Evaluation of Prognostic Value in Thyroid Cancer and Bone Metastasis with I-131 Therapy

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Research Article

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Abstract

Objectives: This study is aimed to evaluate the risk factors for survival and prognostic value in differentiated thyroid cancer (DTC) and bone metastasis (BM) with I-131 therapy.

Methods: 67 consecutive patients with DTC and BM were included between 2006 and 2019. All patients received total or near-total thyroidectomy, radioactive iodine (RAI) treatment, I-131 whole-body scan (WBS) and Fluorine-18-fluorodesoxyglucose positron emission tomography/computed tomography (F-18-FDG PET/CT). Variables including patient’s gender, age, pathology, laboratory examination, characteristics of BM, treatment models, and metabolic parameters of F-18-FDG PET/CT were analyzed for disease progression and survival prognosis.

Results: A total of 207 BM lesions were found in 67 patients and 28 (41.79%) patients experienced disease progression. Age stratiﬁcation, thyroglobulin/thyroid-stimulating hormone (Tg/TSH) level, Tg level, PET (+) ratio and RAI (+) ratio showed signiﬁcant differences between patients with progression and those without progression (p<0.05). The overall survival (OS) rate was 100% at one year, 86.56% at three years, and 43.20% at ﬁve years. Base on survival analysis, Tg/TSH level, PET (+) ratio and RAI(+) ratio were independent risk factors for PFS and OS. Of parameters of PET/CT, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were the signiﬁcant prognostic factors for PFS and OS in DTC and BM patients.

Conclusions: Tg/TSH level, PET (+) ratio and RAI(+) ratio are the independent risk factors for survival in patients with DTC and BM. MTV and TLG are the significant prognosis factors for PFS and OS on PET/CT imaging.

Introduction

Bone metastasis (BM) in differentiated thyroid cancer (DTC) is the second most common site for the spread of distal metastasis[1]. BM is typically associated with an overall worse prognosis than lymph node and lung metastasis[2-4] and may reduce the quality of life in DTC patients and cause other complications[5]. Conventional treatment methods of BM in DTC patients include radioactive iodine (RAI), surgical resection, external beam radiation therapy (EBRT) and chemotherapy. Nevertheless, once BM lesions are no longer amenable to RAI therapy or surgery, the expected survival declines rapidly and death within three years is common[6, 7]. Previous studies have identiﬁed various prognostic factors related to improved survival in patients with metastatic DTC[6, 8-11]. However, only a few factors focused independently on DTC patients with BM.

Fluorine-18-fluorodesoxyglucose positron emission tomography/computed tomography (F-18-FDG PET/CT) is performed in metastatic DTC patients to assess both the locations of distant metastases and FDG status of lesions. It is currently used for prognostic purposes because metabolic parameters of FDG-PET/CT can predict the survival[12-14] and the response of neoplastic foci in RAI treatment[15]. Plenty of
studies also showed the maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) can be suggested as prognostic factors for various tumors [16-19]. However, to date, no data have shown whether parameters of FDG-PET could be used as surrogate markers for progression and survival in DTC with BM patients. Based on clinical observation, We found that DTC patients often exist different RAI and FDG status of BM lesions, and those patients have different clinical outcomes after RAI therapy. To our knowledge, few studies have showed how the BM lesion's status of RAI and FDG influenced the survival of DTC patients.

Based on the findings, the objective of this study was to evaluate risk factors for survival and prognostic value in DTC patients and BM with I-131 therapy.

**Methods**

**Patients**

This retrospective study was approved by the Institutional Review Board of our institution. We reviewed the file records of patients with DTC patients treated at our Department of Xinhua Hospital affiliated to Shanghai Jiaotong University from 2006 to 2020. The eligibility criteria: 1) age >18 years; 2) histological confirmation of DTC; 3) bone metastasis was diagnosed based on at least one of the following modalities: bone lesion showing I-131 abnormal uptake on whole-body scan (WBS); no I-131 uptake, at least one of the imaging (X-ray, computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy or F-18-FDG PET/CT) findings indicating bone metastasis, and with elevated thyroglobulin (Tg) level (≥ 15 ng/mL); pathology or biopsy confirms. BM was classified as synchronous if they were detected at the diagnosis time of DTC and metachronous if they were found later in the follow-up.

The exclusion criteria includes patients with aggressive malignant variants, including tall-cell, insular, poorly differentiated, and diffuse sclerosing thyroid cancer; anaplastic or medullary carcinoma; patients with synchronous cancers and limited life expectancy. Finally, a total of 67 patients were involved in our study. All patients were treated with total or near-total thyroidectomy and received remnant RAI therapy for eliminating residual thyroid. Treatments of the BM included RAI, surgical resection, EBRT, and chemotherapy. All the patients with BM received at least one time RAI therapy for bone metastasis, besides that, small part of patients performed treatment of combinations (RAI plus other measures). After thyroid hormone withdrawal (THW) for 3 weeks, the patient’s thyroid-stimulating hormone (TSH), Tg, thyroglobulin antibody (TgAb) and Tg/TSH level [20] were recorded and calculated during the first RAI therapy. The progression of a patient was defined based on the following conditions [21, 22]: new bone metastases; at least 25% increase in the size of measurable original lesions on CT or MRI; at least 30% increase in uptake on PET/CT imaging; the Tg level increased at least 25% before treatment.

**F-18-FDG PET/CT scan**

All patients received a F-18-FDG PET/CT scan using a Biograph 64 PET/CT scanner (Siemens AG, Munich, Germany) before the first treatment of BM lesions in our Department. Before injection, all
patients were instructed not to eat for $\geq 6$ h to maintain their serum glucose levels at $< 11.1$ mmol/l. FDG doses of $5.55$ MBq/kg were injected after 15-20 minutes of rest. PET image was acquired 1 h following intravenous injection of FDG. The lowest possible milliampere setting was used to acquire the CT scans for attenuation correction, and the scan parameters were set to 120 kV and 100-150 mAs. In this study, 35 patients underwent a PET/CT scan before the first I-131 therapy, and the interval did not exceed 8 weeks.

**I-131 therapy and post-therapy I-131 WBS**

Patients with DTC and BM received more than one-time RAI treatment (3700-136900 Mbq). The positive uptake of bone lesions were recorded at the first I-131 treatment for metastases. Post-therapy I-131 WBS was performed after 4 days following high dose I-131 administration, using Single-Photon Emission Computed Tomography (SPECT) with high energy collimators. The interval between I-131 WBS and PET/CT was no more than 4 weeks. SPECT/CT scan was used to locate the bone metastases.

**Image analysis**

For qualitative analysis, two experienced nuclear medicine physicians reviewed the initial independent visual analysis of both images. For I-131 WBS, any no physiologic iodine uptake was considered as abnormal. For F-18-FDG PET/CT, abnormal findings consisted of either those lesions with FDG uptake or lesions without FDG uptake that were seen on the CT scan. All lesions were confirmed by cytology, histology, or follow up (positive imaging findings with increased Tg). The different uptake models of bone lesions on I-131 WBS and PET/CT images were classified as: RAI-/FDG--; RAI+/FDG--; RAI+/FDG- and RAI-/FDG+. RAI (+) ratio was calculated by the number of RAI (+) BM lesions/ (RAI (+) lesions + FDG (+) lesions), and FDG (+) ratio was calculated by the number of FDG (+) BM lesions/ (RAI (+) lesions + FDG (+) lesions).

PET/CT-based metabolic parameters include maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG). MTV refers to the estimated volume of tumors with increased tracer uptake, while TLG estimates summed metabolic activity inside MTV $^{[23]}$. For quantitative analysis, the SUVmax, MTV and TLG were measured by volume viewer software on PET/CT images. In this study, 40% SUVmax was chosen as the threshold for generating the volume of interest based on methods, which were recommended previously $^{[19]}$. If 40% of the primary tumor SUVmax was below 2.5, an SUV of 2.5 was used as the threshold $^{[24, 25]}$. All the parameters of SUVmax were calculated by the maximum SUV of the lesion divided by the mean SUV of the liver.

**Statistical analysis**

Contiguous data is given in mean ($\pm$ S.D.) or median with range, and categorical variables as numbers or percentage. The optimal cutoff values were calculated by the receiver operating characteristic (ROC) analysis and the area under the curve (AUC). Characteristics including sex, age, histology, confirmed BM time, BM with pulmonary metastases, the number of bone lesions, Tg, TSH, TgAb, Tg/TSH level, uptake
models of RAI and FDG, RAI (+) ratio, PET(+) ratio and therapy models were analyzed between recurrence group and non-recurrence group using t-test, X² tests, and Fisher exact tests.

Progression free survival (PFS) was defined as the time from the day of receiving the treatment to evident tumor progress or the date of death in DTC patients with BM. Overall survival (OS) was defined as the time between the date of diagnosis DTC with BM and the date of death or the last follow-up. Survival time was calculated using the Kaplan-Meier model, whereas Cox regression was performed for multivariate analysis. Variables with statistical significance on univariate analysis were included in the multivariate one. Statistical analyses were performed with the use of SPSS software version 22.0 (SPSS, Chicago, IL, USA). All reported p values are two-sided, and a probability of less than 0.05 was considered significant.

**Results**

**Clinical features**

The clinical characteristics of 67 DTC patients with BM are presented in table 1. This study included 44 females and 23 males with a median age of 58 years old, ranging from 28 to 81 years old. According to the 8th edition of the AJCC/TNM staging system of thyroid cancer [26], the age stratification was classified ≥ 55 years old (n=41) and < 55 years old (n=26). We included 41 patients with DTC and 26 with FTC. Bone metastases were found in 62 patients by I-131 WBS, pathology or biopsy and 52 patients were confirmed at the time of diagnosis with DTC. Twenty-nine patients were accompanied by pulmonary metastases. All patients received RAI treatment for bone metastases. Among them, 22 patients performed surgery, 2 patients underwent surgery and chemotherapy and 5 received surgery and radiotherapy.

**Bone lesions analysis**

A total of 207 BM lesions were detected in 67 patients, including 26 lesions found on FDG PET/CT with elevated Tg level, 74 found on I-131 SPECT/CT, 77 found on both two, 12 found on MRI and 18 confirmed by pathological. Of all bone metastases lesions, RAI-/FDG- were 15 (7.24%), RAI+/FDG+ were 82 (39.61%), RAI+/FDG- were 82 (39.61%) and RAI-/FDG+ were 28 (13.52%). The RAI(+) ratio and FDG (+) ratio in no progression group and progression group were 0.70 ± 0.29, 0.43 ± 0.41 and 0.42 ± 0.34, 0.62 ± 0.36, respectively.

In our study, age stratification, Tg level, Tg/TSH level, PET(+) ratio and RAI (+) ratio showed significant differences between patients with progression and those without (P<0.05). It suggested that DTC and BM patients with age ≥ 55 years old, Tg/TSH level > 4.95 ng/ml after thyroidectomy and low RAI (+) ratio or high PET(+) ratio may more probably progress during the follow-up.

**PET/CT imaging index results**
Of 67 DTC patients with BM, 35 patients underwent PET/CT scan before the first I-131 therapy for thyroid ablation. Owing to most patients bored more than one lesion, the total SUVmax, MTV, and TLG of bone lesions on PET/CT were presented of the status of the patient's tumor load. From ROC analyses, the optimal cutoff values for total SUVmax, MTV, and TLG were 5.73, 26.29cm$^3$ and 111.99g, with the AUCs of 0.577, 0.827 and 0.827, respectively.

The total SUVmax (Fig. 1A and 1B) showed no significant differences in univariate analysis for PFS and OS. The total MTV (Fig.1C and 1D) and total TLG (Fig. 1E and 1F) were the significant prognostic factors for PFS and OS, and the patients with MTV higher than 26.29cm$^3$ or TLG greater than 111.99g showed lower PFS ($p=0.000$ and $p=0.000$) rates and OS rates ($p=0.006$ and $p=0.014$) than those without, respectively.

**Survival analysis**

During the period of the clinical follow-up, 28 (41.79%) patients experienced disease progression and 39 (58.21%) patients did not. Twenty-five patients (37.31%) died. The median OS time and RFS time after diagnosis of BM were 56 months (range, 20-156 mons) and 40 months (4-156 mons), respectively. The OS rate was 100% (95% confidence interval (CI), 54.69-68.67) at 1 year, 86.56% (95% CI, 50.60–74.04) at 3 years, and 43.20% (95% CI, 78.01–96.81) at 5 years. The PFS rate was 94.02% (95% CI, 41.79-56.90) at 1 year, 56.71% (95% CI, 57.21–75.21) at 3 years, and 26.86% (95% CI, 76.61–100.723) at 5 years (Fig. 2 A and B).

The significance of variables for predicting PFS and OS on univariate analysis is shown in Table 2. Our results manifested that Tg level and Tg/TSH level were significant risk factors both for PFS ($p=0.003$ and $p=0.001$) and OS ($p=0.004$ and $p=0.005$). Age stratification was the risk factor for PFS ($p=0.016$).

Tg/TSH is calculated by dividing Tg by TSH, and there was a significant correlation between Tg and Tg/TSH ($r=0.803$, $p=0.000$). Hence, Tg and Tg/TSH were assessed separately. On multivariate analysis, Tg/TSH, RAI(+) ratio and PET(+) ratio were determined to be statistically significant for RFS and OS. Age stratification and Tg level were the independent significant prognosis factors for PFS; the Tg level showed marginal significance for OS ($p=0.054$). Age stratification showed no significant difference for OS. The patients with DTC who have high RAI(+) ratio and low PET(+) ratio in BM lesions or Tg/TSH < 4.95ng/uIU before the first I-131 treatment (thyroid ablation) showed better survival. The results for predicting RFS and OS on multivariate analysis are shown in Tables 3 and 4.

**Discussion**

DTC has a high tendency to metastasize to bone compared to other tumors, and it was reported to be the third most frequent solid tumor after breast and prostate cancer [27]. In most published reports, patients with DTC have a 10-year overall survival rate of 85-93% [28]. However, when distant metastases occur, the overall survival may decrease to 50% at 5 years of follow up [29, 30], and several studies presented 10-year
survival rates ranged from 21% to 27%\textsuperscript{[31]}. Our results showed that survival was 100% at 1 year, 86.56% at 3 years, and 43.20% at 5 years in patients with DTC and BM. Patients with bone metastases generally have a worse survival rate than those with lung metastases\textsuperscript{[6]}. Difficult therapy of bone lesions may be the main reason for short long term survival.

Multiple series studies found that older age, follicular cell type, early BM diagnosis (within 3 years of primary diagnosis), RAI treatment, no avidity in metastasis on the post-RAI scan, and high serum Tg levels are poor prognostic factors\textsuperscript{[1-3, 30]}. The results of this study showed that age stratification, Tg level, Tg/TSH level, PET (+) ratio and RAI (+) ratio have significant differences between patients with progression and those without. Patient age is a risk factor in thyroid cancer based on the American Joint Committee on Cancer (AJCC) and several other staging systems, and has profoundly influenced the risk stratification and management of PTC. The age of 45 years has been conventionally treated as a cutoff point demarcating the age-associated risk in thyroid cancer; however, this has been recently changed to 55 years in the revised eighth edition of AJCC \textsuperscript{[32]}. In our study, we classified the patient age stratification according to the new staging system and found that Patients with age $\geq$ 55years old were more easily to progress during the follow-up. Until now, the prognostic value of age stratification in patients with bone metastases from DTC is controversial. The survival analysis of this study presented that age stratification was a risk factor for PFS, but not for OS. Further studies were needed to confirm the prognostic value.

The serum Tg level has been considered as a significant risk factor for monitoring recurrence, progression and metastasis of patients with DTC\textsuperscript{[33, 34]}. In this study, the serum-stimulated Tg level was significantly higher in the progression group than in the non-progression group. It was the risk factor of PFS in patients with bone metastases. From the ROC analysis, the optimal cutoff of Tg level was 281.17ng/ml, which suggested that DTC and BM patients with Tg level higher than 281.17ng/ml may have a worse survival time. FDG-PET/CT is recommended during follow up when Tg level has empirically been set at 10 ng/mL after thyrotropin (TSH) stimulation or continuously increased more than 3 times in DTC patients \textsuperscript{[35]}. The relations between Tg/TSH level and the risk of abnormal FDG-PET/CT were reported in a previous study \textsuperscript{[36]}. The study from Camila Nascimento \textsuperscript{[37]} et al. also showed that the recommendation of performing FDG-PET/CT for aggressive DTC could be based on the Tg/TSH level. In Tg/TSH $>$10ng/uIU cases, FDG-PET/CT frequently allows the more identification of residual disease not detected on the I-131 WBS. In our study, Tg/TSH level indicated a progression and was a prognostic factor for OS and PFS, and in Tg/TSH $>$ 4.95ng/uIU cases, patients have poorer survival. The possible reasons of Tg/TSH level being progression and survival marker are that Tg secretion is affected by tumor focus and TSH stimulation; TSH level is related to thyroid hormone withdrawal of patients; Tg/TSH level not only reflects the presence of tumor, but also reduces the influence of patient’s factors.

In clinical, we found the bone metastases are frequent in DTC patients with BM, and bone lesions have different uptakes of I-131 and F-18-FDG in one patient. As we all know, PET imaging is particularly helpful for poorly differentiated thyroid cancer, as this tumor type can be negative on I-131 scans due to
mutations that eliminate uptake of iodide. Hence, the presence of FDG avidity of BM has already been proven to be associated with cancer aggressiveness and poor prognosis, and I-131 focus is the opposite [36]. In this study, we use PET (+) ratio and RAI (+) ratio to assess the status of the multiple bone lesions in one patient and found that RAI (+) ratio was an aggressive and survival factor for this kind of patients. Our results suggested that DTC and BM patients with low RAI (+) ratio and high PET (+) ratio have a shorter PFS and OS and more quickly to progress.

In this study, our results found that the total MTV and TLG are the independently prognosis factors and had a strong association with PFS and OS compared to the total SUVmax. MTV and TLG represent the metabolic volume and activity throughout the entire tumor lesion above a minimum threshold designed to exclude background activity[18]. Hence, compared to SUVmax, MTV and TLG can more accurately reflect the metabolic burden of tumor lesions and predict survival prognosis. Based on the ROC curve and Kaplan-Meier method analysis, we suggested higher total MTV and TLG of bone lesions were more likely to progress than those who did not, and bone lesions of DTC patients with total MTV > 26.29cm$^3$ or total TLG >111.99g may have shorter PFS and OS rate (Fig 3). To our knowledge, this is the first study performed on metabolic parameters of PET/CT in patients with DTC and BM.

These results are obtained in a retrospective design and single-center, which are the major limitations of the study. No or low FDG uptake lesions in patients with DTC and BM could be discovered, which would be underestimated in the values of MTV and TLG. In the future study, we would like to involve a large number of samples to evaluate the possible survival factors in DTC with BM.

**Conclusions**

The results of our study showed that Tg/TSH level, PET (+) ratio and RAI (+) ratio are the independent risk factors for survival in DTC and BM patients. The total MTV and TLG of bone metastases on F-18–FDG PET/CT may be the significantly prognostic factors for PFS and OS, compared to SUVmax. Our study suggests early FDG-PET/CT performed concomitantly with I-131 WBS in patients with DTC and BM may not only reflect tumor status but also show the prognostic information to help patients receive tailor therapy and improve the survival time.

**Abbreviations**

- F-18-FDG fluorine-18-fluorodesoxyglucose
- PET/CT positron emission tomography/computed tomography
- RAI radioactive iodine
- DTC differentiated thyroid cancer
- BM bone metastasis
WBS whole-body scan
Tg thyroglobulin
TSH thyroid-stimulating hormone
OS overall survival
PFS progression free survival
TLG total lesion glycolysis
SUVmax maximum standardized uptake value
MTV metabolic tumor volume
CT computed tomography
MRI magnetic resonance imaging
TgAb thyroglobulin antibody

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine.

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

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Authors’ contributions

HW and CL designed and control the research; HS and ZYX collected the clinical data; FF and HLF performed the statistical analysis; CL wrote the whole manuscript and HW revised the report. All authors have read and approved the final manuscript.

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Tables

Table 1 Patients characteristics and follow up
| Characteristics                                      | N(41) | No progress | progress | P   |
|-----------------------------------------------------|-------|-------------|----------|-----|
| Sex                                                 |       |             |          | 0.620 |
| Female                                              | 44    | 24          | 20       |
| Male                                                | 23    | 14          | 9        |
| Age stratification (years)                          |       |             |          | 0.031 |
| ≥ 55                                                | 41    | 19          | 22       |
| <55                                                 | 26    | 19          | 7        |
| Histology                                           |       |             |          | 0.706 |
| PTC                                                 | 41    | 24          | 17       |
| FTC                                                 | 26    | 14          | 12       |
| Confirmed time                                      |       |             |          | 0.377 |
| synchronous                                         | 52    | 28          | 24       |
| metachronous                                        | 15    | 10          | 5        |
| Bone metastases with pulmonary metastases           |       |             |          | 0.471 |
| Y                                                   | 29    | 15          | 14       |
| N                                                   | 38    | 23          | 15       |
| Number of bone lesions                              |       |             |          | 0.179 |
| ≤3                                                  | 43    | 27          | 16       |
| >3                                                  | 24    | 11          | 13       |
| Tg (mean±S.D. ng/ml)                                | 67    | 338.18±382.52 | 553.65±356.85 | 0.022 |
| TSH (mean±S.D. uIU/ml)                              | 67    | 50.18±29.99  | 38.95±16.52  | 0.074 |
| TgAb (mean±S.D. IU/ml)                              | 67    | 6.15±6.54    | 9.50±11.9   | 0.181 |
| Tg/TSH (ng/uIU)                                     |       |             |          | 0.000 |
| ≤4.95                                               | 32    | 26          | 6        |
| >4.95                                               | 35    | 12          | 23       |
| bone lesions                                        |       |             |          | 0.208 |
| RAI+/PET+                                           | 82    | 50          | 32       |
| RAI+/PET-                                           | 82    | 40          | 42       |
| RAI-/PET+                                           | 28    | 13          | 15       |
RAI-/PET-  15  8  7  
RAI(+) ratio ( mean±S.D.)  67  0.70±0.29  0.42±0.34  0.001  
PET(+) ratio ( mean±S.D.)  67  0.43±0.41  0.62±0.36  0.048  
Therapy  
131I  38  25  13  
131I+surgery  22  10  12  
131I+surgery+other therapy  7  3  4

TSH, Tg level, TgAb level and Tg/TSH level were 50.18 ± 29.99 uIU/ml, 338.18 ± 382.52 ng/ml, 6.15 ± 6.54 IU/ml and 8.17 ± 11.3 ng/uIU in no progression group, while the progression group was 38.95 ± 16.52 uIU/ml, 553.65 ± 356.85 ng/ml, 9.50 ± 11.9 IU/ml and 16.34 ± 14.43 ng/uIU, respectively. Tg level and Tg/TSH level showed significant differences between the two groups (P=0.022 and P=0.012). From the ROC analyses, the optimal cutoff value for Tg level and Tg/TSH level was 281.17ng/ml and 4.95 ng/uIU with the AUCs of 0.684 and 0.750.

Table 2 Univariate Analysis of Prognostic Factors for PFS and OS.
| Variable                                      | PFS Median (mo) | P | OS Median (mo) | P |
|----------------------------------------------|-----------------|---|----------------|---|
| Sex                                          |                 |   |                |   |
| Female                                       | 41              | 0.651 | 50              |    |
| Male                                         | 52              | 0.666 | 61.5            |    |
| Age stratification                           |                 |   |                |   |
| ≥55                                          | 38              | 0.016 | 62              | 0.082 |
| <55                                          | 54              | 0.016 | 57              | 0.082 |
| Histology                                    |                 |   |                |   |
| PTC                                          | 41              | 0.674 | 53              | 0.416 |
| FTC                                          | 48              | 0.674 | 65              | 0.416 |
| Confirmed time                               |                 |   |                |   |
| synchronous                                  | 43              | 0.889 | 57              | 0.848 |
| metachronous                                 | 38              | 0.889 | 65              | 0.848 |
| Bone metastases with pulmonary metastases    |                 |   |                |   |
| Y                                            | 40.5            | 0.244 | 53              | 0.537 |
| N                                            | 48              | 0.244 | 62              | 0.537 |
| Number of bone lesions (n)                   |                 |   |                |   |
| ≤3                                           | 38.5            | 0.467 | 62              | 0.615 |
| >3                                           | 44              | 0.467 | 56              | 0.615 |
| Tg/TSH (ng/uIU)                              |                 |   |                |   |
| ≤4.95                                        | 33              | 0.001 | 62              | 0.005 |
| >4.95                                        | 46              | 0.001 | 57              | 0.005 |
| Tg (ng/ml)                                   |                 |   |                |   |
| ≤281.17                                      | 49              | 0.003 | 57              | 0.004 |
| >281.17                                      | 26              | 0.003 | 52              | 0.004 |
Table 3 Multivariate Analysis of Prognostic Factors for OS and PFS (model with Tg/TSH).

| variable          | PFS HR (95%CI) | P  | OS HR (95%CI) | P  |
|-------------------|----------------|----|---------------|----|
| Age stratification| 0.336(0.123-0.917) | 0.033 | 0.551(0.202-1.502) | 0.244 |
| Tg/TSH            | 0.507(0.320-0.802) | 0.004 | 0.483(0.290-0.803) | 0.005 |
| RAI(+) ratio      | 0.087(0.020-0.381) | 0.001 | 0.189(0.046-0.781) | 0.021 |
| PET(+) ratio      | 0.215(0.056-0.827) | 0.025 | 0.134(0.030-0.599) | 0.008 |

Table 4 Multivariate Analysis of Prognostic Factors for OS and PFS (model with Tg).

| variable          | PFS HR (95%CI) | P  | OS HR (95%CI) | P  |
|-------------------|----------------|----|---------------|----|
| Age stratification| 0.322(0.119-0.872) | 0.026 | 0.537(0.196-1.471) | 0.226 |
| Tg                | 0.595(0.385-0.918) | 0.019 | 0.612(0.371-1.009) | 0.054 |
| RAI(+) ratio      | 0.096(0.022-0.410) | 0.002 | 0.219(0.055-0.870) | 0.031 |
| PET(+) ratio      | 0.235(0.061-0.900) | 0.035 | 0.178(0.041-0.784) | 0.022 |

Figures
Figure 1

Kaplan-Meier analysis of PFS and OS in patients with DTC and BM by SUVmax (A and B), MTV (C and D), and TLG (E and F.)
Figure 2

OS and PFS in patients with DTC and BM (n = 67).
Figure 3

A 53-year-old woman with PTC and BM. Focal uptake in the cervical spine was showed (red arrows) both on PET/CT imaging (A) and I-131 WBS (C), and the total SUVmax, MTV and TLG of the lesion are 10.81, 1.69cm³ and 39.82g, respectively. The patient made no progress and the PFS and OS are 37 months and 37 months. A 68-year-old woman with FTC and multiple BM metastasis. Focal uptake was seen in the skull, left fourth rib, and sacral (B, red arrows), and those bone lesions also showed radiotracer foci on I-131 WBS (D). the focus of bone lesions (humerus, right femoral, thoracic vertebrae and ribs) on WBS
showed hypometabolism on PET/CT imaging. The total SUVmax, MTV and TLG are 12.6, 54.87cm³ and 285.09g, respectively. The PFS and OS are 24 months and 42 months and finally the patient died.