU/ml*