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The value of [¹⁸F]FDG PET/CT in avoiding overtreatment of ¹³¹I avidity pulmonary metastasis of differentiated thyroid cancer

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Abstract

Introduction: We usually use ¹³¹I-whole body scan (¹³¹I-WBS) and serum thyroglobulin (Tg) values to determine whether differentiated thyroid cancer (DTC) patients need to receive ¹³¹I treatment, but not all ¹³¹I-avid (functioning) patients have a good response to ¹³¹I therapy. Our study aims to assess the data of [¹⁸F]fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography ([¹⁸F]FDG PET/CT) to research the status of ¹³¹I-avid pulmonary metastases (PMs) and the prognosis of the patients.

Material and methods: The ¹³¹I-avid PMs of DTC patients who underwent [¹⁸F]FDG PET/CT scans were included. The maximum standardized uptake value (SUVmax), metabolic tumour volume (MTV), and total lesion glycolysis (TLG) were used to estimate [¹⁸F]FDG uptake. The mean follow-up period was 34.14 ± 18.64 months. Progression-free survival (PFS) was estimated by the Kaplan-Meier method. The study was based on per-patient and per-lesion analyses.

Results: Among the 42 included patients, 34 (34/42, 81%) showed [¹⁸F]FDG uptake, which was defined as abnormal foci (SUVmax > 1.0) in the lungs. SUVmax, MTV, TLG, and tumour size were the factors that influenced the outcome of ¹³¹I treatment based on Tg levels (p = 0.000, 0.016, 0.000, 0.000) in per-lesion analysis. The only independent factor was the size of the lesion. There was a significant difference in response to ¹³¹I therapy between PMs with F-I+ and F+/I+ according to both Tg levels and Response Evaluation Criteria in Solid Tumours (RECIST) (version 1.1) (p = 0.044, 0.001), in the per-lesion analysis. When the changes in size or metabolism of some lesions are inconsistent the prognosis of these patients is poor (p = 0.003).

Conclusions: We concluded that higher [¹⁸F]FDG uptake and larger tumour size predict poor therapeutic effects and a high risk of disease progression in ¹³¹I-avid PMs of DTC. For evaluating the efficiency of ¹³¹I treatment, per-lesion analyses and assessing the data of [¹⁸F]FDG PET/CT would be more reliable than per-patient evaluation only. And early focal treatment modalities may improve their life span. (Endokrynol Pol 2023; 74 (4): 385–391)

Key words: differentiated thyroid cancer; pulmonary metastasis; FDG avidity; radioiodine

Introduction

The lungs are the distant organs that most frequently have metastases from differentiated thyroid cancer (DTC). For these patients, ¹³¹I therapy has become the main treatment, especially in patients with ¹³¹I-avid (functioning) pulmonary metastases (PMs) [1]. The results of ¹³¹I-whole body scans (¹³¹I-WBS) and serum thyroglobulin (Tg) values are usually used to determine whether DTC patients need to receive ¹³¹I treatment. However, not all ¹³¹I-avid PMs have a good response to ¹³¹I therapy, and more than 10% of them develop into refractory iodine diseases [2]. In this way, it is more likely to cause the ¹³¹I-avid patient to receive overtreatment. Therefore, it is particularly important to screen out ¹³¹I-avid patients who are not sensitive to ¹³¹I treatment and find new indicators that predict

the efficacy. Nowadays, with the popularity of [¹⁸F]fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography ([¹⁸F]FDG PET/CT), its application in DTC patients has also increased. The accumulation of FDG in malignant tumours, to a certain extent, reflects the degree of differentiation of the tissue [3, 4], so [¹⁸F]FDG PET/CT imaging can be used to predict the effect of ¹³¹I treatment of patients with ¹³¹I-avid PMs from DTC and the prognosis of them. Moreover, the status of FDG uptake in different metastatic lesions could be different even in an individual [5–7], and these changes of morphology and metabolism are closely related to the efficacy of ¹³¹I treatment and prognosis of patients. Therefore, in this study, we assessed the value of [¹⁸F]FDG PET/CT for ¹³¹I-avid PMs from DTC and observed the changes in the PMs based on per-patient and per-lesion analyses.



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Material and methods

Patients

Data from 132 patients who were diagnosed with PMs and were treated with ¹³¹I between 2011 and 2018. Among them, 42 patients met the following criteria: (a) [¹⁸F]FDG PET/CT before ¹³¹I treatment for PMs; (b) PMs were positive for iodine uptake; (c) more than one course of ¹³¹I treatment after the diagnosis of PMs; (d) only measurable soft tissue components on CT, as defined by the Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1) [8]. The Xin Hua Hospital Review Board approved this retrospective study.

The diagnosis of PMs was established according to one of the following criteria: (a) the lung lesion was histologically proven; and (b) ¹³¹I uptake on more than one ¹³¹I-WBS with elevated thyroid stimulating hormone (TSH) and increased Tg levels.

Therapeutic approach and follow-up schedule

All patients were instructed to follow a low-iodine diet for at least 3–4 weeks before ¹³¹I treatment. TSH levels were 85.03 ± 35.37 μ IU/mL after stopping levothyroxine (L-T4) for 3–4 weeks. L-T4 therapy was administered 72 h after ¹³¹I treatment.

Adult patients with ¹³¹I-avid PMs of DTC were treated with a high-activity dose of ¹³¹I every 3–12 months. For children aged 10–18 years old, 4.625–7.4 GBq ¹³¹I was administered, and for children aged 5–10 years old, 2.775–4.44 GBq ¹³¹I was administered every 6–12 months. The cumulative activity of ¹³¹I ranged from 3.70 to 75.85 GBq. The number of ¹³¹I therapies ranged from 2–15 cycles (mean 4.5 cycles). The mean follow-up period was 44.7 ± 16.0 months.

Criteria of remission

Tumour size evaluation on anatomical imaging

The CT images of [¹⁸F]FDG PET/CT were obtained with a 3-mm slice thickness and reconstructed with a 1-mm slice thickness starting from the apex of the lungs. All CT images were obtained with the patient in the supine position. The CT images were reviewed in consensus by 2 radiologists who were blinded to the [¹⁸F]FDG PET results and clinical follow-up data.

The CT responses were assessed using Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1) as follows: (i) complete response (CR), disappearance of all lesions; (ii) partial response (PR), $\geq 30\%$ decrease in the sum of lesion diameters, taking the baseline sum of diameters as the reference; (iii) progressive disease (PD), $\geq 20\%$ increase in the sum of lesion diameters or appearance of ≥ 1 new lesion; and (iv) stable disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. CR, PR, and SD were considered good responses to ¹³¹I therapy in this study.

Tg evaluation

Tg and anti-thyroglobulin antibody (TgAb) levels were obtained before ¹³¹I administration using a time-resolved immunofluorometric assay (Anytest, Symbio Lifescience Co., Ltd., Shanghai, China). After all courses of ¹³¹I therapy were administered, we compared the Tg levels of each treatment and at the last follow-up, and classified them into 3 categories [9]: i) effective: a reduction of $> 25\%$ in Tg levels; ii) stable: decreased or increased Tg by $< 25\%$ and iii) progression: Tg increased by $> 25\%$. Effective and stable were considered good responses to ¹³¹I therapy in this study.

Images acquisition and analysis

[¹⁸F]FDG PET/CT imaging

After 3–4 weeks of thyroid hormone withdrawal (THW), patients with PMs were admitted to our department. On the 1st day after admission, [¹⁸F]FDG PET/CT scans together with other conventional assessments, including physical examination, serum TSH, serum-stimulated Tg, and serum TgAb, were performed. On aver-

age, the patients' TSH was 85.03 ± 35.37 μ IU/mL when the scans were performed. ¹³¹I treatment was performed on the 2nd day after admission. A ¹³¹I post-therapy scan was acquired 3 days after ¹³¹I oral administration.

Per-lesion imaging analysis

For each patient, a maximum of 5 lesions with [¹⁸F]FDG uptake were studied. The lesions had to be measurable on the CT scan of the [¹⁸F]FDG PET/CT. The maximum standardized uptake value (SUVmax) of each lesion (SUVmax/lesion) was measured by using a volume of interest with a standardized uptake value (SUV) expressed using the most commonly used definition of SUV (g/mL) = tissue activity (Bq/mL) / (injected activity [Bq] / body weight [g]). The [¹⁸F]FDG metabolic tumour volume of each lesion (MTV/lesion), representing the volume measured in the volume of interest, was determined using margin thresholds set at 40% of the maximum SUV (SUVmax). Total lesion glycolysis (TLG/lesion) represents the [¹⁸F]FDG metabolism in a given lesion and is obtained by multiplying the SUVmean by MTV.

Per-patient imaging analysis

The SUVmax/patient represents the highest SUVmax of all lesions in a given patient. The MTV of each patient (MTV/patient) represents the volume of all lesions with [¹⁸F]FDG uptake for a given patient and is calculated by adding the metabolic tumour volumes of all lesions present in that patient. The TLG of each patient (TLG/patient) represents the sum of the [¹⁸F]FDG metabolism of all lesions in a given patient.

Statistical analysis

SPSS version 22.0 was used for statistical analyses. Continuous data are expressed as the mean \pm standard deviation; categorical data are presented as frequency and percentage. Continuous data were analysed using independent samples t-tests and rank tests, and categorical data were analysed using Pearson's chi-square test. All the factors that may have affected Tg and anatomical imaging of the PMs were analysed by univariate analysis and confirmed by the chi-square test. Logistic regression was performed for multifactor analysis. Spearman correlation and Pearson correlation were used to detect the correlations between categorical variables and continuous variables. Progression-free survival (PFS), as measured by the time between the date of the diagnosis of PMs and the date of disease progression according to RECIST, version 1.1, was the primary endpoint of this study. The effect of different variables on PFS was estimated by Kaplan-Meier survival analysis. A p value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

The patients' characteristics are listed in Table 1. A total of 42 patients who had ¹³¹I-avid lung metastasis were enrolled out of 132 patients with PMs. The mean age of the subjects was 44.07 ± 16.00 years. Our retrospective study consisted of 16 men (16/42, 38%) and 26 women (26/42, 62%). The pathology was papillary TC in 39 cases and follicular TC in 3 cases. [¹⁸F]FDG uptake was found in 34 patients (34/42, 81%), while 8 patients (8/42, 19%) with ¹³¹I-avid PMs of DTC had negative [¹⁸F]FDG results after THW. The median cumulative activity of RAI was 26.83 GBq (range: 3.7–75.85 GBq). There was a good response to ¹³¹I therapy in 34 patients (34/42, 81%) and poor response in 8 (8/42, 19%) based on Tg.

Table 1. Characteristics of 42 patients with ¹³¹I-avid pulmonary metastases (PM) from differentiated thyroid cancer (DTC)

Factors	No. of patients	Positive [¹⁸ F]FDG	Negative [¹⁸ F]FDG
Age			
< 55y	31(74%)	25 (73.5%)	6 (75%)
≥ 55y	11 (26%)	9 (26.5%)	2 (25%)
Gender			
Male	16 (38%)	12 (36.3%)	4 (50%)
Female	26 (62%)	22 (64.7%)	4 (50%)
Histological type			
PTC	39 (93%)	33 (97.1%)	6 (75%)
FTC	3 (7%)	1 (2.9%)	2 (25%)
Extent of metastases			
Lung only	31 (74%)	24 (70.6%)	7 (87.5%)
Lung and other organs	11 (26%)	10 (29.4%)	1 (12.5%)

PTC — papillary thyroid cancer; FTC —follicular thyroid cancer; ¹⁸F-FDG — [¹⁸F]fluorodeoxyglucose

According to RECIST (version 1.1), 18/42 (43%) patients showed PR, while 17/42 (40%) patients had SD, 3/42 (7%) had CR, and 4/42 (10%) had PD; good responses included CR, PR, and SD.

Per-patient analysis

We analysed [¹⁸F]FDG uptake in patients through SUVmax, MTV, and TLG. The median SUVmax of each patient was 1.63 (range 0.43–21.39). The median MTV/patient was 1.85 cm³ (range: 0.4–16.47). The median TLG/patient was 1.74 (range: 0.2–73.34). According to the therapeutic response based on Tg, univariate analyses showed that SUVmax/patient (1.63 ± 1.06, *p* = 0.061), MTV/patient (1.85 ± 0.98 cm³, *p* = 0.217), and TLG/patient (1.74 ± 0.67, *p* = 0.109) were not factors that influenced the outcome of ¹³¹I treatment, and the same results were found with CT response (*p* = 0.493, 0.128, 0.113). We divided the PMs into 2 subgroups according to the [¹⁸F]FDG and ¹³¹I-avid results:

(1) [¹⁸F]FDG-negative and ¹³¹I-positive PMs (F-I+, *n* = 8); and (2) simultaneous accumulation of [¹⁸F]FDG and ¹³¹I (F+/I+, *n* = 34); however, there was no significant difference in response to ¹³¹I therapy between the 2 groups according to both the Tg levels and RECIST (version 1.1) (*p* = 0.306, 1.000) (Tab. 2).

Per-lesion analysis

A total of 188 lesions were studied. The median SUVmax/lesion was 0.94 (range 0.43–21.39). The median MTV/lesion was 0.40 cm³ (range: 0.4–16.47). The median TLG/lesion was 0.31 (range: 0.2–73.34). [¹⁸F]FDG-positive ¹³¹I-avid PMs of DTC were significantly more common in females (*p* = 0.001), older patients (*p* = 0.038), and in patients with larger tumour sizes (*p* = 0.000) and higher TSH (*p* = 0.010). According to the Tg levels, the SUVmax/lesion (0.94 ± 0.58, *p* = 0.000), MTV/lesion (0.40 ± 0.20 cm³, *p* = 0.016), TLG/lesion (0.31 ± 0.10, *p* = 0.000), and the size of the tumour

Table 2. Subgroup analyses of factors predicting therapeutic response based on anatomical imaging changes and thyroglobulin (Tg) on a per-patient and per-lesion basis

Factor	RECIST v. 1.1				p-value	Tg			p-value
	CR	PR	SD	PD		Effectiveness	Stabilization	Progression	
[¹⁸F]FDG									
Positive	3	17	11	3	1	25	1	8	0.306
Negative	0	1	6	1		8	0	0	
[¹⁸F]FDG									
Positive	22	19	43	4	0.044	60	3	25	0.001
Negative	16	12	59	13		90	0	10	

RECIST v. 1.1 — Response Evaluation Criteria in Solid Tumours version 1.1; CR — complete response; PR — partial response; SD — stable disease; PD — progressive disease; ¹⁸F-FDG — [¹⁸F]fluorodeoxyglucose

Table 3. Logistic regression of factors predicting therapeutic response based on thyroglobulin (Tg) in per-lesion analysis

Factors	B	S.E.	Wald	Sig.	Exp (B)
SUVmax	0.185	0.184	1.021	0.312	1.204
MTV	-0.388	0.419	0.860	0.354	0.678
TLG	0.085	0.336	0.064	0.800	1.089
Size	0.225	0.101	4.940	0.026	1.253
Constant	-3.110	0.576	29.153	0.000	0.045

SUVmax — maximum standardized uptake value; MTV — metabolic tumour volume; TLG — total lesion glycolysis

(5.30 ± 4.00 mm, $p = 0.000$) had a significant influence on ¹³¹I treatment response. However, these factors did not lead to a significant difference in response to ¹³¹I therapy according to RECIST (version 1.1) ($p = 0.124, 0.256, 0.273, 0.252$). Logistic regression (Enter) was performed on the above factors. The model likelihood ratio test results are shown: $\chi^2 = 26.349, p = 0.000$, indicating that the model is statistically significant. The only independent factor found from the regression equation was the size of the lesion, see Table 3. In the subgroup analysis, a significant difference in response to ¹³¹I therapy was found between PMs with F-I+ and F+/I+ ($p = 0.044, 0.001$) according to RECIST (version 1.1) and Tg levels (Tab. 2).

Because the status of different metastatic lesions, including size and [¹⁸F]FDG uptake, could be different even in an individual, we observed changes in the lesions and then analysed the relationships between these changes and efficacy. According to RECIST, we usually used the sum of the diameters of all target lesions as the basis for evaluating patients' therapeutic efficacy, but in this study, we found that the changes in size or metabolism of individual lesions was not always consistent with therapeutic efficacy based on RECIST. For example, ¹³¹I therapy showed good responses in a given patient, but an increasing metabolism of the lesion could still be observed. Accordingly, we further divided the patients into 2 groups: (1) the changes of size and metabolism in all lesions were consistent with patients' therapeutic efficacy (group consistency, $n = 31$); and (2) the changes of size and metabolism in all lesions were inconsistent with patients' therapeutic efficacy (group inconsistency, $n = 11$). In the consistency *vs.* inconsistency comparison, we found a significant difference between the 2 groups in response to ¹³¹I therapy ($p = 0.003$).

Survival

The median progression-free interval (PFI) of these DTC patients with PMs was 62 months (ranging from 6 to 69 months). The Kaplan-Meier survival analysis

showed that there was a significant difference in survival between the consistency and inconsistency groups ($p = 0.009$), but no significant differences were seen between the [¹⁸F]FDG-positive and [¹⁸F]FDG-negative groups ($p = 0.966$) (Fig. 1).

Discussion

According to our study, the effective rates of ¹³¹I treatment for DTC with lung metastasis was 81% and 90%, based on Tg levels and RECIST, respectively, which were higher than the levels reported in the literature [10, 11]. This is related to the fact that we only included iodine-avid PM patients. Compared with the evaluated PD based on RECIST, slightly more patients were evaluated as having inefficiency based on Tg levels. This may show that factors regarding the function of the lesion change earlier than the morphology, and it is important to find markers predicting the status of ¹³¹I uptake by metastatic lesions, which are desirable for timely changing of the therapeutic regimen. With the rapid growth of thyroid cancer morbidity [12], [¹⁸F]FDG PET/CT scans can provide a valuable diagnostic method about functional changing [13]. [¹⁸F]FDG-avid tumours tend to be more aggressive in behaviour [14–16]. On the other hand, the reproducibility of CT measurements is known to be lower than the reproducibility of [¹⁸F]FDG calculations. Therefore, [¹⁸F]FDG PET/CT is a powerful tool for assessing DTC.

In the per-patient analysis, we evaluated [¹⁸F]FDG avidity by SUVmax, MTV, and TLG [9, 16]; however, in our study, these factors had no clear significance for predicting the ¹³¹I treatment effect of ¹³¹I-avid PMs. We also did not find a correlation between SUVmax/patient and PFS. This may be related to the limited number of patients or the shorter follow-up time. And as shown in our study, 81% (34/42) of patients showed simultaneous [¹⁸F]FDG and ¹³¹I uptake. The high proportion of [¹⁸F]FDG-positive lesions demonstrated by our study may be due to all of the lung lesions that were measurable on chest CT. [¹⁸F]FDG metabolism patterns are related to the size of the lesions [17]; the larger the lesion, the high-

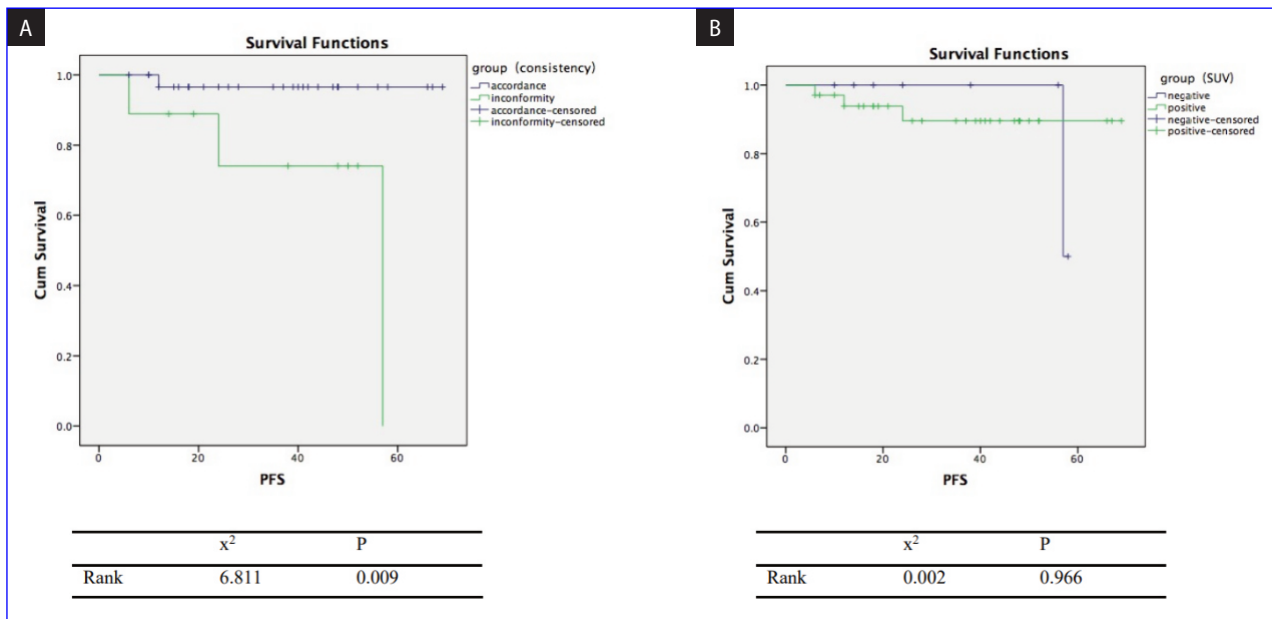


Figure 1. Progression-free survival (PFS) of differentiated thyroid carcinoma (DTC) patients with pulmonary metastases (PMs). PFS according to consistency and inconsistency groups (A) and [^{18}F]fluorodeoxyglucose (^{18}F -FDG)-positive and ^{18}F -FDG-negative groups (B)

er its [^{18}F]FDG uptake. Some of our patients also had extrapulmonary metastases, which may have more aggressive growth than PMs alone [18]. On the other hand, the high [^{18}F]FDG uptake may implicate that the clinical significance of this flip-flop phenomenon has not been fully defined [19, 20].

In the per-lesion analysis, [^{18}F]FDG uptake was related to age, sex, diameter of lesion, and TSH level. [^{18}F]FDG PET/CT may be more useful in older patients, females, patients with larger PMs, or patients with high TSH values. The SUVmax, MTV, TLG, and the size of the tumour were proven to be significant factors for the efficiency of ^{131}I treatment according to Tg levels. It is considered that [^{18}F]FDG-avid tumours tend to be less differentiated and more aggressive than those with low [^{18}F]FDG uptake [9]. In the subgroup analysis, the treatment for lesions with simultaneous [^{18}F]FDG and ^{131}I uptake had poor efficacy. Several reasons may account for this phenomenon: firstly, this may imply that the lesions are partially dedifferentiated, which is prone to happen during the process of metastasis or ^{131}I treatment [21, 22]; in addition, it may also be related to the diameter of the lesion, which is positively correlated with [^{18}F]FDG uptake. The longer the diameter of the lesion, the more ^{131}I treatment is required [11, 23]. The above factors mean that the absorbed dose fails to eliminate the lesion completely. Some studies have shown that [^{18}F]FDG-avid metastases of DTC with or without ^{131}I uptake are resistant to ^{131}I therapy [10], which is in line with our research. Therefore, [^{18}F]FDG-avid lesions are seldom eradicated by radioiodine therapy alone, and it

should be considered for close monitoring and other options, such as surgery or external radiation. However, the only independent influencing factor was the size of the lesion. This may be related to interference from other factors.

Considering the multicentricity and polyclone of DTC, the status of different metastatic lesions could be different even in an individual [5–7]. In this study, we found that the changes in size or metabolism in some lesions were not consistent with the changes in therapeutic efficacy of some patients. Although some patients can achieve CR, PR, or SD, they still have some lesions that show a tendency to progress. We can also conclude that these patients have poor prognosis through subgroup analyses. This phenomenon shows that some lesions exhibit different degrees of differentiation in a given patient. These lesions may progress and affect the patient's response to ^{131}I treatment. Therefore, when we evaluate the therapeutic efficiency of patients, lesion-based analyses and quantitatively assessing the data of [^{18}F]FDG PET/CT using SUVmax, MTV, and TLG to predict ^{131}I -avidity for metastatic DTC would be more reliable than qualitative per-patient evaluation only. The [^{18}F]FDG uptake PMs may be resistant to ^{131}I treatment, and these lesions may lead to a poor prognosis for the patient. Thus, tailored treatment modalities should be chosen for the lesions that have a malignant tendency, after balancing the toxicity of systemic treatment. This approach will effectively improve the patient's response to treatment and avoid the ^{131}I overtreatment of patients.

The limitations of our study are that it was a retrospective study with a relatively short follow-up period (less than 10 years). The number of patients was limited in the evaluation of ¹³¹I therapeutic effects in the subgroup analysis. Moreover, the partial volume effect and respiratory motion can also significantly influence the perception of [¹⁸F]FDG uptake.

Conclusion

[¹⁸F]FDG PET/CT is a powerful tool for predicting the ¹³¹I therapeutic efficiency of patients with ¹³¹I-avid PMs of DTC. Early postoperative [¹⁸F]FDG PET/CT for them may not only reflect tumour status but also reveal prognosis information. Lesions with a larger size and higher SUV_{max}, MTV, and TLG may have a poor response to therapy, and the only independent factor affecting treatment response is the size of the lesion. For the patients who accepted ¹³¹I treatment, lesion-based analyses and quantitative assessment of the [¹⁸F]FDG PET/CT data would be more desirable than qualitative per-patient evaluation only. The [¹⁸F]FDG uptake PMs may lead to a poor prognosis for the patient, and early focal treatment modalities may improve their life span. A limited number of patients had ¹³¹I avidity and high [¹⁸F]FDG avidity, which may suggest refractory disease.

Compliance with ethical standards

This study was approved by the Ethics Review Board of XinHua Hospital. Because of the retrospective nature and the fact that no individually identifiable or sensitive information was involved, informed consent from the patients was waived.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Conflict of interest

The authors declare that they have no competing interests.

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Authors' contributions

Z.X., S.W., H.W., and H.F. conceived and designed the experiments. Z.X., C.L., and F.F. performed experiments. Z.X. and H.F. wrote the manuscript, performed analysis, and assembled the tables and figure.

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