

F-18 FDG PET/CT imaging in the diagnostic work-up of thyroid cancer patients with high serum thyroglobulin, negative I-131 whole body scan and suppressed thyrotropin: 8-year' experience

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Abstract. – OBJECTIVE: Fluorodeoxyglucose positron emission tomography/computed tomography imaging in the follow-up of patients with differentiated thyroid carcinoma who have high serum thyroglobulin, negative iodine-131 whole body scan and suppressed thyrotropin.

PATIENTS AND METHODS: A total of 90 patients (31 male and 59 female) with differentiated thyroid carcinoma who have high serum thyroglobulin and negative iodine-131 whole body scan were included in the study between July 2006 and March 2014. All patients had undergone surgery (total thyroidectomy ± lymph node dissection) followed by iodine-131 ablation. Of the patients, 82 had papillary thyroid carcinoma and 8 follicular thyroid carcinoma. Serum thyrotropin was suppressed ($< 2 \mu\text{IU/ml}$) during the Fluor-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging procedure.

RESULTS: The overall sensitivity of fluor-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging in the detection of metastasis of differentiated thyroid cancer was 84.8%, the specificity 79.1%, respectively. The sensitivity and specificity of fluor-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging in classic type of papillary cancer was 83.3% and 54.5%, respectively. The corresponding figures for the tall cell variant was 85.7% and 87.5%, respectively. The difference between the two histological subtypes was statistically significant ($p < 0.05$).

CONCLUSIONS: Our results suggest that fluor-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging could be a valuable test for the routine follow-up of patients with differentiated thyroid carcinoma.

Key Words:

Thyroid neoplasms, Whole body imaging, Positron emission tomography, Thyroglobulin.

Introduction

Differentiated thyroid cancers (DTC) carry a relatively good prognosis, the outcome of patients with recurrent or metastatic DTC depends on the size and extent of tumour when detected, indicating that early discovery of the tumour lesion is important¹. Diagnostic I-131 whole body scan (WBS) and measurement of thyroglobulin (Tg) are the current standard methods for the follow-up of these patients. Elevated serum thyroglobulin levels without circulating thyroglobulin autoantibodies after surgery plus total thyroid ablation indicate recurrent thyroid carcinoma or metastatic disease^{2,3}. However, in some patients, well-differentiated cancers may not accumulate I-131 to allow for detection of metastasis.

Such I-131 negative, undetectable tumors are associated with significantly higher morbidity, and mortality and the use of more efficient tools for the identification of metastatic foci in these patients is of vital importance^{4,5}. Although investigators are in disagreement regarding the best option for the treatment and follow-up of metastatic tumors in patients with high serum Tg and negative I-131 WBS, most believe that high dose I-131 remains the best and the only treatment option making the detection of metastatic disease in these patients clinically relevant^{6,7}.

Fluorine-18-fluorodeoxyglucose (FDG) has been demonstrated to accumulate in different kinds of tumor⁸. The high glycolytic rate of cancer cells has been exploited in 2-[18f]-fluoro-2-deoxy-d-glucose positron emission tomography (F-18 FDG PET) as an effective tumor imaging tool. There is a growing body of evidence on the sensitivity of this technique for the detection of metastatic spread of DTCs⁹⁻¹². It has been claimed that F-18 FDG-PET could be useful for the detection of metastasis that are not detected by I-131 WBS due to lack of I-131 accumulation in the tumor cells, and compared to other radiopharmaceutical techniques, has better sensitivity and specificity¹³. The main indication for FDG PET in DTC is for the evaluation of patients with high serum Tg and negative I-131 WBS. Other potential indications include:

1. In I-131 WBS-positive patients for the detection of other sites of metastasis that do not accumulate I-131,
2. All patients considered to be at high risk based on histopathological and clinical features, regardless of Tg levels and results of I-131 WBS,
3. Patients with detectable titers of anti-Tg antibody,
4. Evaluation of suspicious lesions detected by other imaging modalities,
5. Determination of prognosis.

The aim of this study was to present our case load with F-18 FDG PET/CT in patients with DTC during the last 8 years and compare our findings with the previously published results.

Patients and Methods

Patients

This study was performed in patients with DTC between July 2006 and April 2014 with the approval of the Local Ethics Committee. Inclusion into the study required the presence of elevated serum Tg levels and a negative I-131 WBS. Increased serum thyroglobulin was accepted as the main criterion for the presence of recurrence and/or metastasis. A total of 90 patients (31 male and 59 female) were enrolled in the study, with a mean age of 44.1 years (range 17-88). Histopathological diagnosis includes papillary thyroid carcinoma (n: 82) and thyroid follicular carcinoma (n: 8).

I-131 Whole Body Scan

All patients underwent surgical treatment (total thyroidectomy ± lymph node dissection) and I-131 ablation. Post-treatment whole body I-131 scan was performed a week after therapeutic I-131 ingestion. Our standard protocol requires I-131 whole body scan if serum thyroglobulin is increases/remains increased during follow-up after I-131 remnant ablation. I-131 WBS is performed under increased TSH after withdrawal of thyroxin and strict iodine low diet for 3 weeks.

Imaging with F-18 FDG PET/CT

Sequential transmission and emission images of patient's body between the base of the skull and the proximal femur with the patient in a supine position (hands on sides) were obtained 60 minutes after intravenous injection of 10-15 mCi (370-555 MBq) F-18 FDG. The patient relaxed in a quiet room in a long chair after radiopharmaceutical injection. PET/CT images obtained for each patient were evaluated by two independent nuclear medicine physicians who were blinded to patients' clinical details. Standardized uptake values (SUV) were calculated for each site of abnormal metabolic activity detected on PET images. The PET/CT images were classified as positive or negative. The location(s) of the increased uptake was noted. The threshold of SUV for a positive result was 3.0. Some of the patients underwent surgical removal of the recurrence or metastasis (mainly lymph nodes) (n: 65), and histopathological examination was carried out on the surgical specimen. If the surgery was not indicated, needle aspiration biopsy was used for cytological sampling. Taking into consideration the findings of histopathology, cytology and serum Tg measurements, the result of PET/CT imaging in each patient was classified as:

- True positive: Pathological FDG accumulation, which is confirmed by histological or cytological examination.
- True negative: no abnormal FDG accumulation in a patient whose clinical, radiological and/or histological findings are not suggestive of metastatic disease.
- False positive: Increased FDG accumulation, where there is a lesion diagnosed as 'no malignancy' by histological or cytological examination.
- False negative: No FDG accumulation in any location in a patient with high serum thyroglobulin.

Statistical Analysis

Data were analyzed by the software program of SPSS 15.00 (SPSS for Windows, Chicago, IL, USA). Comparisons of nominal variables were performed using Fisher's Exact Chi-square and the McNemar tests. Two-way comparisons of numerical variables were made using the Mann Whitney U test. Sensitivity and specificity values were calculated with a confidence interval of 95% using the binomial method. A *p* value less than 0.05 was considered to be statistically significant.

Results

The demographic, clinical and histopathological features of the study population are summarized in Table I. Overall, increased metabolic activity was detected by F-18 FDG PET/CT in 61 of the 90 patients whose I-131 WBS results were negative (Figures 1 and 2). Of the 29 patients with a negative F-18 FDG PET/CT result, 10 had metastatic foci confirmed by histopathology/cytology (false negative) while the remaining 19 patients were classified as true negative. Eighteen of the "true negative" cases remain under follow-up by our department, all of which had first-year serum Tg levels < 2. The other died of non-thyroid cancer related causes. F-18 FDG PET/CT was classified as true positive in 56 of 61 patients but false positive in 5 patients. F-18 FDG PET/CT had an overall sensitivity of 84.8% and a specificity of 79.1%, respectively. The association between histological type and F18 FDG PET/CT results could only be evaluated for the histological types that had sufficient numbers, i.e. classical type thyroid papillary carcinoma (n: 35) and the tall cell variant (n: 22). The sensitivity of FDG PET/CT for the classical type was 83.3% with a specificity of 54.5%, compared to a sensitivity of 85.7% and specificity of 87.5 % for the tall cell variant. The difference between the two histological subtypes was deemed statistically significant (*p* < 0.05).

Out of the 56 patients who were considered true positive, 49 had papillary carcinoma, and 7 had follicular carcinoma. In term of subtypes of the 49 papillary carcinoma cases, 20 patients had the classical type, 12 had the tall cell variant, 7 had the follicular variant, 5 had the Hurthle cell variant, 3 had sclerosing variant and 2 had the insular variant. The average maximum SUV for the 20 cases of classical type papillary carcinoma was 6.4±5.8 compared to a mean value of 14.3±7.6 for the 12 cases with the tall cell vari-

ant. The difference between the two subtypes was deemed statistically significant (*p* < 0.05).

Discussion

DTC treated by surgical resection followed by ablation therapy with I-131 carries an excellent prognosis. The current approach for the follow-up of "patients with thyroid cancer after surgery and I-131 ablation therapy involves regular I-131 WBS and Tg measurements¹⁴.

It is well established that DTC cells expressing the sodium iodide symporter (NIS) will concentrate radioiodine¹⁵. However, as these cells dedifferentiate (disease becoming more aggressive), they become low in expressing NIS protein and lose their iodine concentrating capacity thereby making whole body iodine scan negative. Prognosis of I-131 negative DTC metastasis, the so-called non-functioning metastasis, is significantly worse¹⁶. In these patients, an early diagnosis of non-functioning metastasis and their surgical extirpation remains to be the optimal therapeutic approach. At this stage there is an activation of cellular glucose metabolism, enabling F-18 FDG uptake in these dedifferentiated cells. By virtue of their increased growth rate and subsequent increased utilization of glucose, these lesions then become detectable by F-18 FDG PET/CT imaging. This pattern of differential radiotracer uptake is called "flip-flop phenomenon"¹⁷. The whole

Table I. The demographic, clinical and histopathological features of the patients.

Criteria	Number of the patient
Age	
< 45	42
≥ 45	48
Histological type	
Papillary carcinoma	
Classical type	53
Tall cell variant	22
Follicular variant	4
Hurtle cell type	3
Follicular carcinoma	
Minimally invasive	3
Widely invasive	5
Stage	
Stage I	19
Stage II	29
Stage III	24
Stage IV	18

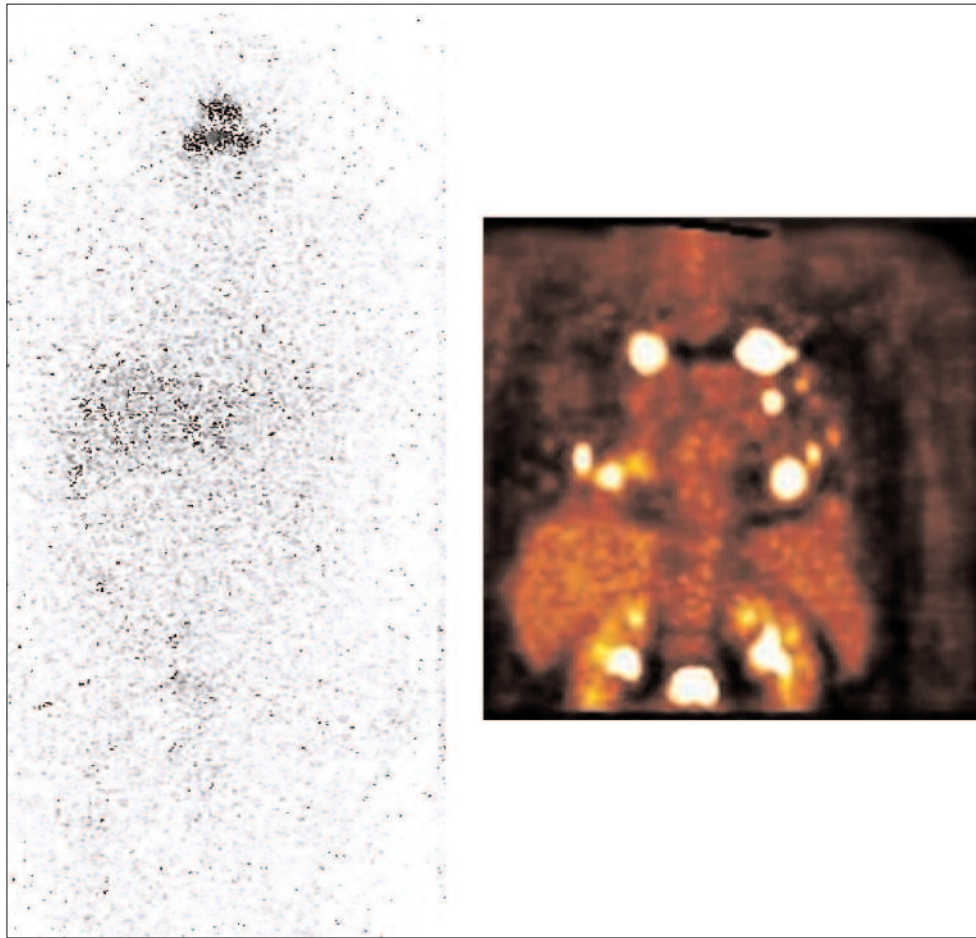


Figure 1. I-131 WBS compared with F-18 FDG PET/CT in a patient with papillary thyroid cancer and increased thyroglobulin level (>300 ng/dL). No pathological radioiodine accumulation is seen on I-131 WBS scan and lesions in the lungs detected on F-18 FDG PET/CT images.

body iodine and the F-18 FDG PET/CT scans are, therefore, complementary in this clinical scenario. Most often, a tumor lesion will take up either only radioiodine or F-18 FDG, but some patients can have both radioiodine and F-18 FDG avid lesions due to varying grades of differentiation among various lesions^{18,19}. The optimal goal here is to identify surgically resectable lesions to render a patient disease free.

In 1987, Joensuu and Ahonen²⁰ were the first to evaluate the role of FDG PET in thyroid cancer, followed by another study in 1993 by Sisson et al¹². Prospective studies²¹ have shown that combining FDG PET with I-131 WBS is associated with a sensitivity of up to 94%. Our results are in concordance with these studies which have demonstrated a benefit of FDG PET for the follow-up of DTC patients who are Tg-positive but I-131 WBS-negative^{13,22-26}. The overall sensitivity of F-18 FDG PET/CT for the detection of

metastatic disease in our study was 84.8% with a specificity of 79.1%, a positive predictive value of 91.1% and a negative predictive value of 73.3%, values which are comparable to those of similar studies. Additionally, we managed to show that the tall cell variant of DTCs, which is known to have a poor prognosis, is associated with a positive FDG PET result more frequently than the classic type.

Another issue that remains a source of controversy regarding the use of FDG PET in thyroid cancer is the relationship between FDG accumulation and TSH levels. TSH stimulates cellular metabolism in normal thyroid tissue while also increasing the expression of glucose transporters thus accelerating the rate of glucose consumption^{10,11}. Although hypothyroidism has been shown to increase FDG accumulation in metastatic tissue, some studies have reported on the contrary, showing decreased FDG accumula-

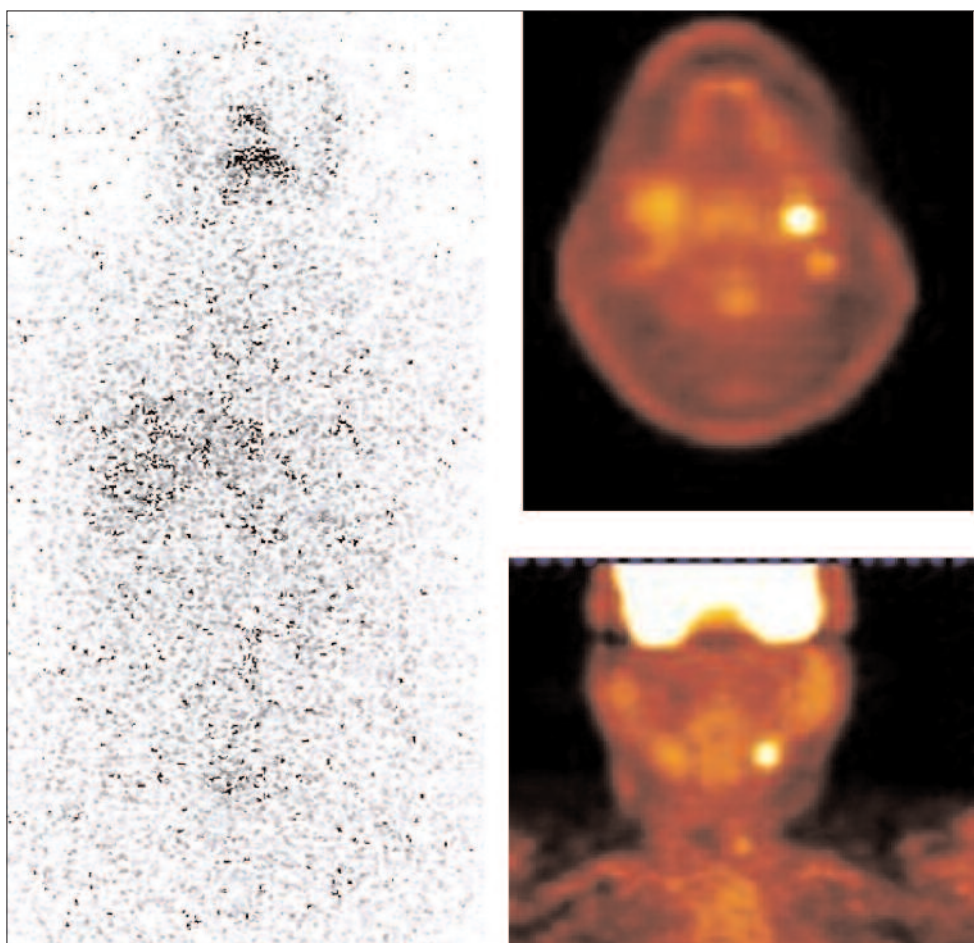


Figure 2. I-131 WBS compared with F-18 FDG PET/CT in a patient with papillary thyroid cancer and increased thyroglobulin level (41.4 ng/dL). WBS failed to demonstrate any focus of increased uptake on anterior image. F-18 FDG PET/CT images (transaxial and coronal PET scan) showed an FDG-avid metastatic lesion in the left upper cervical region.

tion due to a slower metabolism associated with the low thyroid hormone status¹². In a multicenter study¹³, F-18 FDG PET was found to be more sensitive in patients with low TSH levels. The TSH level of all patients enrolled in our study was $< 2 \mu\text{IU/ml}$ at the time of the F-18 FDG PET/CT procedures.

Conclusions

Our findings suggest that FDG PET/CT could be a valuable test for the routine follow-up of patients with DTC. However, 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. This modality is particularly helpful for the detection

of residual foci of de-differentiated neoplastic tissue that has lost the capacity to accumulate I-131.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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