ORIGINAL RESEARCH

FDG PET Predicts the Effects of ^{131}I and Prognosis for Patients with Bone Metastases from Differentiated Thyroid Carcinoma

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Background: ^{18}F-FDG PET and ^{131}I scans are important in the detection of metastases from differentiated thyroid carcinoma (DTC). The relationship of FDG and radioiodine (RAI) metabolism in bone metastases (BMs) from DTC and its prognostic value on RAI treatment is not clear.

Methods: The retrospective study included DTC patients with BMs from two medical centers, who underwent ^{18}F-FDG PET/CT scans and RAI therapy. Therapeutic response was evaluated by serum thyroglobulin (Tg) levels and anatomical imaging changes.

Results: The analyses were performed on 30 patients with 72 BMs. Forty-two (42/72, 58%) lesions displayed simultaneous ^{131}I and ^{18}F-FDG uptake. BMs with positive ^{18}F-FDG uptake had a less favorable response to RAI therapy in comparison to those with negative ^{18}F-FDG uptake ($p = 0.018$), even in ^{131}I-avid lesions ($p = 0.033$). Sixteen (53%) patients had disease progression with a median PFI of 26 months (range: 3 to 89 months). Compared to those with ^{131}I-avid but non-FDG-avid BMs, patients presenting with ^{18}F-FDG-avid BMs had shorter PFI, whether with ^{131}I uptake ($p = 0.002$) or without ($p = 0.002$).

Conclusion: More than half of BMs (58%) from DTC show simultaneous ^{18}F-FDG and ^{131}I uptakes which are contrary to the flip-flop phenomenon (^{131}I negative and ^{18}F-FDG positive). Regardless of ^{131}I uptake, ^{18}F-FDG uptake of BMs portends a less favorable therapeutic response and poorer prognosis for patients with DTC.

Keywords: bone metastasis, differentiated thyroid carcinoma, FDG, PET, prognosis

Introduction

Differentiated thyroid carcinoma (DTC) has a favorable long-term prognosis in general. Most patients with DTC are well managed with a combined treatment of radical surgery, radioiodine (RAI) ablation and thyroid hormone replacement/suppression with a 20-year overall survival rate of approximately 90%.[1,2] However, the presence of distant metastases, especially of bone metastases (BMs), can remarkably worsen the prognosis of DTC patients.[3–7]

For BMs, the preferred progression of treatment is surgical excision of locoregional disease in potentially curable patients, followed by RAI therapy for RAI-responsive disease and external beam radiation therapy or other directed treatment modalities as dictated by disease response.[2] Although RAI has been applied in the treatment of distant metastases from DTC for more than 60 years, the efficacy of RAI for BMs was reported variably.[5,8–12] The question that who will benefit from RAI therapy remain unresolved. Recent investigations have indicated that

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[18]F-fluorodeoxyglucose (^{18}F-FDG) accumulation on a positron emission tomography (PET) scan is a strong predictor of poor prognosis for DTC patients.[9,13–16] However, due to the lower frequency of BMs, these studies included only a small number of patients with BMs. In addition, the correlation of ^{18}F-FDG uptake with the prognosis of BMs cannot be fully assessed, because it was analyzed in conjunction with metastases to other organs.[16] Therefore, in our study, patients with BMs from DTC who underwent ^{18}F-FDG PET/computed tomography (CT) before RAI treatment were collected and analyzed.

Patients and Methods

Patients

From January 2009 to August 2019, patients with BMs from DTC who received RAI therapy and ^{18}F-FDG PET/CT for pre- or post-treatment evaluation in the Department of Nuclear Medicine at Xinhua Hospital and Tenth People's Hospital of Tongji University were retrospectively selected. A total of 37 patients were diagnosed with BMs from DTC based on either of the following criteria: (1) histological confirmation of BMs from primary DTC; (2) no histological records, but either ^{131}I-whole body scintigraphy (WBS) or ^{18}F-FDG PET/CT revealing suspicious BMs with the confirmation of at least one of the other imaging findings (X-ray, computed tomography [CT] or magnetic resonance imaging [MRI]) and elevated level of serum thyroglobulin (Tg). Patients were diagnosed either at the time of their initial evaluation or during subsequent follow-up. Six patients who showed a limited number of BMs and who underwent surgical resection before or during the RAI treatment were excluded, because of concerns that the therapeutic effects of RAI might overlap the effects of surgery. Another patient who received only one RAI therapy was also excluded for insufficient follow-up time and data. Finally, 30 patients were included in this study.

This study was conducted in accordance with the Declaration of Helsinki. Written ethics approval from the Hospital Research Ethics Committee of Shanghai Jiaotong University, School of Medicine affiliated Xinhua Hospital and The Tenth People's Hospital was obtained, and participants provided their written informed consent to participate in this study.

RAI Therapy and Follow-Up

All the patients withdrew from taking levothyroxine and began a low-iodine diet 3–4 weeks before RAI therapy,

with achieved serum thyroid-stimulating hormone (TSH) levels above 30 mIU/L. Patients with BMs were admitted to our department after thyroid hormone withdrawal (THW). On the first day after admission, ^{18}F-FDG PET/CT scans together with conventional measurements, including physical examination, serum TSH, serum Tg, and serum anti-thyroglobulin antibodies (TgAb) were performed. An ^{18}F-FDG PET/CT scan was performed at the diagnosis of BM for all patients, and subsequent PET/CT scans were performed selectively. RAI was administered to these patients on the second day after admission. A ^{131}I post-therapy scan was performed three days after oral administration of RAI. A RAI activity of 1.85–7.4 gigabecquerel (GBq) was used to ablate the thyroid remnants according to patients' risk stratification and pathology features or for the treatment of known metastases at the same time. For the subsequent treatment of BMs, the activities of oral administration of RAI were empirically divided into three tiers (5.55, 7.4 and 9.25 GBq) for each treatment according to the tumor burden. If the number of BMs from DTC patient were less than 5, 5.55–7.4 GBq ^{131}I would be administered, and 7.4–9.25 GBq ^{131}I was administered in patients with the number of BMS equal/more than 5 without other organ (lymph node or lung) metastases based on post-therapy scans and CT or PET/CT. The doses of ^{131}I were 7.4–9.25 GBq in BMs from DTC with other organ metastases. For the RAI positive BMs on the first post RAI therapy scan, the second treatment will be started four to six months later. Later on, treatment intervals between the two subsequent RAI treatments of BMs varied from six to 12 months according to the therapeutic response. The follow-up period was one to 11 years (yrs) with a median follow-up of 3.21 yrs.

^{18}F-FDG PET/CT Imaging

^{18}F-FDG PET/CT examinations were performed using a Biograph mCT-64 scanner (Siemens/CTI, Knoxville, TN) in a state of thyroid hormone withdrawal (above 30 mIU/L) before RAI treatment. Before the examination, patients fasted for at least six hours to ensure a serum glucose concentration of less than 150 mg/dL. Patients were injected intravenously with 5.55 MBq/kg of ^{18}F-FDG, and no intravenous or oral contrast agents were administered. Sixty minutes later, patients were scanned with a whole-body, three-dimensional PET/CT scan from the base of the skull to the mid-thigh. The acquisition consisted of a CT scan (120 kV; 300 mAs; slice thickness, 3 mm; pitch, 1.5) for the purpose of

attenuation correction for anatomical co-registration of PET data, followed by three-dimensional emission imaging for two minutes per bed position. The standard uptake value (SUV) of BMs was obtained.

Criteria of Remission
Per Lesion Evaluation
The local efficacy of RAI was evaluated in view of the structural and size changes of a well-defined lesion on CT. A lesion was defined as responsive if it met one of the following criteria during the follow-up and showed no more signs of disease progression until the end of the follow-up: (1) complete or partial sclerotic rim or sclerotic fill-in was seen in a lytic lesion; (2) the lesion showed over 50% decrease in size, compared with pretreatment. The size of a well-defined lesion was deemed as the sum of perpendicular bidimensional measurements of its greatest diameters. Otherwise, the lesion was regarded as unresponsive. To ensure adequate follow-up times, all patients included in the study underwent at least two cycles of RAI treatment.

Per Patient Evaluation
The response assessment on a per patient level was based on CT and serum Tg changes after the last cycle of RAI therapy, compared with the time point when BMs were found. With regard to CT changes, the therapeutic response of each patient was assigned to one of four categories based on MD Anderson criteria,[17] namely complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Similar to the evaluation of local response, both structural and size changes were taken into consideration when assessing the therapeutic response. The percentage change of serum Tg was also calculated, and according to that, the outcomes of assessment were classified into three categories: (1) effective, Tg decrease $\geq$ 25%; (2) stable, Tg increase or decrease <25%; and (3) ineffective, Tg increase $\geq$ 25%.

Statistical Analysis
Statistical analysis was performed using SPSS Statistics 19.0. Factors that might relate to ^{18}F-FDG uptake of BMs and the correlation between ^{18}F-FDG uptake and serum Tg variation or anatomical imaging changes were analyzed by univariate analysis and confirmed by χ^2 test or Fisher's exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) for therapeutic response per lesion were calculated. Differences of the distribution of SUV_{max} between groups

were compared using the Mann–Whitney U-test. P <0.05 was considered statistically significant. The progression-free interval (PFI), as measured from the date of BMs diagnosis to the date of death or disease progression according to MD Anderson criteria, was described as the primary end point of this study. The effect of different variables involving in PFI was estimated by Kaplan–Meier survival analysis and the differences between groups were compared using the Log rank test. Multivariate analysis based on Cox proportional hazards model was applied in order to analyze the relationship between PFI and several variables simultaneously.

Results
Patient Characteristics
Thirty patients (19 females, 11 males; mean age: 59; age range: 28–81) were included. Pathology was papillary thyroid carcinoma (PTC) in 17 cases and follicular thyroid carcinoma (FTC) in 13 cases. According to the American Joint Committee on Cancer (AJCC) 7th TNM classification, a primary tumor was postoperatively staged as pT1 in six patients, pT3 in one patient and pT4 in five patients. In 18 patients, T feature was not reported (Tx). Lymph node metastases (pN1) were found in nine subjects. Characteristics of the patients are listed in Table 1. The diagnosis of BM was established at the time of the initial evaluation in 25 patients on the post RAI treatment imaging, SPECT/CT, CT or MRI, FDG PET/CT and elevated Tg, and three to four months later during subsequent follow-up in five patients with elevated Tg and positive lesions on FDG PET/CT. Among the cases, 17 patients had only BMs, and 13 patients had other metastatic sites (12 lung and one lung + adrenal). By the end of the study, all of the patients went through two to 15 cycles of RAI therapy. Among them, 13 (43%) patients had fewer than five cycles, 14 (47%) had five to 10 cycles, and 3 (10%) had more than 10 cycles. The RAI treatment interval between the first and second administration ranged from four to six months, and the subsequent RAI was administered every six to 12 months according to the therapeutic response. The median cumulated dose of ^{131}I was 36.3 GBq, ranging from 9.3 GBq to 122.1 GBq. The median pre-therapeutic serum Tg was 217.6 ng/mL, ranging from 4.7 ng/mL to 2363.8 ng/mL. Twelve patients (22/30, 73%) complained bone pain, and one of them had pathological fracture. BMs were distributed on spine (32/72), pelvis (17/72), the limbs including humerus and femur (9/72), ribs (10/72), sternum (3/72) and jaw (1/72).

Table 1 Characteristics of the Patients

Factors	N (%)
Gender	
Female	19 (63%)
Male	11 (37%)
Age at the diagnosis of BMs	59 [28–81]
Histology	
PTC	17 (57%)
FTC	13 (43%)
Multifocal	
Yes	20 (67%)
No	10 (33%)
Nonosseous metastases	
Yes	13 (43%)
No	17 (57%)
RAI therapy	
Median cumulated dose (GBq)	36.3 [9.2–122.1]
Median pre-therapeutic Tg level (ng/mL)	217.6 [4.7–2363.8]

Abbreviations: BMs, bone metastases; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; RAI, radioiodine.

Per Lesion Analysis

With regard to the distribution of bone lesions, 10 patients presented with solitary BMs and 20 patients presented with multifocal lesions. In total, 72 BMs in 30 patients were analyzed. BMs were distributed on skull, spine (32/72), pelvis (17/72), the limbs including humerus and femur (9/72), ribs (10/72), sternum (3/72) and jaw (1/72). The size of the osteolytic disease was 2.77±1.64cm, ranging from 0.4cm to 7.6cm. Fifty-four BMs showed positive accumulation on ^{18}F-FDG PET/CT at the diagnosis of BMs, which included four (7%, 4/54) lesions that were regarded as responsive, and the other 50 (93%, 50/54) were unresponsive. Eighteen BMs showed no accumulation of FDG on ^{18}F-FDG PET/CT, of which six (33%, 6/18) lesions responded to RAI, whereas the other 12 (67%, 12/18) were unresponsive. According to univariate analysis, BMs with negative ^{18}F-FDG uptake were more inclined to respond to RAI ($p = 0.018$; Table 2) than were ^{18}F-FDG-avid BMs. However, in the quantitative analysis of ^{18}F-FDG avidity, the distribution of SUV_{max} between responsive (25th, 50th and 75th percentile SUV_{max}: 1.25, 1.88 and 9.72) and unresponsive (25th, 50th and 75th percentile SUV_{max}: 2.33, 5.17 and 11.17) lesions showed no significant difference according to the Mann–Whitney U-test ($p = 0.130$).

Table 2 ^{18}F-FDG/^{131}I Uptake and Local Therapeutic Response

	Responsive	Unresponsive	χ^2	P
^{18}F-FDG uptake				
F+	4	50	5.574	0.018
F−	6	12		
^{131}I uptake				
I+	10	48	1.574	0.214
I−	0	14		

In terms of ^{131}I avidity, 58 lesions showed positive accumulation on ^{131}I WBS at the diagnosis of BMs, of which 10 lesions (17%, 10/58) responded to RAI therapy. Although there was no statistically significant association between ^{131}I uptake and the local therapeutic response ($p = 0.214$; Table 2), none of the ^{131}I-negative lesions responded to RAI therapy. Further, we divided the ^{131}I-avid BMs into two subgroups according to ^{18}F-FDG PET/CT results: (1) simultaneously positive accumulation on ^{18}F-FDG PET/CT (F+/I+, n = 42), see Figure 1 and Figure 2; (2) no accumulation of FDG on ^{18}F-FDG PET/CT (F-/I+, n = 16). Ten percent (4/42) of the F+/I+ and 38% (6/16) of the F-/I+ BMs were regarded as responsive after RAI therapies. Statistically, F-/I+ BMs were more likely to respond to RAI therapy than were F+/I+ BMs (OR = 0.175; 95% CI = 0.041–0.744; $p = 0.033$, Table 3).

Per Patient Analysis

Twenty-three (77%) patients showed positive accumulation on ^{18}F-FDG PET/CT and 25 (83%) patients had positive accumulation on ^{131}I WBS at the diagnosis of BMs. A simultaneous uptake of ^{18}F-FDG and ^{131}I was observed in 18 (60%)

Response Assessment Based on Anatomical Imaging

According to MD Anderson criteria, the numbers of patients who obtained PR, SD, and PD were six (6/30, 20%), 11 (11/30, 37%), and 13 (13/30, 43%), respectively. No patients showed CR based on CT results. Univariate analyses results demonstrated that the ^{18}F-FDG uptake had significant impact on the therapeutic response of RAI therapy based on anatomical imaging changes ($p = 0.026$; Table 4). Fifty-two percent (12/23) of ^{18}F-FDG positive patients had PD, whereas the ratio was 14% (1/7) in patients with negative ^{18}F-FDG uptake. Although the ^{131}I uptake was not statistically related to anatomical imaging evaluation outcomes, none of the ^{131}I negative patients obtained CR or PR (Table 4).
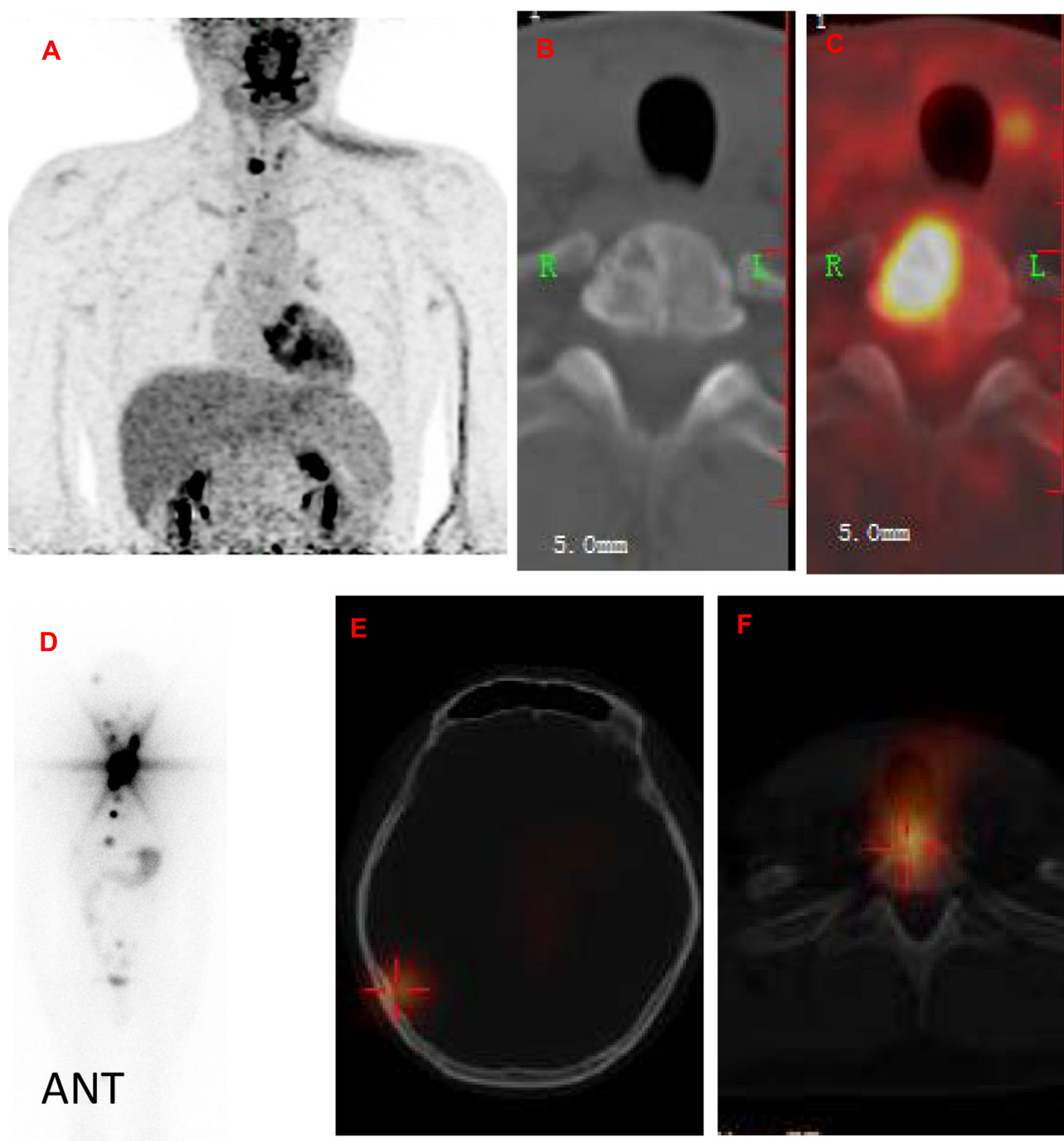
Figure 1 A 32 years old man had ^{131}I avid and ^{18}F-FDG avid/non-avid bone metastases from papillary thyroid cancer (T4bN1bM1) with an elevated thyroglobulin at 864.12ng/mL (TSH 117.48uIU/mL). 18F-FDG PET/CT maximum intensity projection (MIP) (**A**) under TSH stimulation before ^{131}I treatment showed increased uptake in the middle of the lower neck. The transverse section of CT (**B**) and PET/CT (**C**) displayed a mixed bone destruction with intense uptake of FDG (SUVmax 12.7) in the second thoracic vertebra (T$_2$). The whole-body post-therapy scan (**D**) and SPECT/CT (**E** and **F**) fusion imaging after administration of 7400MBq ^{131}I showed thyroid remnant and multiple bone metastases including right occipital bone (**E**) and T$_2$ (**F**).

Response Assessment Based on Serum Tg

The median pre-therapeutic serum Tg was 303.97 ng/mL and 171.31 ng/mL in ^{18}F-FDG-positive patients and ^{18}F-FDG-negative patients, respectively, and no significant difference was found in the distribution of serum Tg between the two groups (p = 0.446, Mann–Whitney U-test). After the last cycle of RAI therapy, the median serum Tg values in ^{18}F-FDG-positive and ^{18}F-FDG-negative patients were 241.07 ng/mL and 109.02 ng/mL,
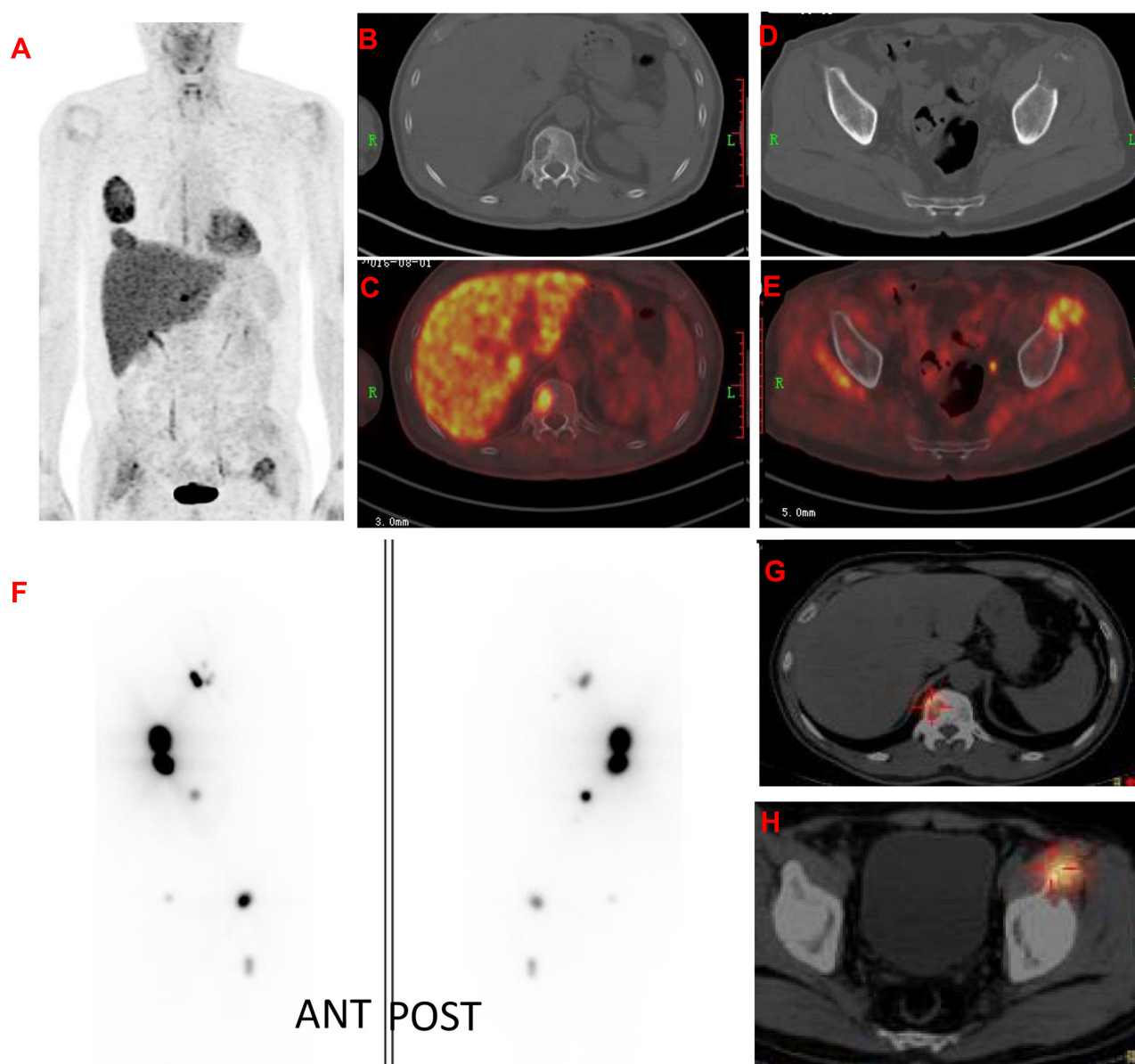
Figure 2 A 56 years old man had 131I avid and 18F-FDG avid bone metastases from papillary thyroid cancer (T3N0M1) with an elevated thyroglobulin at 1000ng/mL (TSH 32.25uIU/mL). 18F-FDG PET/CT MIP (**A**) under TSH stimulation (thyroid hormone withdrawal for 4 weeks) before ^{131}I treatment showed increased uptake in the multiple bones including left ribs (SUVmax 5.7). The transverse section of CT (**B** and **D**) and PET/CT (**C** and **E**) displayed a bone destruction with intense uptake of FDG (SUVmax 11.5) in the 12th thoracic vertebra (T$_{12}$) and the left ilium (SUVmax 4.8). The whole-body post-therapy scan (**F**) and SPECT/CT (**G** and **H**) fusion imaging after administration of 9250MBq ^{131}I showed thyroid remnant and multiple bone metastases including T$_{12}$ (**G**) and the left ilium (**H**).

respectively. The serum TgAb value of each individual was also recorded, because TgAb can interfere with the detected values of serum Tg. In this study, three patients showed increased serum TgAb levels after 3, 4 and 5 courses of ^{131}I treatment with simultaneous high serum Tg. And later on, the three patients' TgAb returned to negative again. Serum Tg decrease 25%, representing effectiveness, was seen in nine (9/30, 30%) patients. Twenty-two percent (5/23) of patients with positive accumulation on ^{18}F-FDG PET/CT and 57% (4/7) with negative ^{18}F-FDG uptake achieved a Tg decrease ≥25%. However, as shown in Table 4, univariate analyses indicated no significant correlation between serum Tg level variation and ^{18}F-FDG uptake ($p = 0.212$). ^{131}I uptake proved to be correlated with serum Tg variation according to the analysis ($p = 0.013$). Stable disease or ineffective therapy was defined when patients with negative ^{131}I accumulation after two cycles of RAI therapies.

Table 3 ^{18}F-FDG Uptake and Local Therapeutic Response for [131]I Positive Lesions

	Responsive	Unresponsive	χ^2	P
F+/I+	4	38	4.546	0.033
F–/I+	6	10		
OR = 0.175; 95% CI = 0.041–0.744				

Abbreviations: OR, odds ratio; CI, confidence interval.

Progression-Free Survival

Of all the patients, 16 (53%) had disease progression. The median PFI of these patients was 26 months (range: three to 89 months). According to univariate analysis, only the ^{18}F-FDG uptake and ^{131}I uptake were correlated with PFI ($p < 0.001$; Table 5). Subsequent pairwise comparisons were performed. Compared with F-/I+ patients, a less favorable PFI was seen in both the F+/I+ group and the F+/I- group ($p = 0.002$ and 0.002, respectively). In this study, patients with both positive ^{18}F-FDG PET/CT and ^{131}I WBS outcomes were categorized as F+/I+ group. However, three patients in this group showed mixed ^{18}F-FDG and ^{131}I uptake in the BMs; namely, both F+/I+ and F-/I+ lesions were seen in the same patient. We then conducted a subgroup analysis to examine the difference of PFI between the patients with mixed ^{18}F-FDG and ^{131}I uptake and the other F+/I+ patients, but no significant difference was found ($p = 0.376$).

Multivariate analysis based on a Cox proportional hazard model also confirmed that disease progression was correlated with ^{131}I and ^{18}F-FDG uptake (p = 0.004; Table 5). When the ^{18}F-FDG uptake was substituted for the number of ^{18}F-FDG-avid lesions in the multivariate analysis, no significant correlation was found between the number of ^{18}F-FDG-avid lesions and PFI ($p = 0.192$).

Discussion

The alternating ^{131}I and ^{18}F-FDG uptake pattern, the flip-flop phenomenon (ie, ^{131}I negative and ^{18}F-FDG positive) has been regarded as a common feature of metastases from DTC and observed in approximately 90% of the patients.[16,18] Our previous study also found that out of the 83 patients, 25 showed F-FDG uptake in the pulmonary metastases of DTC.[19] Metastases of DTC including lymph node, lung and bone in 37 patients with 44 lesions were evaluated and found that sixteen lesions (70%) were increased and 7 (30%) showed no change or reduction when there was positive accumulation on FDG PET/CT and no accumulation of FDG on I-131 group.[21] In the study, BMs from DTC were included and in this series, only 39% (28/72) of the BMs displayed alternating ^{131}I and ^{18}F-FDG uptake, and over half of the metastases (58%, 42/72) displayed simultaneous uptake of both tracers. These discordant findings may result from differences in the study population, because our study focused on BMs, which could represent a more progressive state of disease. ^{18}F-FDG and ^{131}I avidity of a metastasis from DTC may reflect the grade of tumor differentiation and malignancy. ^{18}F-FDG-avid tumors tend to be less differentiated and more aggressive in behavior, whereas the presence of ^{131}I uptake could imply a more differentiated and benign phenotype.[16] Therefore, the simultaneous uptake of ^{131}I and ^{18}F-FDG might indicate that a mixture of variously differentiated tumor cells exist in the same lesion, including dedifferentiated cells with elevated ^{18}F-FDG uptake and differentiated cells with retained ^{131}I uptake. We assume that differentiated BMs cells from DTC with retained ^{131}I uptake tend to dedifferentiate and become hypermetabolic; based on that, the simultaneous uptake of ^{131}I and ^{18}F-FDG may indeed be a depiction of such a dedifferentiation process.

Table 4 ^{18}F-FDG/[131]I Uptake and Therapeutic Response Based on Anatomical Imaging and Serum Tg Changes

Factors	Changes of Anatomical Imaging			P*	Changes of Serum Tg			P*
	PR	SD	PD		Eff	Sta	Ine	
^{18}F-FDG uptake								0.212
F+	2	9	12	0.026	5	4	14	
F-	4	2	1		4	0	3	
[131]I uptake								0.013
I+	6	9	10	0.687	9	1	15	
I–	0	2	3		0	3	2	

Note: *P value was calculated using Fisher's exact test.
Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; Eff, effectiveness; Sta, stabilization; Ine, ineffectiveness.

Table 5 Univariate and Multivariate Analyses of Factors Predicting Progression-Free Survival

Factors	Number of Patients (n)		Median PFI (Month)	p value (UNIV)	p value (MULTIV)
	Total	PD or Death			
Age					
≥45 yr	28	15	57	0.354	0.694
<45 yr	2	1	5		
Gender					
Female	19	12	60	0.841	0.836
Male	11	4	57		
Histology					
PTC	17	9	38	0.131	0.867
FTC	13	7	66		
Number of BMs					
1	10	6	57	0.895	0.846
>1	20	10	60		
Extent of metastases					
Bone only	17	9	57	0.881	0.610
Bone and other organs	13	7	37		
Metabolic pattern					
$^{18}F+/^{131}I+$	18	9	37	< 0.001	0.004
$^{18}F+/^{131}I-$	5	4	3		
$^{18}F-/^{131}I+$	7	3	44		

Abbreviations: PD, progressive disease; PFI, progression-free interval; UNIV, univariate analysis; MULTIV, multivariate analysis; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma.

Hitherto, RAI therapy was the only systemic treatment modality that demonstrated therapeutic efficacy against widely metastatic disease from thyroid carcinoma.[20] The efficacy of RAI is primarily based on the ^{131}I avidity of local lesions, whereas metastases with no accumulation on ^{131}I WBS may not be able to concentrate or retain enough RAI to achieve a therapeutic benefit. As shown by the aforementioned results, none of the BMs with negative ^{131}I uptake responded to RAI therapy. However, the existence of ^{131}I uptake did not necessarily relate to a better therapeutic response, and a surprisingly low response rate was observed even in ^{131}I-avid BMs. Instead of the presence of ^{131}I uptake, the absence of ^{18}F-FDG uptake was more likely to predict a higher rate of local therapeutic response, because our study revealed that the coexisting ^{18}F-FDG avidity would lower the response rate of ^{131}I-avid BMs. These findings are consistent with the results of a previous investigation that concluded that ^{18}F-FDG-avid metastases whether with or without ^{131}I uptake are resistant to RAI therapy.[21]

We also tried to evaluate the impact of quantitative ^{18}F-FDG uptake (ie, SUV) on the therapeutic response to

RAI in BMs. However, no significant difference was found between the distribution of SUV_{max} of responsive lesions and that of unresponsive lesions. Therefore, we assumed that although ^{18}F-FDG-avid BMs are more likely to be resistant to RAI therapy, the additional value of quantitative SUV in predicting therapeutic response seemed to be limited. Nevertheless, further studies are still needed with a larger sample size to confirm our findings.

Serum Tg was considered a prognostic indicator that could reflect disease progression and tumor burden in the evaluation of recurrent and metastatic DTC.[22] A major problem that hampers accurate Tg measurement is the interference by TgAb. Therefore, TgAb should be measured in the same serum sample taken for Tg assay. Although for clinical purposes the measurement of Tg and TgAb before thyroidectomy for a suspected or proven DTC is not recommended, a pre-thyroidectomy Tg and TgAb measurement might be used as an "in-vivo" recovery test in order to assess the reliability of Tg for use as a postoperative tumour marker. In this study, three patients (3/30, 10%) showed increased serum TgAb levels with simultaneous high serum Tg. Our study indicates that

^{18}F-FDG uptake was not significantly related to serum Tg variations, which may discredit the ability of ^{18}F-FDG PET/CT to predict therapeutic response. However, in five patients with positive ^{18}F-FDG uptake who exhibited a decrease of more than 25% of serum Tg, only two achieved partial response according to the post-treatment anatomical imaging, and the remaining three were regarded as having stable or progressive disease. Therefore, we assume that the decrease of serum Tg in patients with BMs from DTC, especially in those with ^{18}F-FDG-avid lesions, might not only reflect a decrease in tumor burden but also signal dedifferentiation of the tumor cells.[15,23] The variety in tumor burden, as indicated by serum Tg, among the patients included in this study may interfere with the analysis of the impact of ^{18}F-FDG avidity on patient outcome. Thus, we performed a Kruskal–Wallis H-test to compare the distribution of pretreatment serum Tg among different groups of patients who showed PR, SD or PD according to follow-up CT results after RAI therapies, and no significant difference was found (p = 0.278).

With regard to prognostic factors for patients with BMs from DTC, inconsistent findings were reported in the previous literature. Overall, factors including the absence of non-osseous metastases, the cumulative dose of RAI therapy, BM surgery, solitary BMs, and ^{131}I uptake by BMs were listed as the prognostic factors that were associated with improved survival.[8,12,24] However, neither age at the diagnosis of BMs nor the involvement of non-osseous organs had significant impact on the PFI in our study. This difference may be caused by the small sample size of the study population with only two patients less than 45 years of age. Patients who underwent surgical resection of BMs were excluded from this study to eliminate the overlapping effect of local surgery on RAI therapy while analyzing the efficacy of RAI.

^{18}F-FDG PET/CT is primarily considered in high-risk DTC patients with elevated serum Tg and negative ^{131}I WBS. A couple of studies proposed that ^{18}F-FDG PET/CT can also act as a prognostic tool that can identify patients at high risk of rapid disease progression and cancer-associated mortality.[13–15] The aforementioned studies dealt with the prognostic performance of ^{18}F-FDG uptake in all types of distant metastases from DTC, whereas our study mainly focused on BMs, which is considered a more dire type of metastatic disease. Based on our data, ^{18}F-FDG uptake in BMs was correlated with a worse PFI, regardless of ^{131}I uptake. Thus, both high

frequency of positive ^{18}F-FDG uptake in BMs and the predictive value of ^{18}F-FDG uptake for disease progression emphasizes the importance of applying ^{18}F-FDG PET/CT scans in the management of patients with BMs from DTC.

The main limitation that may restrain the validity of our conclusions is the limited number for subgroup analysis in this study. Larger-scaled studies are needed to further confirm our findings, especially those that systematically analyze the impact of variable ^{18}F-FDG and ^{131}I avidities among different metastatic sites of thyroid carcinoma.

In conclusion, the relationship between ^{18}F-FDG and ^{131}I uptake in BMs does not conform to the "flip-flop" phenomenon. The higher frequency of simultaneous ^{18}F-FDG and ^{131}I in BMs may indicate the tendency toward dedifferentiation and aggressiveness of BMs from DTC, compared to other common sites of metastases. ^{18}F-FDG-avid BMs are less likely to respond to RAI therapy, even in those that can concentrate ^{131}I. Our findings also suggest that the presence of ^{18}F-FDG uptake in BMs may predict disease progression and be associated with a worse prognosis in patients with BMs from DTC. For patients with ^{18}F-FDG-avid BMs, treatments other than RAI therapy, such as surgery, external beam radiation or targeted ablation (eg, cryotherapy) in combination with supportive therapies (bisphosphonates, denosumab) should be considered.

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