CLINICAL STUDY

The role of F-18-fluorodeoxyglucose positron emission tomography in the postoperative evaluation of differentiated thyroid cancer

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Abstract

Objectives: The objective of the study was to compare F-18-fluorodeoxyglucose position emission tomography (FDG-PET) with diagnostic whole body scanning (DxWBS) and post-ablation radioiodine whole body scanning (TxWBS) and to assess its prognostic value in newly diagnosed differentiated thyroid cancer (DTC) patients, hypothesizing that FDG-PET is more likely to disclose locoregional and distant metastases.

Patients and methods: DxWBS and FDG-PET scanning were performed in 26 newly diagnosed DTC patients who underwent thyroidectomy and TxWBS in 24 cases who had radioactive iodine ablation. The results of the FDG-PET scans were correlated with the stage of the disease and the long-term outcome of DTC.

Results: Overall, 18 FDG-PET scans (69.2%) were positive showing a total of 40 foci while 8 scans (30.8%) were negative. The corresponding 26 DxWBS were all positive and showed a total of 47 foci. DxWBS and TxWBS showed similar foci in the 24 patients who had ablation therapy. In contrast to the FDG-PET scans that showed uptake of 26 foci (65%) outside the thyroid bed, 45 foci (95.7%) on DxWBS were in the thyroid bed while 2 foci (4.3%) were in cervical lymph nodes and no focus was seen outside the neck area ($P=0.000$). There was a clear correlation between the FDG-PET results, the stage of the disease and long-term outcome; seven of the eight negative FDG-PET scans were in stage 1, while all patients with disease higher than stage 1 (six patients) had positive scans. Over a median of 30 months (10–48), seven out of eight patients (87.5%) with negative FDG-PET scans were in remission compared with only eight patients (44.4%) with positive FDG-PET ($P=0.04$).

Conclusions: In the postoperative evaluation of DTC, compared with DxWBS and TxWBS, FDG-PET scans are more likely to reveal uptake outside the thyroid bed and to correlate with the stage of the disease and long-term outcome.

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Introduction

Differentiated thyroid cancer (DTC) is generally considered a rare malignancy with good prognosis (1). However, its incidence has been increasing over the last decade (1, 2). The initial diagnosis depends largely on fine needle aspiration biopsy (3). The classical approach after establishing the cytological diagnosis is to proceed with total or near-total thyroidectomy (4). Following initial surgery, high-dose radioiodine-131 (I-131) is usually administered for thyroid remnant ablation (3–5). The objective of such ablation is to eradicate any residual thyroid tissue that may not have been removed surgically and to improve the accuracy of diagnostic whole body scanning (DxWBS) and serum

thyroglobulin (Tg) in the long-term follow-up (5). In addition, such therapy was shown to decrease long-term recurrence and mortality rates (6). Pre-therapy (DxWBS) and/or post-ablation therapy whole body scan (TxWBS) are usually performed. The aims of DxWBS and TxWBS are to define the extent of residual thyroid tissue and locoregional or distant metastases (5). In the presence of residual normal thyroid tissue, there is usually a preferential uptake of radioactive iodine (RAI) by this tissue and local or distant metastatic disease may be missed. F-18-fluorodeoxyglucose position emission tomography (FDG-PET) is a relatively new imaging technique. Its role in DTC has been most consistently demonstrated in the follow-up of patients, especially those with high Tg and a negative DxWBS (7–15). Its role in the postoperative evaluation of patients with DTC

has not been studied. In this study, we investigated the potential role of FDG-PET in the immediate post-operative evaluation of patients with DTC. In contrast to RAI, which is most avidly taken up by normal thyroid tissue, the uptake of FDG is more likely to be seen in the more metabolically active malignant tissue rather than in benign tissue (16). Therefore, we hypothesized that FDG-PET may be superior to DxWBS in disclosing lymph nodal or distant metastatic DTC in patients who have had surgery, but have not yet received RAI ablation. Therefore, FDG-PET could potentially play an important role in the initial staging of the disease. Furthermore, since positive FDG-PET scans were found previously to correlate with the prognosis in patients who were treated in the past (17, 18), we also aimed to investigate its potential prognostic value in DTC patients who have not yet received RAI, hypothesizing that those patients with positive FDG-PET following the initial surgery are more likely to continue to have persistent disease or develop recurrence or metastases during their follow-up.

Materials and methods

We performed conventional FDG-PET whole body scanning in 26 consecutive new DTC patients who had thyroid surgery but had not yet received RAI ablation. We compared the FDG-PET scans with DxWBS done in those 26 patients who had both scans. We also compared the FDG-PET scans with TxWBS in those patients who subsequently underwent RAI ablation (24 patients). In addition, we correlated the long-term outcome with the results of FDG-PET in all the 26 patients studied. All patients signed an informed written consent and the study was approved by the institutional review board.

Patients

We prospectively studied 26 consecutive patients who agreed to participate in the study (3 males and 23 females, median age 34 years, range 14–76 years) in the period between September 2003 and May 2005. Patients who refused to participate in the study, those with uncontrolled diabetes (blood sugar > 8 mmol/l, as high blood sugar may interfere with FDG uptake) and those with other known malignancy or inflammatory conditions were excluded. All patients underwent thyroidectomy at their local hospitals and were subsequently referred to our hospital for further management. After confirming the outside diagnosis of DTC by reviewing the histopathological specimens, L-thyroxine was discontinued for at least 5 weeks and triiodothyronine (cytomel) for at least 2 weeks in preparation for DxWBS, measurement of serum Tg, and FDG-PET scanning. The median Tg level was 23.9 ng/dl (range 2.9–2565) and the corresponding median TSH level was 133 U/l

(range, 59.5–501). Tg was measured using the sandwich technique with electrochemiluminescence immunoassay (Cobas, Roche Diagnostics GmbH, D-68298 Mannheim) with 0.1 ng/ml lower limit of detection, 1.4–78 ng/ml normal range in healthy subjects and 1.7 and 2.7% within-run and total coefficients of variation respectively. Overall, 23 cases underwent total or near-total thyroidectomy and unilateral (16 cases) or bilateral (7 cases) modified neck dissection, and three patients underwent total or near-total thyroidectomy without neck dissection. The final histopathological examination showed classic PTC in 24 patients, tall cell variant PTC in 1 patient and minimally invasive follicular thyroid cancer in 1 patient. Of the 23 patients who underwent unilateral or bilateral neck dissection, 16 patients (69.6%) had evidence of lymph node metastases. Twenty patients were in TNM stage I, 1 in stage II, 1 in stage III, 1 in stage IVa, 2 in stage IVc, and 1 could not be staged due to lack of information on tumor size and lymph nodes (the AJCC Cancer Staging Manual, Sixth Edition (2002), Springer-Verlag New York). Following surgery, two patients were not given I-131 ablation therapy (one had microscopic unifocal PTC confined to the thyroid and one patient refused I-131). Twenty four patients received I-131 ablation therapy (median activity 147 mCi (range 65–299.7)). The stage I and II disease with uptake limited to the thyroid bed received I-131 activity of 100 mCi or less, those with stage III or IV with thyroid bed uptake received activity of 100–150 mCi when the uptake was limited to the thyroid bed and 150–200 mCi when there was an uptake outside the thyroid bed. One patient (Fig. 1) received large activity of 299.7 mCi since the spinal metastasis was not taking up I-131 on DxWBS. During follow-up, six patients received additional therapies for persistent disease as follows: a second dose of I-131 therapy in two patients, a second dose of I-131 and additional surgeries in two patients, a second dose of I-131 and external beam radiotherapy in one patient and a second dose of I-131, surgery, and external beam radiotherapy in one patient. The primary tools that were used for the follow-up of these patients were the measurement of serum Tg (with concomitant measurement of anti-Tg antibodies) and DxWBS in addition to high-resolution ultrasonography. All patients except the two who did not receive I-131 had at least one follow-up withdrawal DxWBS with measurement of serum Tg. Discernable focal activity on the DxWBS with measurable uptake was considered positive. Lymph nodes that were oval in shape with fatty hila and no calcification or cystic formation were considered benign. In other situations, fine needle aspiration biopsy was done whenever feasible. The median follow-up period was 30 months (range, 10–48).

Fifteen patients (57.7%) achieved complete remission defined as a negative clinical examination, negative DxWBS, and a Tg level < 2 ng/dl off thyroid hormone therapy (TSH > 30 mU/l) with negative Tg autoantibodies

Figure 1 (A) Coronal and (B) sagittal views of the FDG-PET scan showing a hypermetabolic focus in the upper dorsal spine and another focus of less intensity at the left pericardial border. (C) A reconstruction CT scan of the dorsal spine shows a lytic lesion at T2 vertebral body. Biopsy of that lesion revealed metastatic papillary thyroid cancer. (D and E) The corresponding DxWBS shows an uptake limited to the thyroid bed only.

and negative ancillary imaging studies when done (high-resolution neck ultrasonography, CT scans of the neck and the chest, and FDG-PET scans). Nine patients (34.6%) continued to have evidence of persistent disease ($Tg \geq 2$ ng/dl off L-thyroxine, positive DxWBS, and/or positive fine needle aspiration biopsy of neck ultrasonographic findings) and two patients (7.6%) had progression of the disease with development of new distant metastases.

Pre-ablation (DxWBS) and post-ablation (TxWBS) whole body scanning

Patients were kept off thyroid hormone therapy as described above. They were also prescribed a low-iodine diet for at least 1 week before scanning. Patients had not had any contrast-enhanced study for at least 3 months prior to DxWBS. At our institution, we routinely use I^{123} isotope for DxWBS and we have previously demonstrated its comparability to I-131 isotope (19). In all the 24 patients who underwent I-131 remnant ablation, TxWBS were similar to DxWBS without additional foci. Patients were given 10 mCi of I-131 in the form of oral solution. Whole body scanning was done 24 h later using gamma camera. TxWBS was done 3–5 days after RAI ablation therapy. Planar whole body scans as well as dedicated films of the neck and chest regions were obtained for each patient.

FDG-PET scanning

All FDG-PET scans were performed while patients were off thyroid hormone therapy. Patients fasted for at least 8 h before scanning. Capillary blood sugar testing was done before scanning and patients with blood sugar > 8 mmol/l were excluded. Images were obtained with an ECAT EXACT camera (CTI, Knoxville, TN, USA) using a full-width at half-maximum of 4.5 mm and a transaxial field of view of 15 cm. After i.v. administration of 10 mCi (370 MBq) FDG, the patients were kept at rest in a quiet,

dimly lit room for at least 40 min. The patients were scanned while lying supine along the central axis of the PET table. Seven sequential emission images were obtained from the head to the upper thigh, requiring 56 min using a two-dimensional mode. Transmission scans were obtained with ^{68}Ge rod sources for attenuation correction (3 min per bed position). The emission and transmission scans were obtained in an alternating sequence per bed position. Reconstruction of both the transmission and emission scans was performed using accelerated maximum-likelihood reconstruction and ordered subset expectation maximization (two iterations, eight subsets). Standardized uptake values (SUVs) were calculated as the ratio of the regional radioactivity concentration divided by the injected amount of radioactivity normalized to body weight. The average SUV in all the suspected lesions were measured with a region-of-interest technique.

The FDG-PET scans, DxWBS and TxWBS were interpreted independently and at different points in time by two trained qualified nuclear medicine radiologists (A R and A A). When disagreement arises, a review by a third nuclear medicine radiologist (M A) was obtained and a consensus was reached. The FDG-PET scans were compared with DxWBS (and TxWBS in 24 patients) in terms of sites and number of foci of uptake and the concordance rate between scans was calculated.

Statistical analysis

Comparison of the FDG-PET scans with DxWBS was carried out in terms of the sites and number of foci of uptake. The χ^2 test was used to compare the proportions of foci of uptake outside the thyroid bed between the two types of scans. The long-term outcome of those patients with positive FDG-PET scans was compared with the outcome of those patients with negative FDG-PET scans using Fisher's Exact test. $P < 0.05$ was considered significant.

Results

Comparison of FDG-PET with DxWBS and TxWBS

In all the 24 cases who received RAI ablation, the TxWBS were similar to DxWBS in terms of sites and number of lesions, though some lesions were better visualized on TxWBS. Therefore, the comparison of FDG-PET is the same for DxWBS and TxWBS. Of the 26 FDG-PET scans, 18 scans (69.2%) were positive while 8 scans (30.8%) were negative. A total of 40 foci were seen in the 18 positive FDG-PET scans (thyroid bed, 14; cervical lymph nodes, 15; lungs, 1; bone, 1; axillae, 7; and breast, 2). The median SUV was 3.7 (1.4–12.2). The corresponding DxWBS showed a total of 47 foci. The 24 TxWBS showed 45 lesions (each of the two patients who were not treated with RAI had one focus on DxWBS). In contrast to the uptake on FDG-PET that showed uptake of 26 foci (65%) outside the thyroid bed, 45 foci (95.7%) on DxWBS were in the thyroid bed while 2 foci (4.3%) were in cervical lymph nodes and no focus was seen outside the neck area ($P=0.0000$). Table 1 summarizes the sites of uptake by patients in the FDG-PET and the DxWBS scans.

Of the 26 FDG-PET and DxWBS scan pairs, only 3 pairs (11.5%) were identical, showing the same foci in both sites. Two scan pairs (7.7%) showed uptake in the same sites, but with more foci on DxWBS than on the FDG-PET scans. In seven scan pairs (26.9%), the FDG-PET scans showed the same foci seen on DxWBS in addition to foci in other areas. In 14 cases (53.9%), the scan pairs were completely discordant, showing foci in different locations.

FDG-PET uptake outside the neck region

Of the 26 patients studied, 4 patients (15.3%) had FDG-PET uptake outside the neck region as follows: lungs and dorsal spine (1 patient; Fig. 1), breast (1 patient)

and axillae (2 patients). Biopsies were obtained from one of the two patients with axillary uptake and showed granulomatous lymphadenitis; fungal and tuberculosis stains and cultures were negative (Fig. 2). In the second patient, biopsy was not done because the uptake was too faint (maximum SUV 1.4) and ultrasound of the axilla showed only small benign-looking lymph nodes. In the patient with breast uptake, fine needle aspiration biopsy of a corresponding 1.5 cm nodule seen on ultrasonography showed that only fat necrosis and mammography was negative. In contrast, the patient with lung and dorsal spine uptake underwent biopsy of a dorsal spine vertebra and that confirmed the presence of metastatic papillary thyroid cancer (Fig. 1).

Prognostic value of the FDG-PET scans

The FDG-PET scans were more likely to be positive in higher stage disease; of the 18 cases with positive FDG-PET, 13 were in stage I, one in stage II, one in stage III, one in stage IVa, and two in stage IVc. In contrast, all eight cases with negative FDG-PET scans were in stage 1 except one patient who could not be staged due to lack of information. Furthermore, patients with negative FDG-PET were more likely to achieve remission than those with positive FDG-PET scans; over a median follow-up period of 30 months (range 10–48), only 8 out of 18 patients (44.4%) with positive FDG-PET were in remission while 8 patients (44.4%) had evidence of persistent disease and 2 patients (11.2%) had progression of their disease (Table 2). The median Tg level in those with persistent disease was 21 ng/ml (range 13.3–167 ng/ml) and in those with progression, Tg was 734 ng/ml and > 5000 ng/ml. In contrast, seven out of eight cases (87.5%) with negative FDG-PET scans were in remission (Tg 0–1.4 ng/ml with negative imaging studies) and only one case had persistent disease with Tg of 16.7 ng/ml ($P=0.04$).

Discussion

In this study, we investigated the potential role of FDG-PET scanning in the initial evaluation of patients with DTC. Our motive was the fact that aggressive forms of thyroid cancer are more likely to metastasize and at the same time to be more metabolically active and therefore to take up FDG and be seen on FDG-PET whole body scanning (16–18, 20). On the other hand, cells of high-grade tumors usually lose some of their differentiated functions such as uptake of iodine and therefore are likely to be missed on DxWBS and TxWBS (16). In that respect, FDG-PET could play an important role in the staging of aggressive DTC and may affect the choice and intensity of management options. For example, disclosure of a distant metastasis that may have been missed on the conventional RAI whole body scan may indicate the need for surgical removal if feasible, or administration of external

Table 1 Sites of uptake by patients in F-18-fluorodeoxyglucose position emission tomography (FDG-PET) and diagnostic whole body scanning (DxWBS) scan pairs done in 26 patients with differentiated thyroid cancer (DTC).

Location	FDG-PET (no. of patients)	DxWBS (no. of patients)
Thyroid bed alone	8	22
CLN alone	4	
Thyroid bed and CLN	2	2
Thyroid bed, CLN, and axilla	1	
CLN, lungs, and bone	1	
CLN and axilla	1	
CLN and breasts	1	
Negative	8	2
Total	26	26

CLN, cervical lymph nodes.

Figure 2 (A) FDG-PET whole body scan shows two hypermetabolic foci in the right upper neck (arrows). FNA of cervical lymph nodes at this site revealed metastatic PTC. There is also another focus of less intensity in the left mid-neck and three additional foci of uptake in the left axilla (arrows), better seen on (B). Excision biopsy of a left axillary lymph node revealed a necrotizing granuloma without evidence of malignancy. (C and D). The corresponding DxWBS shows a significant uptake limited to the thyroid bed area.

beam radiotherapy or higher doses of RAI. In contrast to DxWBS and TxWBS, which were mostly positive in the thyroid bed area, we have demonstrated that the FDG-PET scans were more likely to reveal foci of uptake in locations outside the thyroid bed. While most of the foci were in cervical lymph nodes, FDG-PET also showed foci outside the neck area including lungs, bone, mediastinum, and others. Some of these foci could be false positive uptake as demonstrated in some cases; in some other cases, FDG-PET was crucial in demonstrating metastatic disease. For example, in one patient with a high-grade tumor, the DxWBS and the TxWBS revealed an uptake that was limited to the thyroid bed while FDG-PET revealed a significant focus in the dorsal vertebrae, the biopsy of which confirmed metastatic papillary thyroid cancer (Fig. 1). Previous studies have rarely assessed the role of FDG-PET scanning in the early evaluation of the disease. The majority of studies focused on its role in the follow-up of patients suspected to have recurrent or persistent disease in whom one or more findings indicate the presence of the disease but its exact location or extent are not clear. It has been shown to be most consistently useful in cases of high Tg and negative DxWBS in which the FDG-PET scans have a sensitivity of about 47–100% and a specificity of 25–95% (7, 8). While serum Tg and DxWBS are excellent tools for follow-up of patients who were treated by surgery and I-131 in the past, they have a limited role in the postoperative period before I-131 ablation. The potential role of FDG-PET, if confirmed in

future studies, could be of significant help in defining the extent of the disease at this stage with potential implications on the management.

Only a few studies have investigated the role of FDG-PET scanning in patients who had not yet received RAI. These studies, however, had different aims from our study. A recent study compared the diagnostic accuracy of fused FDG-PET/CT scans with neck ultrasonography and contrast-enhanced CT scans of the head and neck area in defining cervical lymph nodes with metastases in newly diagnosed DTC patients who have not yet undergone any thyroid surgery (21). It was found to be comparable with these two imaging modalities in all level cervical lymph nodes and also in the lateral cervical lymph nodes (21). This study did not comment on FDG uptake outside the neck area. Another study assessed the value of FDG-PET scanning in thyroid nodules with inconclusive fine needle aspiration (FNA) biopsy and showed that FDG-PET was positive in all cases of malignancy with a negative predictive value of 100% but was also positive in 34% of benign nodules (22). In that study, FDG-PET decreased the number of unnecessary hemithyroidectomies for inconclusive FNA by 66% (22). In another study, FDG-PET was assessed as a preoperative evaluation tool for patients with thyroid nodules; in 31 patients with 48 lesions, it was found that 9 out of 15 malignant lesions were FDG-avid while 30 out of 33 benign lesions were FDG-cold giving positive and negative predictive values of 75 and 83% respectively (23). A few other studies assessed the prevalence of thyroid cancer in thyroid incidentalomas detected by the FDG-PET scans done for other purposes and found an overall prevalence of incidentalomas of about 1.2–2.2% with a relatively high malignancy rate of 14–50% (24–27).

The prognostic value of FDG-PET scans in thyroid cancer has been demonstrated in patients who were treated in the past (17, 18). Our study suggests that FDG-PET could be of prognostic value in the initial evaluation of patients with DTC. This is demonstrated by the fact that the majority of cases with high-grade

Table 2 The long-term outcome of 26 differentiated thyroid cancer (DTC) patients based on the results of F-18-fluorodeoxyglucose position emission tomography (FDG-PET) scanning at the postoperative evaluation.

	Remission	Persistence	Progression	Total
FDG-PET				
Positive	8	8	2	18
Negative	7	1	0	8
Total	15	9	2	26

malignancy were FDG-PET positive, while the vast majority of patients with negative scans were in stage 1 disease. Furthermore, a larger percentage of patients with persistent or progressive disease were FDG-PET positive, while most of those with negative FDG-PET scans achieved remission. Robbins *et al.* retrospectively studied 400 patients who were treated in the past with surgery and RAI and found a high correlation between survival and the results of FDG-PET in these patients. In a multivariate analysis – among multiple prognostic factors including age, initial stage, histology, Tg, RAI, and FDG-PET results – only age and FDG-PET results continued to be strong predictors of survival. Furthermore, the most active lesions and the number of lesions of FDG-PET scanning inversely correlated with survival (17). Some studies evaluated FDG-PET in the more aggressive forms of DTC such as hurthle cell and insular subtypes and found high positive rates in these tumors consistent with their high-grade malignancy and poor prognosis (28–30). If the prognostic value of FDG-PET at the postoperative evaluation is confirmed in larger studies, it could add a more objective tool than the currently widely used clinicopathological staging systems which have their limitations in clinical practice.

Our study has some limitations. Due to ethical reasons, the findings on the FDG-PET scans could not be always confirmed by the fine needle biopsy or histopathological examination except when indicated, such as in the case described in Fig. 1. However, the foci on FDG-PET were confirmed by at least two independent reviewers and the SUV values were significantly high. Moreover, 16 out of the 18 patients with positive FDG-PET scans had lymph node metastases on the original surgery. This suggests that the findings on the FDG-PET scans in the neck area are related to additional lymph nodes metastases that were not resected. The rate of lymph node metastases is variable and the high rate in our study may have contributed to the high rate of positive FDG-PET uptake in the neck region. Another shortcoming of our study is the relatively short follow-up duration. DTC is generally a malignancy with excellent prognosis but with significant long-term recurrence rate. The prognostic value of FDG-PET scanning in this relatively short period of follow-up may change over time. The study showed that FDG-PET revealed more foci of uptake outside the thyroid bed, presumably lymph node metastases. In that respect, it may have an implication on the staging of the disease especially in patients older than 45 years and also on the I-131 ablation activity. However, in our study, FDG-PET was of no significant help in revealing distant metastases except in one patient (Fig. 1). This might be due to the small sample size and the low rate of distant metastases at the initial presentation. In this study, our patients were relatively young; however, their disease tended to be more aggressive with high rate of lymph node metastases and extrathyroidal extension. This may have contributed to the high positive rate of the

FDG-PET scan in this group of patients. Another point to mention is that our study was done with conventional FDG-PET scanning; fused CT-PET scanning is emerging as a standard technique for the FDG-PET scanning and its use may have added positively to the findings in this study.

In conclusion, our study demonstrates that FDG-PET is more likely to disclose locoregional or distant foci in DTC than DxWBS and TxWBS. Our study, however, does not conclusively indicate that these foci are always related to presence of malignant disease since there is no histopathological confirmation. However, the high median SUVs and the correlation between positive FDG-PET scans and long-term course of the disease suggest that in the vast majority of these cases, the FDG-PET foci represented real foci of the disease. Our study calls for further exploration of the potential role of FDG-PET in the initial evaluation of DTC. If our findings are confirmed in future studies, FDG-PET may help define the extent of the disease more accurately with subsequent institution of appropriate therapy. In this respect, it has the potential role of being an important objective staging tool. FDG-PET also seems to have an important prognostic value when used in the initial evaluation of patients with DTC.

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