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ORIGINAL ARTICLE

The influence of I-131 therapy on FDG uptake in differentiated thyroid cancer

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Abstract
Objective 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) [or PET/computed tomography (CT)] is more likely to show false-negative results when it is performed shortly after chemotherapy and/or radiotherapy because of "metabolic stunning". The present study aimed to evaluate the influence of I-131 therapy on FDG uptake and the detection of recurrence or metastasis of differentiated thyroid cancer (DTC).
Methods We retrospectively enrolled 16 consecutive FDG-PET/CT studies which had been performed in patients with DTC with elevated thyroglobulin (TG) but negative I-131 whole-body scan. All studies were performed under L-thyroxine suppression. The patients were divided into groups A and B for PET/CT performed within 4 months of I-131 therapy or no such therapy, respectively. Each lesion identified on PET/CT was characterized using a 5-point scale by visual analysis: 0 = definitely benign, 1 = probably benign, 2 = equivocal, 3 = probably malignant, and 4 = definitely malignant. The maximum standardized uptake value (SUV_{max}) in each lesion was also measured for semiquantitative analysis. We compared the visual grading and SUV_{max} of the lesion of highest FDG uptake between groups A and B.
Results For visual analysis, group B had significantly more patients with an uptake score of 3 or 4 than group A (80% vs. 17%, $P = 0.01$). In addition, there were significantly more equivocal results from group A than from group B (67% vs. 10%, $P = 0.02$). If the patients with the highest uptake scores of 2, 3, and 4 were considered to be positive for local recurrence or metastasis, there would be no significant difference between the positive rates of groups A and B (83% vs. 90%, $P = 0.7$). However, the mean SUV_{max} of positive results was significantly lower for group A than for group B (3.1 ± 0.9 and 6.6 ± 3.5, respectively, $P = 0.02$).
Conclusions The preliminary results suggested that FDG uptake in DTC may be negatively influenced by I-131 therapy within 4 months, resulting in lower FDG uptake and more equivocal results. Further studies are necessary to determine whether it is secondary to "metabolic stunning" caused by I-131 therapy.

Keywords Stunning · FDG · I-131 therapy · PET/CT · Differentiated thyroid cancer

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Introduction

On the basis of increased glucose metabolism in cancer cells, 18F-fluorodeoxyglucose positron emission

tomography [FDG-PET, or better with PET/computed tomography (CT)] has been widely used in the diagnosis, treatment evaluation, and follow-up of various kinds of malignancies. However, earlier studies have noted that FDG uptake may be transiently reduced or absent shortly after chemotherapy and/or radiotherapy, so-called metabolic stunning, and that FDG-PET is more likely to show false negatives when performed during this period [1, 2]. The exact time interval after chemo- and/or radiotherapy needed to avoid stunning of FDG uptake is still controversial and has been suggested to range from 6 weeks to 4 months [3].

FDG-PET has been found to be very useful in the detection of recurrence or metastasis of differentiated thyroid cancer (DTC) for patients with elevated thyroglobulin (TG) but negative I-131 whole-body scan (WBS) [4]. In this subgroup of patients, I-131 therapy is still considered to be useful and results in a decrease in TG levels in more than one half of patients [5]. In addition, the sensitivity of I-131 WBS was found to be related to the dose used [6], and thus, some centers, including our hospital, prefer to directly administer I-131 therapy with a post-therapeutic scan without a diagnostic scan for patients with elevated or increasing TG. For those with negative post-therapeutic I-131 WBS and scheduled for FDG-PET study, whether "metabolic stunning" exists shortly after I-131 therapy has still not been studied. We retrospectively reviewed our data and aimed to evaluate the influence of I-131 therapy within 4 months on the FDG uptake and the detection of recurrent or metastatic DTC.

Materials and methods

FDG-PET/CT scans from 16 consecutive patients with DTC studied from September 2006 to July 2007 at the Changhua Christian Hospital were retrospectively reviewed. All patients received total thyroidectomy and I-131 ablation therapy. All 16 patients were studied under L-thyroxine suppression. In addition, all of them had elevated TG levels in a euthyroid or hypothyroid state, negative TG-antibody and negative diagnostic, or post-therapeutic I-131 WBS. The 16 patients were further divided into groups A and B for PET/CT performed within 4 months of I-131 therapy or no such therapy.

All studies were performed using an integrated PET/CT scanner (Gemini GXL; Philips Medical Systems, Cleveland, OH, USA), which integrates a PET scanner of GSO crystal and a 16-slice multidetector computed tomography scanner. Patients were asked to fast for at least 6 h before an intravenous injection of 370 MBq of FDG, and imaging was started 60 min after the injection. Non-contrast enhanced CT scanning was performed first, typically from base of the skull to midthigh, for attenuation correction and anatomical reference with the following parameters: 100 mAs, 120 kV, slice thickness 5 mm, pitch 0.938, and collimation 16×1.5. Emission data were then acquired for 8–10 beds with an acquisition time of 1.5 min/bed position and with the same range of CT scanning. Four of the 16 patients who all had negative post-therapeutic I-131 WBS also received IV contrast administration after acquisition of emission data with the same position and scanning range for obtaining CT images of diagnostic quality. A 3D iterative reconstruction algorithm (3D-row action maximum likelihood algorithm; 3D-RAMLA) was used for reconstruction of PET images.

The PET and CT portions of the PET/CT images were jointly interpreted using a dedicated image fusion workstation. Each lesion identified on PET/CT was characterized using a 5-point scale by visual analysis: 0 = definitely benign, 1 = probably benign, 2 = equivocal, 3 = probably malignant, and 4 = definitely malignant. The scoring was done by an experienced nuclear medicine physician and a radiologist in consensus. Basically, a lesion was scored as 0 or 1 if it showed only mild-FDG activity (less than mediastinum) or was considered as non-tumoral uptake, such as blood vessels, salivary glands, vocal cords, muscle, fat, and lymphoid tissues (symmetric pattern). A lesion was scored as 3 or 4 if it showed high FDG activity (higher than the liver) and was considered as tumoral uptake, such as local recurrence, regional lymph node metastasis, or lung and bone metastasis. If a lesion showed moderate FDG activity (between the mediastinum and liver) and was difficult to categorize according to the above criteria, it was scored as 2.

For semi-quantitative analysis, a region of interest was contoured around the areas of increased FDG uptake, and the maximum standardized uptake value (SUV_{max}) was calculated. In addition, the size of the positive lesions was also measured on the CT images.

Continuous variables were expressed as mean ± SD and tested by Student's *t* test. Noncontinuous variables were tested by a chi-square contingency table. A *P* value lower than 0.05 was considered to be a significant difference.

Results

The detailed demographic data and clinical characteristics were summarized in Table 1. There were 6 and 10 patients in groups A and B, respectively, and there were no significant differences in age or sex between them

Table 1 Detailed demographic data and clinical characteristics

	Group	Age (years)	Sex	SUV_{max} of lesion	Highest score of PET/CT	Lesion size (mm)	TG (ng/ml)	TSH (μIU/ml)	Time interval (days)
A	1	34	F	NA	1	10.3	219	148	47
	2	22	F	2.6	2	5.9	41.3	164.6	28
	3	58	F	2.8	2	12.6	694.0	96	112
	4	63	F	2.3	2	8.6	17.4	0.006	25
	5	40	F	2.7	2	11.5	97.7	139	33
	6	32	M	4.7	4	6.7	103.0	86	28
B	1	43	M	NA	NA	NA	5.6	0.005	591
	2	69	F	2.8	2	11.7	9.3	0.15	881
	3	33	M	3.2	3	8.9	11.3	1.5	184
	4[a]	53	F	6.9	4	9.4	84.7	53.2	849
	5	75	F	13.5	4	10.0	56.2	0.0028	864
	6[a]	73	F	10.3	4	12.2	207.0	0.0217	667
	7	55	M	5.1	4	11.0	13.9	0.0451	884
	8	65	M	4.9	4	7.7	44.9	0.0146	529
	9	30	F	7.8	4	10.3	6.2	0.102	2330
	10	73	F	5.3	4	11.4	106.0	0.001	1071

SUV_{max} maximum standardized uptake value, *PET/CT* positron emission tomography/computed tomography, *TG* thyroglobulin, *TSH* thyroid-stimulating hormone, *M* male, *F* female, *NA* not available; SUV_{max} was not measured for those considered as "negative"
[a] Case nos. 4 and 6 of group B received surgical intervention after PET/CT study, and the histopathologic examinations revealed lymph node metastasis of papillary carcinoma in both cases

Table 2 Summary of PET/CT results by visual analysis and mean SUV_{max} of groups A and B

	Negative		Positive[a]	
	Scored 0–1	Scored 2 (equivocal)	Scored 3–4	SUV
Group A	1 (17%)	4 (67%)	1 (17%)	3.1 ± 0.9
Group B	1 (10%)	1 (10%)	8 (80%)	6.6 ± 3.5
P		<0.05	<0.05	<0.05

[a] The results of PET/CT were considered as positive if the highest 18F-fluorodeoxyglucose uptake score was ≥2

(both P = NS). The time interval between the PET/CT study and latest I-131 therapy for groups A and B was 45 ± 34 and 885 ± 565 days, respectively.

The results of the PET/CT studies were summarized in Table 2. For visual analysis, group B had significantly more patients with an uptake score of 3 or 4 than group A (80% vs. 17%, P = 0.01). In addition, there were significantly more equivocal results from group A than from group B (67% vs. 10%, P = 0.02). If the patients with the highest uptake scores of 2, 3, and 4 were considered as positive for local recurrence or metastasis, there would be no significant difference between the positive rates of groups A and B (83% vs. 90%, P = 0.7). However, the mean SUV_{max} of positive results was significantly lower for group A than for group B (3.1 ± 0.9 and 6.6 ± 3.5, respectively, P = 0.02). There was no significant difference in the size of positive lesions (9.1 ± 2.9 mm and 10.3 ± 1.5 mm, respectively, P = 0.42) between groups A and B.

Representative PET/CT images of scores 2, 3, and 4 were demonstrated in Fig. 1.

Discussion

Metabolic heterogeneity has been noted in recurrent or metastatic lesions of DTC, in which tumors showed uptake of only FDG, only I-131, or both [7]. The lesions of DTC might show positive results in I-131 WBS but negative ones in FDG-PET, or vice versa, the so-called flip-flop phenomenon. The combined images of I-131 WBS and FDG-PET in the follow-up of DTC were found to have a sensitivity of approximately 95% in the detection of recurrence and metastasis, and the foci of FDG uptake were considered an indicator of less-differentiation or de-differentiation of thyroid cancer cells [8]. For the patients with positive TG but negative I-131 WBS, I-131 therapy alone might not be sufficient to eradicate the metastases [9]; and further imaging studies would be important to identify the extent of disease for planning other treatment methods. FDG-PET (or better with PET/CT) seemed to be the method of choice for these patients not only for its accuracy [10, 11] but also for its prognostic value [12, 13].

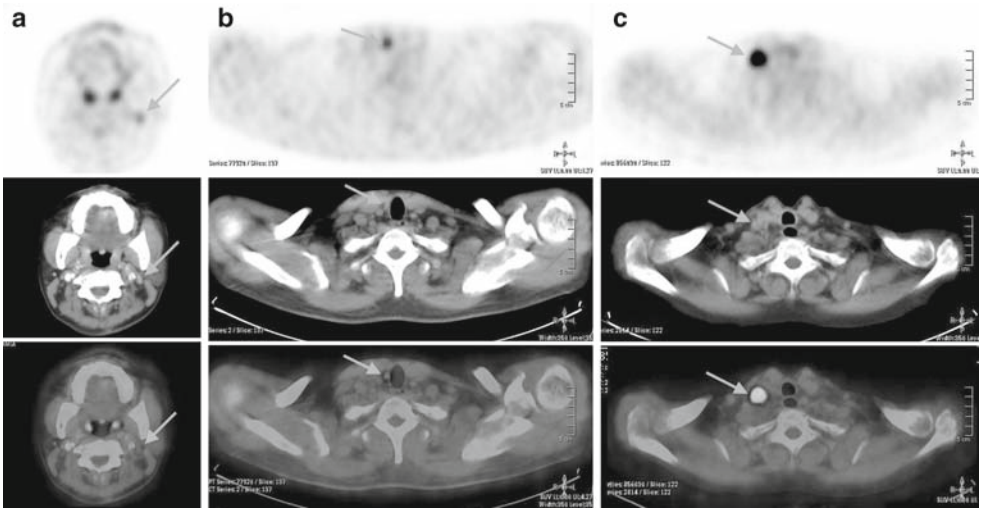

Fig. 1 Representative positron emission tomography/computed tomography (PET/CT) images of scored 2 (**a**), scored 3 (**b**), and scored 4 (**c**). *Upper*, *middle*, and *lower columns* were PET, CT, and fused PET/CT images, respectively; and the lesions were marked with *arrows*. Images (**a**), (**b**), and (**c**) came from case no. 5 of group A, case no. 3 of group B, and case no. 6 of group B, respectively

The uptake of FDG was found to decline rapidly following chemotherapy or radiotherapy, which was predictive of the therapeutic response and correlative of a better prognosis. However, some authors also suggested that FDG-PET had higher false-negative rates when performed shortly after therapy because of "metabolic stunning". Greven et al. [14] evaluated 45 patients with head and neck cancer with FDG-PET before and at 1, 4, 12, and 24 months after radiotherapy. Residual tumors were found in 7 of the 28 scans interpreted as negative when the patients were studied 1 month after radiotherapy, but all 18 negative scans were true negative when studied 4 months after therapy. Cremerius et al. [15] evaluated 33 patients with metastatic germ cell cancer with FDG-PET performed after the initial diagnosis, within 2 weeks after completion of chemotherapy or 14–375 days after chemotherapy. There were five false-negative results in nine cases of PET scans studied within 2 weeks of chemotherapy, but only two false negatives in nine cases studied at least 2 weeks after therapy. To the best of our knowledge, the influence of recent I-131 therapy on the FDG uptake of DTC has still not been studied.

In our preliminary data, the FDG uptake in lesions of suspected local recurrence or metastasis was negatively influenced by I-131 therapy within 4 months of PET/CT studies on the basis of either visual or semiquantitative analysis. Possible explanations for this might include that the residual tumor volumes were smaller after destruction with I-131 therapy and/or the metabolic activity was transiently suppressed by I-131 therapy. As we know, the uptake of smaller lesions was more likely to be underestimated because of partial volume effect. However, there was no significant difference in the size of the positive lesions (scored 2–4) between the two groups of patients. Therefore, the reduction of FDG uptake should be related to the suppressive effects of I-131 therapy, which may be similar to the "metabolic stunning" phenomenon observed in patients receiving chemotherapy or radiotherapy. Although all our patients in group A had negative I-131 post-therapeutic scanning, partially therapeutic effects on the occult cancer cells may still have existed either caused by the small amounts of specific I-131 uptake still present or by non-specific radiation from circulating I-131. This hypothesis could be supported by the findings of decreased TG level after empiric I-131 therapy in considerable numbers of patients with elevated TG but negative I-131 scanning [5].

The major limitation of our study was that a definitively histopathologic result was only available in 2 of the 14 positive cases. However, the positive rate of our PET/CT studies was almost the same as the sensitivity of a recent study of PET/CT in DTC [11]. As a tool of "metabolic biopsy", FDG-PET has both high positive predictive and negative predictive values in both thoracic and non-lung lesions [16, 17]. Furthermore, recent studies found that the diagnostic accuracy of PET/CT, especially its specificity, was significantly better than PET alone in the evaluation of recurrent or metastatic DTC [10]. With the integration of anatomical information provided by CT scan, several potential false-positive findings, including FDG uptake in muscle and brown fat, the salivary glands, vocal cords, tonsils, and other lymphoid tissues, can be effectively eliminated. Therefore, the numbers of false-positive results in our positive cases would be small, and would be more likely to fall in the subgroups of equivocal cases (scored 2). If only those cases scored 3 and 4 were considered as positive, the positive rate of FDG-PET/CT would be significantly lower in group A than in group B (17% vs. 80%, $P < 0.005$).

All our patients received FDG-PET/CT studies under L-thyroxine suppression. Earlier studies have found that the FDG uptake in lesions was higher and the sensitivity of FDG-PET was greater under endogenous or exogenous TSH stimulation [18, 19]. Moog et al. [18] investigated 10 DTC patients under L-thyroxine suppression and after L-thyroxine withdrawal, and found that the tumor-background ratio increased from 3.85 to 5.84 following TSH stimulation. Similar results were also reported by Petrich et al. [19] who found an increase in the SUV from 1.3 to 4.4 after stimulation by recombinant TSH. Whether TSH stimulation can overcome "metabolic stunning" shortly after I-131 therapy is another issue worthy of further investigation.

In conclusion, our preliminary data found that the FDG uptake of suspected lesions in patients with DTC was significantly lower in those studied within 4 months of I-131 therapy than those without I-131 therapy. If the patients were referred for FDG-PET (or PET/CT) resulting from high TG but negative post-therapeutic I-131 scanning, the possibility of "metabolic stunning" should be considered in interpreting the images, especially for those with negative or equivocal results. Further studies with prospective design with/without TSH stimulation may be helpful to clarify the phenomenon of "metabolic stunning" after I-131 therapy and to provide optimal protocols for FDG-PET (or PET/CT) studies in patients with DTC.

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