

# The Value of $^{18}\text{F}$ -FDG PET/CT in avoiding overtreatment of $^{131}\text{I}$ Avidity Pulmonary Metastasis of Differentiated Thyroid Cancer

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## Research article

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# Abstract

**Background:** We usually use  $^{131}\text{I}$  whole body scan and serum thyroglobulin (Tg) values to determine whether differentiated thyroid cancer (DTC) patients need to receive  $^{131}\text{I}$  treatment, but not all  $^{131}\text{I}$ -avid (functioning) patients have good responses, which is more likely to cause the  $^{131}\text{I}$ -avid patient to receive overtreatment. Our study aims to assess the date of  $^{18}\text{F}$ -FDG PET/CT to avoid  $^{131}\text{I}$  overtreatment and research the status of  $^{131}\text{I}$ -avid pulmonary metastases (PMs) and the prognosis of the patients.

**Methods:** The  $^{131}\text{I}$ -avid PMs of DTC patients who underwent  $^{18}\text{F}$ -FDG PET/CT scans were included. The SUVmax (maximum standardized uptake value), MTV (metabolic tumour volume) and TLG (total lesion glycolysis) were used to estimate  $^{18}\text{F}$ -FDG uptake. The mean follow-up period was  $34.14 \pm 18.64$  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  $^{18}\text{F}$ -FDG uptake, which was defined as abnormal foci (SUVmax  $>1.0$ ) in the lungs. SUVmax, MTV and TLG and tumour size were the factors that influenced the outcome of  $^{131}\text{I}$  treatment based on Tg levels ( $p=0.000, 0.016, 0.000, 0.000$ ). The only independent factor was the size of the lesion. There was a significant difference in response to  $^{131}\text{I}$  therapy between PMs with F-I+ and F+/I+ according to both Tg levels and RECIST (version 1.1) ( $p=0.044, 0.001$ ), according to the per-lesion analysis. When the changes in size or metabolism of some lesions are inconsistent with therapeutic efficacy of patients, it indicates that these patients have a poor prognosis ( $P=0.003$ ).

**Conclusions:** We concluded that higher  $^{18}\text{F}$ -FDG uptake and larger tumour size predict poor therapeutic effects and a high risk of disease progression in  $^{131}\text{I}$ -avid PMs of DTC. For evaluating the efficiency of  $^{131}\text{I}$  treatment, per-lesion analyses and assessing the data of  $^{18}\text{F}$ -FDG PET/CT would be more reliable than per-patient evaluation only. The increasing  $^{18}\text{F}$ -FDG uptake or diameter of PMs may lead to a poor prognosis for the patient, and early focal treatment modalities may improve their life span.

## Background

The lungs are the distant organs that most frequently have metastases from differentiated thyroid cancer (DTC), for these patients,  $^{131}\text{I}$  therapy has become the main treatment, especially in patients with  $^{131}\text{I}$ -avid (functioning) pulmonary metastases (PMs) [1]. The result of  $^{131}\text{I}$ -whole body scan ( $^{131}\text{I}$ -WBS) and serum thyroglobulin (Tg) values are usually used to determine whether DTC patients need to receive  $^{131}\text{I}$  treatment. However, not all  $^{131}\text{I}$ -avid PMs have good responses to  $^{131}\text{I}$  therapy, and more than 10% of them developed into refractory iodine diseases [2]. In this way, it is more likely to cause the  $^{131}\text{I}$ -avid patient to receive overtreatment. Therefore, it is particularly important to screen out  $^{131}\text{I}$ -avid patients who are not sensitive to  $^{131}\text{I}$  treatment and find new indicators that predict the efficacy. Nowadays, with the popularity of  $^{18}\text{F}$ -fluorodeoxyglucose (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<sup>[3,4]</sup>, so <sup>18</sup>F-FDG PET/CT imaging can be used to predict the effect of <sup>131</sup>I treatment of patients with <sup>131</sup>I-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<sup>[5-7]</sup>, and these changes of morphology and metabolism are closely related to the efficacy of <sup>131</sup>I treatment and prognosis of patients. Therefore, in this study, we assessed the value of <sup>18</sup>F-FDG PET/CT for <sup>131</sup>I-avid PMs from DTC and observed the changes in the PMs based on per-patient and per-lesion analyses.

## Methods

### Patients

Data from 132 patients who were diagnosed with PMs were treated with <sup>131</sup>I between 2011 and 2018, among them, 42 patients met the following criteria: (a) <sup>18</sup>F-FDG PET/CT before <sup>131</sup>I treatment for PMs; (b) PMs were positive for iodine uptake; (c) more than one course of <sup>131</sup>I 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)<sup>[8]</sup>. The Shanghai Jiaotong University, Medical School Affiliated Xinhua 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; (b) <sup>131</sup>I uptake on more than one <sup>131</sup>I-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 <sup>131</sup>I treatment. TSH levels were  $85.03 \pm 35.37$   $\mu$ U/ml after stopping levothyroxine (L-T4) for 3-4 weeks. L-T4 therapy was administered 72 h after <sup>131</sup>I treatment.

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

### Criteria of remission

### Tumour size evaluation on anatomical imaging

The CT images of <sup>18</sup>F-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 two radiologists who were blinded to the  $^{18}\text{F}$ -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  $\geq 1$  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  $^{131}\text{I}$  therapy in this study.

### **Tg evaluation**

Tg and anti-thyroglobulin antibody (TgAb) levels were obtained before  $^{131}\text{I}$  administration using a time-resolved immunofluorometric assay (Anytest, Symbio Lifescience Co., Ltd., Shanghai, China). After all courses of  $^{131}\text{I}$  therapy were administered, we compared the Tg levels of each treatment and at the last follow-up were classified into three 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  $^{131}\text{I}$  therapy in this study.

### **Images acquisition and analysis**

#### **$^{18}\text{F}$ -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,  $^{18}\text{F}$ -FDG PET/CT scans together with other conventional assessments, including physical examination, serum TSH, serum-stimulated Tg, and serum TgAb, were performed. On average, the patients' TSH was  $85.03 \pm 35.37$   $\mu\text{IU/ml}$  when the scans were performed.  $^{131}\text{I}$  treatment was performed on the 2nd day after admission. A  $^{131}\text{I}$  post-therapy scan was acquired 3 days after  $^{131}\text{I}$  oral administration.

#### **Per-lesion imaging analysis**

For each patient, a maximum of five lesions with  $^{18}\text{F}$ -FDG uptake were studied. The lesions had to be measurable on the CT scan of the  $^{18}\text{F}$ -FDG PET/CT. The 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 ( $\text{g/mL}$ ) = (tissue activity ( $\text{Bq/mL}$ )/ [(injected activity ( $\text{Bq}$ )/ body weight ( $\text{g}$ ))]. The  $^{18}\text{F}$ -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  $^{18}\text{F}$ -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  $^{18}\text{F}$ -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  $^{18}\text{F}$ -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 patient characteristics are listed in Table 1. A total of 42 patients who had  $^{131}\text{I}$ -avid lung metastasis were enrolled out of 132 patients with PMs. The age of the subjects was  $44.07 \pm 16.00$  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.  $^{18}\text{F}$ -FDG uptake was found in 34 patients (34/42, 81%), while 8 patients (8/42, 19%) with  $^{131}\text{I}$ -avid PMs of DTC had negative  $^{18}\text{F}$ -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  $^{131}\text{I}$  therapy in 34 patients (34/42, 81%) and poor responses in 8 (8/42, 19%) based on Tg. 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  $^{18}\text{F}$ -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  $1.85 \text{ cm}^3$  (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 ( $1.63 \pm 1.06$ ,  $P=0.061$ ), MTV/patient ( $1.85 \pm 0.98 \text{ cm}^3$ ,

P=0.217) and TLG/patient ( $1.74\pm 0.67$ , P=0.109) were not the factors that influenced the outcome of  $^{131}\text{I}$  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  $^{18}\text{F}$ -FDG and  $^{131}\text{I}$ -avid results: (1)  $^{18}\text{F}$ -FDG-negative and  $^{131}\text{I}$ -positive PMs (F-I+, n =8); and (2) simultaneous accumulation of  $^{18}\text{F}$ -FDG and  $^{131}\text{I}$  (F+/I+, n =34); however, there was no significant difference in response to  $^{131}\text{I}$  therapy between the two groups according to both the Tg levels and RECIST (version 1.1) (p= 0.306,1.000), see Table 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  $0.40\text{ cm}^3$  (range: 0.4–16.47). The median TLG/lesion was 0.31 (range: 0.2-73.34).  $^{18}\text{F}$ -FDG-positive  $^{131}\text{I}$ -avid PMs of DTC were significantly more common in females (p=0.001), older patients (p=0.038), patients with larger tumour sizes (P=0.000) and higher TSH (P=0.010). According to the Tg levels, the SUVmax/lesion ( $0.94\pm 0.58$ , P=0.000), MTV/lesion ( $0.40\pm 0.20\text{ cm}^3$ , P=0.016), TLG/lesion ( $0.31\pm 0.10$ , P=0.000) and the size of the tumour ( $5.30\pm 4.00\text{mm}$ , P=0.000) had a significant influence on  $^{131}\text{I}$  treatment response. However, these factors did not lead to a significant difference in response to  $^{131}\text{I}$  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  $X^2 = 26.349$ , 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  $^{131}\text{I}$  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, see Table 2.

Because the status of different metastatic lesions, including size and  $^{18}\text{F}$ -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 lesion was not always consistent with therapeutic efficacy based on RECIST. For example,  $^{131}\text{I}$  therapy showed good responses in a given patient, however, an increasing metabolism of the lesion could still be observed, see Figure 1. Accordingly, we further divided the patients into two 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 two groups in response to  $^{131}\text{I}$  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  $^{18}\text{F}$ -FDG-positive and  $^{18}\text{F}$ -FDG-negative groups ( $P=0.966$ ), see Figure 2.

## Discussion

According to our study, the effective rates of  $^{131}\text{I}$  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 PMs' patients. Compared with those evaluated PD based on RECIST, slightly more patients were evaluated inefficiency based on Tg levels. This may show that factors about function of the lesion change earlier than the morphology, and it is important to find markers predicting the status of  $^{131}\text{I}$  uptake by metastatic lesions, which are desirable for timely changing therapeutic regimen. With the rapid growth of thyroid cancer morbidity [12],  $^{18}\text{F}$ -FDG PET/CT scans can provide a valuable diagnostic method about functional changing [13].  $^{18}\text{F}$ -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  $^{18}\text{F}$ -FDG calculations. Therefore,  $^{18}\text{F}$ -FDG PET/CT is a powerful tool for assessing DTC.

In the per-patient analysis, we evaluated  $^{18}\text{F}$ -FDG avidity by SUVmax, MTV, TLG [9,16], however, in our study, these factors had no clear significance for predicting the  $^{131}\text{I}$  treatment effect of  $^{131}\text{I}$ -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  $^{18}\text{F}$ -FDG and  $^{131}\text{I}$  uptake. The high proportion of  $^{18}\text{F}$ -FDG-positive lesions demonstrated by our study may be due to all of the lung lesions that were measurable on chest CT.  $^{18}\text{F}$ -FDG metabolism patterns are related to the size of the lesions [17]; the larger the lesion is, the higher its  $^{18}\text{F}$ -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  $^{18}\text{F}$ -FDG uptake maybe implicate that the clinical significance of this flip-flop phenomenon has not been fully defined [19,20].

In the per-lesion analysis,  $^{18}\text{F}$ -FDG uptake was related to age, sex, diameter of lesion and TSH level.  $^{18}\text{F}$ -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  $^{131}\text{I}$  treatment according to Tg levels. It is considered that  $^{18}\text{F}$ -FDG-avid tumours tend to be less differentiated and more aggressive than those with low  $^{18}\text{F}$ -FDG uptake [9]. In the subgroup analysis, the treatment for lesions with simultaneous  $^{18}\text{F}$ -FDG and  $^{131}\text{I}$  uptake had poor efficiency. 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  $^{131}\text{I}$  treatment [21,22]; in addition, it may also be related to the diameter of the lesion, which is positively correlated with  $^{18}\text{F}$ -FDG uptake. The longer the diameter of the lesion, the more  $^{131}\text{I}$  treatment are required [11,23]. The above factors cause that the absorbed dose fails to eliminate the lesion completely. Some studies have shown

that  $^{18}\text{F}$ -FDG-avid metastases of DTC with or without  $^{131}\text{I}$  uptake are resistant to  $^{131}\text{I}$  therapy [10], which is in line with our research. Therefore, FDG-avid lesions are seldomly eradicated by radioiodine therapy alone, 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 tendency to progression. 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  $^{131}\text{I}$  treatment. Therefore, when we evaluate the therapeutic efficiency of patients, lesion-based analyses and quantitatively assessing the data of  $^{18}\text{F}$ -FDG PET/CT using SUVmax, MTV, TLG to predict  $^{131}\text{I}$ -avidity for metastatic DTC would be more reliable than qualitative per-patient evaluation only. The  $^{18}\text{F}$ -FDG uptake PMs may show resistant to  $^{131}\text{I}$  treatment, and these lesions may lead to a poor prognosis for the patient. Thus, tailored treatment modalities should be chosen for the lesions which 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  $^{131}\text{I}$  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  $^{131}\text{I}$  therapeutic effects in the subgroup analysis. Moreover, the partial volume effect and respiratory motion can also significantly influence the perception of  $^{18}\text{F}$ -FDG uptake.

## Conclusion

$^{18}\text{F}$ -FDG PET/CT is a powerful tool for predicting the  $^{131}\text{I}$  therapeutic efficiency of patients with  $^{131}\text{I}$ -avid PMs of DTC. Early postoperative  $^{18}\text{F}$ -FDG PET/CT for them may not only reflect tumour status but also reveal prognosis information. Lesions with a larger size and higher SUVmax, 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 accepted  $^{131}\text{I}$  treatment, lesion-based analyses and quantitatively assessing the data of  $^{18}\text{F}$ -FDG PET/CT would be more desirable than qualitative per-patient evaluation only. The  $^{18}\text{F}$ -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  $^{131}\text{I}$  avidity and high  $^{18}\text{F}$ -FDG avidity, which may suggest refractory disease.

## List Of Abbreviations

<b>Abbreviations</b>	<b>Abbreviate from</b>
DTC	Differentiated thyroid carcinoma
PTC	Papillary thyroid carcinoma
FTC	Follicular thyroid carcinoma
PMs	Pulmonary metastases
FDG	Fludeoxyglucose
PET/CT	Positron emission tomography/ computed tomography
CT	Computed tomography
SUVmax	Standardized uptake value max
MTV	Metabolic tumor volume
TLG	Total lesion glycolysis
Tg	Thyroglobulin
TgAb	Antithyroglobulin
L-T4	Levothyroxine
TSH	Thyroid stimulating hormone
WBS	Whole body scan
PFS	Progression-Free-Survival
CR	Complete response
PR	Partial response
PD	Progressive disease
SD	Stable disease

## Declarations

### Ethics approval and consent to participate

This study was approved by the ethics review board of the Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine. Because of the retrospective nature, plus no individually identifiable or sensitive information was involved, informed consents from all patients had been 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].

### Competing interests

The authors declare that they have no competing interests

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## Authors' contributions

All authors made substantial contribution to the conception of this commentary. HLF and ZYX have made design of the work; Material preparation, data collection, and analysis were performed by ZYX, FF, and LLZ. The first draft of the manuscript was written by ZYX and was revised by ZYX and CL; SQW and HW commented on the previous versions of the manuscript. HLF supervised the study.

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## Tables

**Table 1: characteristics of 42 patients with  $^{131}\text{I}$ -avid PM from DTC**

factors	no. of patients	Positive <sup>18</sup> F-FDG	negative <sup>18</sup> 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%)

Abbreviations: PTC: papillary thyroid cancer; FTC: follicular thyroid cancer.

**Table 2: Subgroup analyses of factors predicting therapeutic response based on anatomical imaging changes and s-Tg on a per-patient and per-lesion basis.**

Factor	RECIST1.1				P value	Tg			P value
	CR	PR	SD	PD		Effectiveness	Stabilization	Progression	
<sup>18</sup> F-FDG									
Positive	3	17	11	3	1	25	1	8	0.306
Negative	0	1	6	1		8	0	0	
<sup>18</sup> F-FDG									
Positive	22	19	43	4	0.044	60	3	25	0.001
Negative	16	12	59	13		90	0	10	

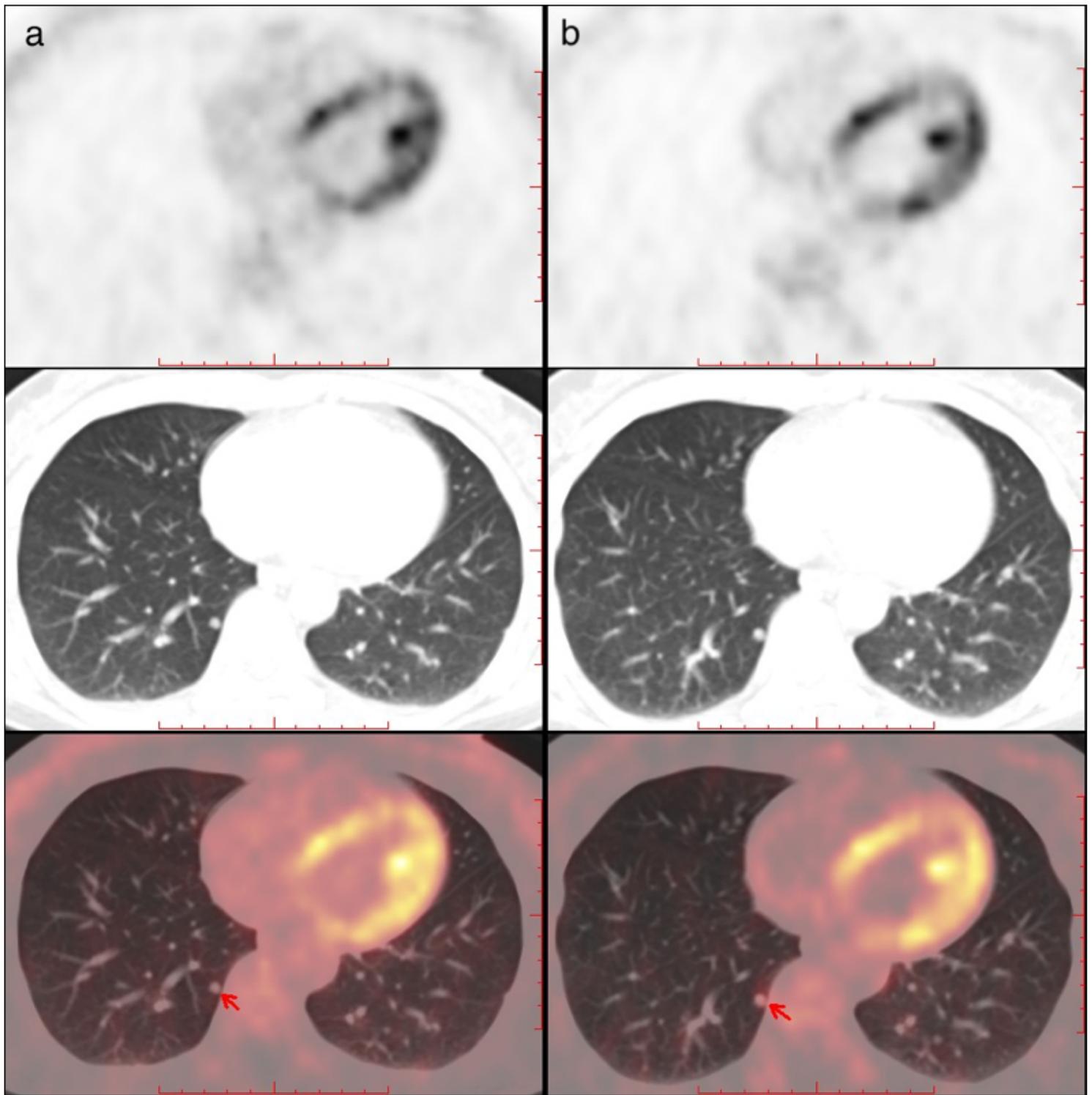
Abbreviations: CR: complete response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease.

**Table 3: Logistic regression of factors predicting therapeutic response based on s-Tg on 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

Abbreviations: SUVmax: maximum standardized uptake value; MTV: metabolic tumor volume; TLG: total lesion glycolysis.

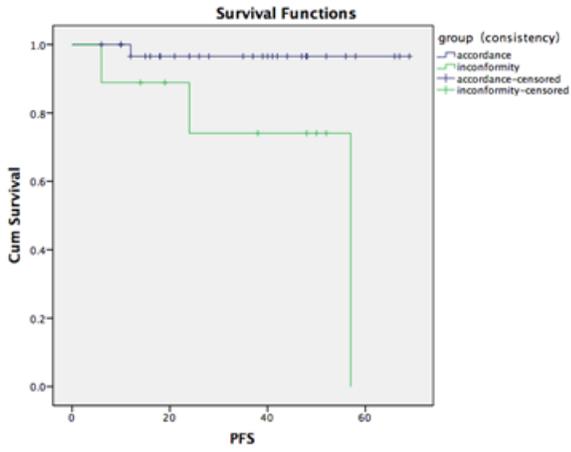
## Figures



**Figure 1**

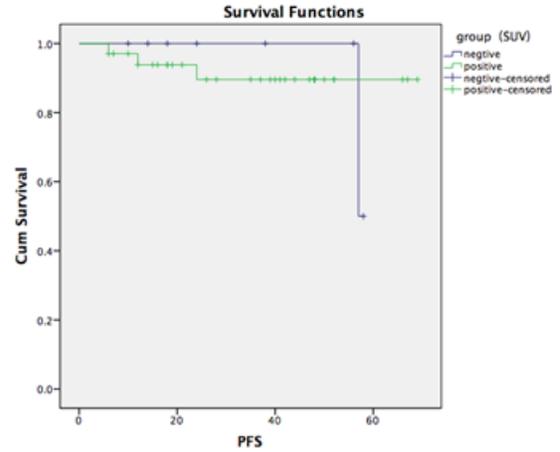
A 42 years old woman with  $^{131}\text{I}$ -avid metastases from papillary thyroid cancer (T4aN1M1). She was evaluated as PR based on RECIST (version 1.1) after  $^{131}\text{I}$  treatment. However, comparing the  $^{18}\text{F}$ -FDG PET-CT before (a) and after (b), we can still see the lesion in the lower lobe of the left lung, and its SUVmax is increasing than before (SUVmax=0.81, 2.81).

a)



	$\chi^2$	P
Rank	6.811	0.009

b)



	$\chi^2$	P
Rank	0.002	0.966

**Figure 2**

PFS according to consistency and inconsistency groups (a) and 18F-FDG-positive and 18F-FDG-negative groups (b)