Initial experience in use of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography in thyroid carcinoma patients with elevated serum thyroglobulin but negative iodine-131 whole body scans

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ABSTRACT

Introduction: This study aims to examine the usefulness of fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in thyroid carcinoma patients with elevated serum thyroglobulin (Tg) but negative iodine-131 (I-131) whole body scans.

Methods: 17 patients with differentiated thyroid carcinoma who underwent FDG PET/CT scans were reviewed retrospectively over a period of one year from July 2003 to June 2004. All these patients had completion thyroidectomy and subsequently presented with elevated serum Tg but negative post-therapy I-131 whole body scans. Nine of these patients underwent FDG PET/CT in a hypothyroid state, while the remainder underwent FDG PET/CT while on thyroxine replacement.

Results: 15 out of 17 PET/CT scans revealed lesions consistent with metastases, giving a sensitivity of 88.2 precent. Four of these patients were amendable to surgical treatment. Two scans were negative.

Conclusion: FDG PET/CT is a sensitive diagnostic tool to detect radioiodine-negative recurrences/metastases in patients with thyroid carcinoma. Our preliminary results are comparable with published results based on PET.

Keywords: computed tomography, fluorine-18-fluorodeoxyglucose, positron emission tomography, thyroglobulin, thyroid cancer

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INTRODUCTION

Thyroid carcinoma is an uncommon disease in Singapore, accounting for 1% of all cancers among the Singaporean males and about 3% of all cancers among the Singaporean females. The majority of thyroid cancers (90%) in Singapore are due to differentiated thyroid carcinoma (DTC), either papillary or follicular types[1]. A significant number of these patients undergo total thyroidectomy followed by iodine-131 (I-131) ablation. Follow-up of these patients include periodic I-131 whole body scans (WBS) and serial serum thyroglobulin (Tg) measurements, with the aim of detecting either local recurrence or distant metastases[2,3].

There is an excellent correlation between the Tg levels (in the absence of thyroglobulin autoantibody) and persistence of disease. In most cases, undetectable Tg levels suggest absence of either thyroid tissue or distant metastases[2-4]. An elevated serum Tg suggests disease, and is usually associated with an abnormal I-131 WBS, with either local recurrence or distant metastases. However, discordant results between I-131 WBS and serum thyroglobulin have been encountered. In particular, approximately 15-20% of patients with high serum Tg have negative I-131 diagnostic WBS[5,6]. These false-negative scans may be due to the low dose of iodine administered (diagnostic dose), presence of tumour deposits too small to be detected by a scintillation camera, or loss of iodine concentration as a result of tumour dedifferentiation.

Several recent studies have shown that fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) can be used to detect local recurrences and distant metastases of thyroid carcinoma, especially in those patients who present with high serum Tg but negative I-131 WBS[6-8]. The aim of this study is assess the sensitivity of detecting thyroid cancer local recurrence and distant metastases using FDG positron emission tomography/computed tomography (PET/CT) in patients with elevated serum Tg but negative I-131 post-therapeutic WBS.

METHODS

This retrospective study recruited 17 patients (11 females and six males) for FDG PET/CT over a period of one year from July 2003 to June 2004. The average age of these patients was 53.7 years. All these patients have a history of DTC and were previously treated with total thyroidectomy and at least one dose of I-131 for thyroid ablation (minimum of 1.1 gigabecquerels [GBq]).

Table I. Demographical characteristics and results summary of thyroid carcinoma patients.

No.	Gender	Age	Cell type	TSH	PET/CT findings	Remarks
1	F	51	Papillary	Suppressed	Lung metastases, local recurrence, cervical nodes	
2	F	60	Papillary	Raised	Negative	
3	M	64	Papillary	Suppressed	Bone metastases	
4	F	73	Papillary	Suppressed	Lung metastases	
5	F	65	Papillary	Suppressed	Local recurrence, left cervical node	Excision of lesions
6	M	37	Papillary	Raised	Left supraclavicular and retrosternal nodes	
7	F	83	Papillary	Suppressed	Left cervical nodes	
8	M	42	Follicular	Raised	Anterior mediastinium metastasis eroding the sternum	Excision of lesions
9	M	47	Hurthler's cell	Raised	Local recurrence and suprasternal notch node	Excision of lesions
10	M	40	Papillary	Raised	Lung metastases	
11	F	38	Papillary	Raised	Bilateral cervical nodes, lung metastases	
12	F	52	Papillary	Raised	Local recurrence, left cervical nodes	
13	F	47	Papillary	Suppressed	Left cervical nodes	Excision of lesions
14	F	60	Papillary	Raised	Lung metastases, right cervical nodes	
15	F	35	Papillary	Suppressed	Left cervical node	
16	M	58	Papillary	Raised	Negative	
17	F	61	Papillary	Suppressed	Lung metastases, pelvic nodes	

Serial monitoring was carried out using serum Tg measurements and WBS. Both the WBS and Tg level were performed after a month of L-thyroxine withdrawal. The WBS was performed 3-4 days after at least a minimum ablative dose of radioiodine (post-therapy WBS), using a dual-head large-field gamma camera equipped with high-energy collimators. WBS results were deemed negative when there was absence of a clear focus of abnormal I-131 uptake by visual inspection of the scan.

Serum Tg as well as anti-Tg antibody levels were determined by radioimmunoassay using commercial kits (BRAHMS Tg-plus DYNOtest and BRAHMS anti-Tgn DYNOtest). As there is no universal agreement on specific cut-off levels, we defined serum Tg levels as abnormal if levels were >10ug/L when TSH was elevated and >1 ug/L when TSH was suppressed[3]. All our patients did not have elevated thyroglobulin antibodies.

PET imaging was done with a dedicated PET/CT scanner (Siemens Biograph LSO, Erlangen, Germany). The PET/CT study was timed as close to the I-131 WBS as possible with all but two cases performed within three months. The remaining two cases were performed within a one year time frame. PET/CT imaging was performed 50-70 minutes after intravenous administration of FDG. Standard patient preparation included at least six hours of fasting and a serum glucose level of less than 120mg/dL before tracer injection. Fasting is necessary to minimise competitive inhibition of FDG uptake by high blood glucose. The administered dose of FDG was between 333 to 444 MBq.

Unenhanced CT scans (110 mAs, 130 kV) were obtained for the purpose of attenuation correction and anatomical localisation. Emission scanning was performed from the base of skull to the femur for three minutes at each bed position. Total time taken for PET scan is about 21 minutes (7 bed positions). Images were viewed in the coronal, transaxial and sagittal planes on a computer monitor screen that allows co-registration of all three orthogonal views. The PET/CT images were independently reviewed by two nuclear medicine physicians and any disagreement was resolved by consensus. A visually-abnormal FDG PET/CT finding was defined as a focal FDG uptake relatively higher than that of the surrounding tissue and which corresponds to a recognised anatomical structure on the CT image.

RESULTS

In our group of patients with elevated serum Tg but negative I-131 WBS, PET/CT identified lesions in 15 out of 17 patients, giving a sensitivity of 88.2% (Table I). Eight out of the 15 patients showed limited loco-regional disease. This is defined as disease limited to local recurrence and/or cervical/mediastinal lymph nodes. Four of these eight patients have undergone surgery and all these four have histological confirmation of DTC disease (Figs. 1a, 1b and 2). The remaining seven patients showed distant metastases, consisting of six patients with lung metastases and one patient with bone metastases (Figs. 3a and 3b). Two patients were deemed to have negative FDG PET/CT scans, i.e. no abnormal focal FDG uptake was detected.

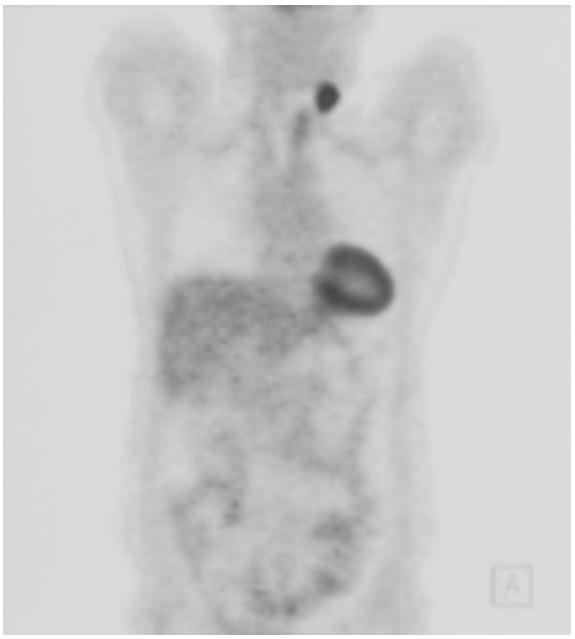

Fig. 1a Case 5. PET image of a hypermetabolic left cervical lymph node in a 65-year-old woman. This lesion was surgically removed and histologically proven to be papillary carcinoma.

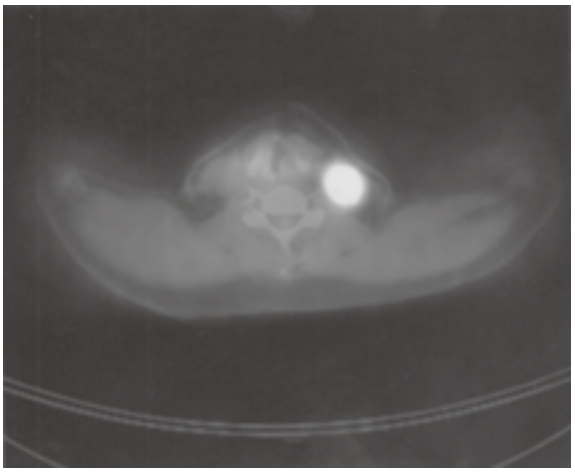

Fig. 1b PET/CT fusion image of the same lesion in Fig. 1a.

DISCUSSION

For many years before the advent of FDG PET, localisation of thyroid cancer recurrences/metastases that do not accumulate radioiodine was largely based on conventional structural imaging such as ultrasonography, CT, and magnetic resonance imaging. But these methods are often of limited value in the post-thyroidectomy patients due to the difficulties in discriminating local recurrence from scar tissue in cases of altered anatomy, particularly after neck dissection.

Several nuclear medicine approaches using tumour-seeking radiopharmaceuticals, such as technetium-99m sestamibi and thallium-201, have also been applied and have a certain degree of success. In particular, technetium-99m sestamibi has been found to be useful in detecting cervical

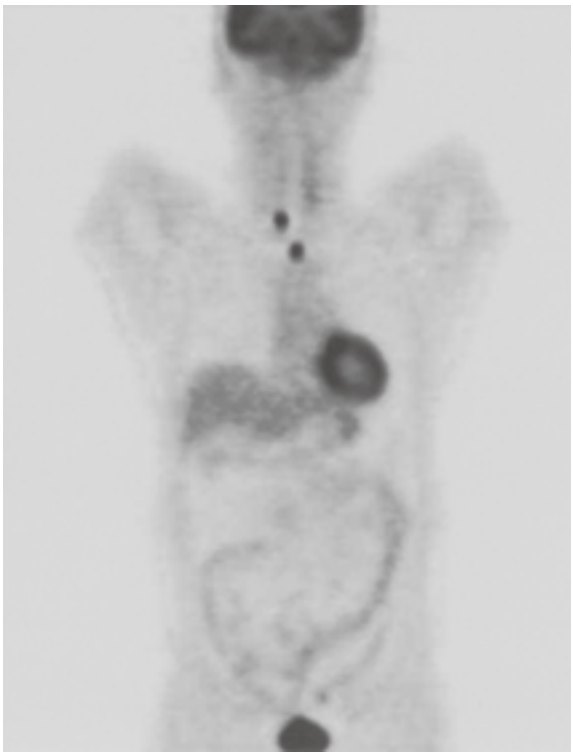

Fig. 2 Case 9. PET image of hypermetabolic local recurrence and suprasternal notch lymph node disease in a 47-year-old man with Hurthle's disease. Histological correlation showed follicular carcinoma.

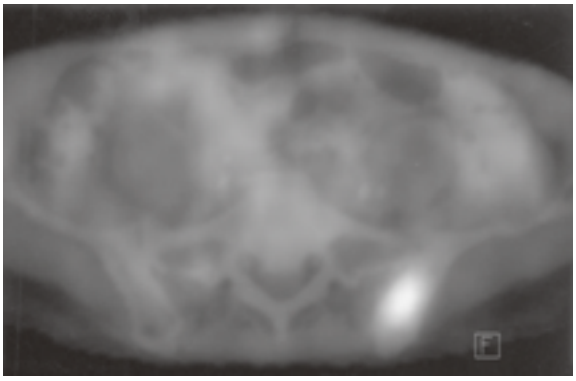

Fig. 3a Case 3. PET/CT fusion image of a hypermetabolic metastasis in the left iliac bone in a 64-year-old man with papillary cell thyroid carcinoma. Several bony metastases involving the vertebrae and ribs are also present (not shown).

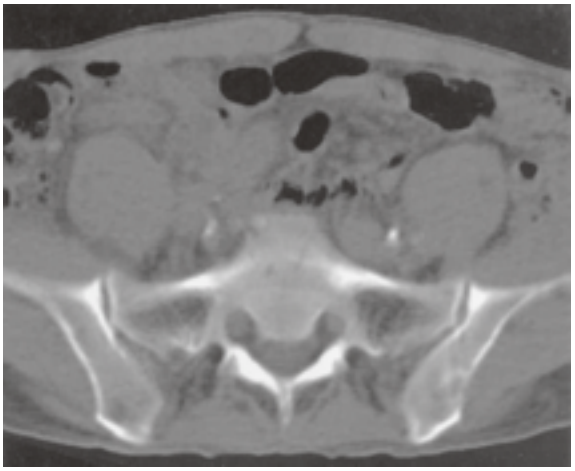

Fig. 3b CT (bone window) of the same patient as in Fig. 3a shows a corresponding lytic lesion in the left iliac bone.

lymph node disease[9]. These conventional gamma camera-based techniques however suffer from technical (resolution) as well as sensitivity limitations.

FDG PET has been used as a tumour-seeking agent for various cancers for many years. However, the major studies that first identified its use in thyroid cancer appeared in the mid-1990s. Feine et al[7], in a study of 33 patients, calculated a sensitivity of 94% for FDG PET in patients with elevated serum Tg but negative I-131 WBS. At the same time, iodine-avid lesions are found to have low or no FDG uptake. Other investigators (all using PET only scanners) have quoted sensitivity of 71% (study of 18 patients)[6] and 89% (study of 37 patients)[10], with a median sensitivity of 77% according to a recent review article[11]. Our results are in concordance with these studies.

The clinical significance of FDG PET imaging in this category of patients lies in the fact that these lesions do not concentrate iodine and are thus often not amenable to radioiodine therapy. This peculiar molecular behaviour was first described by Feine et al[7] as the flip-flop phenomenon. The functionally more differentiated thyroid carcinoma cells retain their iodine trapping mechanism and have low glucose metabolism while the dedifferentiated thyroid carcinoma cells lose their iodine trapping mechanism and have high glucose metabolism. These lesions are therefore treated by surgery when possible, as seen in four of our patients. Other treatment modalities include empiric radioiodine therapy, focused external beam radiation, dedifferentiation therapy or continued TSH suppression.

As these patients often require surgery, precise locations of these lesions are of utmost importance. The CT component of a hybrid PET/CT offers precise anatomical localisation, creating a one-stop diagnostic tool that combines functional information with anatomical details. A PET alone scanner would often require patients to undergo CT scanning on separate occasions. Subsequent correlation between PET lesions and CT structures would be done either visually or software fusion, in which inaccuracies, such as those due to motion, can occur.

The advent of PET/CT, with the information provided by the CT allows for immediate and precise localisation of these lesions. Conversely, the use of conventional imaging alone such as ultrasonography and CT does not provide functional information. The advantages of PET/CT are seen in its ability to detect metabolically-active tissue from scar tissue as well as detecting disease in lymph nodes that are not enlarged. However, to the authors' knowledge, there is no randomised trial comparing PET/CT to either contrast-enhanced CT or magnetic resonance imaging.

The role of thyroid stimulating hormone has been alluded to by various authors and has remained controversial[6,7,11-13]. Earlier studies by Feine et al[7] and Wang et al[6] did not find a clinically – significant difference in FDG uptake in both euthyroid and hypothyroid states. Recent studies by Moog et al[12] and Petrich et al[12] have however detected significant increase in FDG uptake in scans done with TSH stimulation compared to scans done without TSH stimulation, and have recommended that FDG PET/CT be carried out under conditions of TSH stimulation.

In our study, slightly more than one-half of our patients (nine out of 17) underwent PET/CT imaging in hypothyroid condition, while the remaining patients were under thyroxine suppression. We did not detect any significant difference in the detection rate of metastatic lesions between these two groups of patients. Both our PET-negative cases were in hypothyroid state. Statistical significance however cannot be reached due to the small sample size.

In conclusion, our study shows that FDG PET/CT can detect radioiodine-negative recurrences/metastases in thyroid carcinoma patients. Our preliminary results are comparable with published results based on PET. However, as a substantial proportion of iodine-avid lesions are not FDG-avid, FDG PET/CT is not recommended as a substitute for I-131 WBS. Instead, the role of FDG PET/CT is most valuable as a complementary test for the specific group of patients with elevated Tg but negative WBS. Future investigations with a larger study number and longer follow-up should further confirm these findings, as well as clarify issues such as the role of elevated TSH prior to PET/CT scanning in DTC patients.

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