European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-025-07339-3

ORIGINAL ARTICLE

Less is more: once *vs.* multiple radioactive iodine (RAI) therapy in patients with RAI-avid pulmonary micrometastatic differentiated thyroid cancer

Cong Shi[1] · Di Sun[1] · Yu-Qing Sun[1] · Xin Zhang[1] · Sheng-Yan Liu[1] · Qi-Jun Li[1] · Yi-Jin Pan[1] · Wen-Ting Guo[2] · Ying-Qiang Zhang[1] · Xiao-Na Jin[1] · Yu Liu[1] · Yan-Song Lin[1]

Received: 7 January 2025 / Accepted: 8 May 2025

Abstract

Purpose To date, the survival benefits of multiple radioactive iodine therapies (RAIT) in RAI-avid pulmonary micrometastatic differentiated thyroid cancer (DTC) remain debatable. This study aimed to compare the progression-free survival (PFS) benefits between those received only once RAIT (o-RAIT) and multiple RAITs (m-RAIT) in such patients.

Methods Patients with RAI-avid pulmonary micrometastatic DTC were included and divided into either o-RAIT or m-RAIT group according to the number of RAIT cycles. The response to first RAIT in all patients and last RAIT in m-RAIT were evaluated and classified as partial response (PR), stable disease (SD), and progressive disease (PD). PFS was defined as the time from first RAIT to PD. Logistic regression analysis and Kaplan–Meier survival curves were employed to identify risk factors and estimate PFS, with propensity score matching (PSM) to reduce confounders.

Results A total of 117 patients with RAI-avid pulmonary micrometastatic DTC were retrospectively included, with 38 (32.5%) from o-RAIT and 79 (67.5%) from m-RAIT. Patients from m-RAIT exhibited younger age at diagnosis, more local persistent disease before RAIT, and more metachronous metastasis compared with o-RAIT group (all $P < 0.05$). In the comparison of RAIT response, there was no difference in the first RAIT response between the o-RAIT and m-RAIT, while the last RAIT response of m-RAIT is worse not only than o-RAIT ($P = 0.005$), but also than their own first RAIT response ($P = 0.0003$). Multivariate analysis revealed age at diagnosis (over 45 years old) ($P = 0.006$) and local persistent disease before RAIT ($P = 0.001$) were independent risk factors for PD after RAIT, while number of RAIT cycles was not. To minimize potential confounders, the risk factors for PD and follow-up time were matched by PSM, after which, no significant difference in PFS was observed between the matched o-RAIT and m-RAIT (5-year PFS rate: 83.6% vs. 81.6%, $P = 0.808$).

Conclusions In patients with RAI-avid pulmonary micrometastatic DTC, o-RAIT exhibited non-inferior PFS benefits compared with m-RAIT, suggesting the "less is more" management strategy of RAIT towards such patients.

Keywords Differentiated thyroid cancer · Pulmonary micrometastasis · Radioactive iodine-avid lesion · Propensity score matching · Progression-free survival

Introduction

Thyroid cancer is one of the most common endocrine malignancies and differentiated thyroid cancer (DTC) accounts for 94%. In China, it ranks as the third most common malignant tumor among women and its incidence continues to rise [1]. While most DTC patients have favorable prognosis, still 4–27% develop distant metastases [2–4], leading to poorer outcomes — a 5-year survival rate of 42.6% for those with distant metastasis (DM) compared with 92.9% for patients without DM, according to the latest data from China [5]. The Surveillance, Epidemiology, and End Results (SEER)

✉ Yan-Song Lin
linyansong1968@163.com; linys@pumch.cn

[1] Department of Nuclear Medicine, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

[2] Biomedical Engineering Facility of National Infrastructures for Translational Medicine, Institute of Clinical Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Published online: 26 May 2025

Program also reported a 5-year survival rate of 51.9% for patients with DM versus 98.2% for those without [6]. Of note, patients with only pulmonary metastases usually have favorable long-term outcomes, with 5-year cancer-specific survival (CSS) rates reaching 78% [7, 8], particularly those with RAI-avid pulmonary micrometastases (shown as Fig. 1A), the 5-year CSS is even higher, which can approach 100% [9, 10]. These statistics highlight the critical need of precise management in patients with RAI-avid pulmonary micrometastatic DTC.

Since RAI-avid metastases of DTC keep the expression of sodium iodide symporter (NIS) to some extent, which allows radioactive iodine therapy (RAIT) as the first-line treatment following total thyroidectomy. In multiple studies, RAIT has been demonstrated to effectively reduce the risk of recurrence and tumor-related mortality in patients with RAI-avid DM-DTC [11–16]. A retrospective study involving 444 DM-DTC patients with long-term follow-up found that the 10-year overall survival (OS) rate was 56% for RAI-avid metastatic patients, while it drops dramatically to only 10% for iodine-refractory patients [17].

Current guidelines recommend repeating RAIT every 6–12 months for RAI-avid pulmonary micrometastatic DTC with persistent RAI uptake and favorable clinical responsive to prior RAIT [18, 19]. However, so far, the benefits of repeated RAIT in such patients remain debatable. Song et al. reported that among 256 RAI-avid pulmonary metastatic patients received repeated RAIT, 60.9% experienced significant decrease in thyroglobulin (Tg) levels and 93.5% had structural response or stability [10]. While Sabra et. al found no patient achieved complete response (CR) and 54% had progressive disease (PD) despite retaining RAI avidity after repeated RAIT [20]. Similarly, DM-DTC patients with positive post-therapy whole-body scan (RxWBS) failed to show any structural response after repeated RAIT in another study [21].

Over the recent years, with the increasing concerns including radiation exposure risk, secondary malignancies, and patients' preferences, a conservative strategy of active surveillance (AS) after one round of RAIT has been gradually considered. Therefore, the RAIT choice for patients with RAI-avid pulmonary micrometastases tend to be categorized into two clinical scenarios: 1) repeated multiple RAITs administered at an interval of every 6 to 12 months; 2) AS after one round of RAIT (shown as Fig. 1B).

So far, although repeating RAIT is recommended for patients with RAI-avid pulmonary micrometastatic DTC, existing studies have not demonstrated the clear benefits of multiple RAITs (m-RAIT) over only once RAIT (o-RAIT). Particularly, the long-term survival benefits comparison

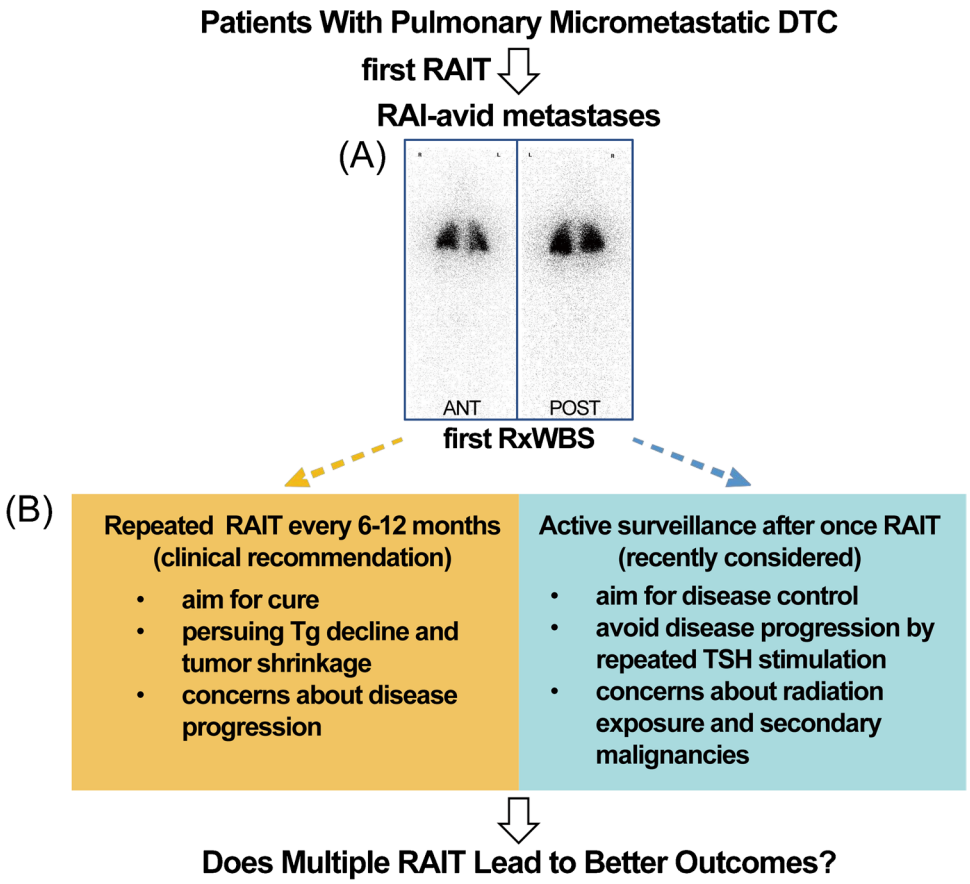

Fig. 1 Two clinical scenarios of RAIT choice for patients with RAI-avid pulmonary micrometastatic DTC. Abbreviation: DTC, differentiated thyroid cancer; RAIT, radioactive iodine therapy; RxWBS, post-therapy whole-body scan; Tg, thyroglobulin; TSH, thyroid-stimulating hormone

between o-RAIT and m-RAIT are rarely mentioned. Moreover, there is a lack of high-quality clinical evidence on survival outcomes, such as prospective cohort studies and randomized controlled trials, which are challenging to conduct, even matched retrospective cohort studies are still limited.

This retrospective study was conducted with an aim to address whether repeated RAIT can achieve better outcome in patients with RAI-avid pulmonary micrometastatic DTC.

Methods

The study was approved by the Hospital Ethics Committee of Peking Union Medical College Hospital (JS-2432) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects in the study.

Subjects

This study included patients who meet the following criteria successively: (1) underwent total or subtotal thyroidectomy between 2000 and 2022 and pathologically diagnosed as DTC; (2) patients with only pulmonary micrometastases (< 1 cm which cannot be assessed by RECISTv1.1) were included; (3) received at least once RAIT and exhibited obvious and persistent RAI-avid pulmonary metastases on each RxWBS. Exclusion criteria: 1) patients who developed pulmonary micrometastases after the first RAIT for remnant or adjuvant therapy were excluded; 2) patients with massive thyroid tissue on the first RxWBS were excluded for it might interfere with RAI uptake over metastasis and confuse our assessment; 3) patients who exhibited disease progression in radiographic examinations within 6 months after RAIT were excluded to avoid the possible iodine refractoriness and thereby introducing confounding factors. For patients who underwent a previous subtotal thyroidectomy, supplementary total thyroidectomy and lymph node dissection were performed due to the suspicious recurrent and/or persistent lymph node metastasis and pulmonary metastasis to enable the subsequent RAIT. Clinicopathological characteristics and RAIT metabolic data were systematically collected.

Definition for metastasis and local recurrence or local persistent disease

The pulmonary micrometastasis was defined through positive RAI-avid imaging (DxWBS or RxWBS) integrated by elevated Tg/TgAb, as well as chest CT during the follow-up. When the diagnostic interval between the primary lesion and pulmonary micrometastasis is within 12 months, patients were classified as synchronous metastasis, otherwise were classified as metachronous metastasis [22]. The appearance of new local lesions after a postoperative disease-free status more than 12 months (with support of structural imaging evidence and corresponding biopsy or postoperative pathological results) was defined as local recurrence, conversely, the presence of ongoing local disease within 12 months was considered as local persistent disease [23, 24]. All local recurrence and local persistent disease we reported were diagnosed before the first RAIT, the recurrence or progression of local disease after RAIT were classified as PD.

Procedure of RAIT administration and response assessment

All patients in our cohort had structural lesions confirmed on imaging prior to RAIT and received at least once RAIT aimed for treating pulmonary micrometastases. RAIT was usually given after 3–4 weeks of thyroid hormone withdrawal and at least 2 weeks of iodine-restricted diet, all patients only received RAIT when the serum thyroid-stimulating hormone (TSH) levels reached at least 30 mIU/L, each patient underwent the RxWBS within 5–7 days after RAIT. The RAIT administration dose for patients were given based on the ATA and Chinese guidelines and 5.55 GBq is usually administered for those with only pulmonary micrometastases.

For RAIT response, we applied the criteria from the updated 2025 edition "Chinese Anti-Cancer Association (CACA) Guidelines for Holistic Integrative Management of Thyroid Cancer". We comprehensively assess tumor burden and RAIT response of patients from three aspects: 1) structural imaging (such as chest CT); 2) serological assessing [ΔTg: (before RAIT-after RAIT)/before RAIT]; 3) RAI-avid imaging (RxWBS) [25]. The response was classified into CR, partial remission (PR), stable disease (SD), and PD. Specific descriptions and criteria were shown in the Supplementary Table 1. Considering there were no patients with target lesion by RECISTv1.1 in our cohort, the PR was defined as a decrease of $\Delta Tg \geq 25\%$ or the disappearing/reduced RAI-avid lesions on RxWBS, the PD was defined as the appearance of one or more new lesions, aligning with the definition of PD by RECISTv1.1 when only non-target lesions are present. Based on the above criteria, we evaluated the response of first RAIT in all patients and last RAIT in patients received m-RAIT. The time from the first RAIT administration to the first imaging evidence of PD was defined as the progression-free survival (PFS) in our study.

Statistical analysis

Comparison of characteristics between o-RAIT and m-RAIT group was conducted using the Mann–Whitney U test, Chi-square test or Fisher's exact test as appropriate. Univariate and multivariate logistic regression analysis were utilized to identify risk factors for PD after RAIT, variables with a P value < 0.1 for univariate analysis were included in multivariate analysis. Results were shown as odds ratio (OR) with 95% confidence intervals (CIs). To reduce confounders, PSM was employed to balance risk factors for PD between o-RAIT and m-RAIT group, with a matching ratio of 1:1 and a caliper value of 0.05. PFS was compared in the matched cohort and subgroup analysis using Kaplan–Meier curves with log-rank tests. Cut-off values for age at diagnosis and maximum primary tumor size in the subgroup analysis were obtained using X-tile calculation recommendation (Version 3.6.1; Yale University School of Medicine, New Haven, USA) [26]. A two-tailed P value < 0.05 was considered statistically significant. All statistical analysis were performed using SPSS software (version 22.0, Chicago, IL, USA) and GraphPad Prism 8.0.2 (GraphPad Software Inc., USA).

Results

Clinicopathological characteristics and comparison between o-RAIT and m-RAIT group

In this study, a total of 117 DTC patients who had RAI-avid pulmonary micrometastases were included. The clinicopathological characteristics of total cohort were showed in Table 1. The median age of the cohort was 29.9 (19.2, 39.4) years old and female accounts for 61.5%. PTCs were identified in 97.4% and FTCs were only identified in 2.6%. The median maximum primary tumor size was 2.5 (1.5, 3.5) cm, 50.4% and 88.0% patients were advanced AJCC_T stage and AJCC_N stage, respectively. Patients were classified into low risk (1/117), intermediate risk (4/117), and high risk (112/117), respectively according to 2015 ATA guideline. Before the first RAIT, 10 (8.5%) patients had local recurrence, 30 (25.6%) patients had local persistent disease. Additionally, 102 (87.2%) patients were found to have synchronous metastasis. While among 15 (12.8%) patients with metachronous metastasis who underwent non-total thyroidectomy long time ago, RAIT was not timely administered accordingly and resulting in local recurrence in 66.7% (10/15) and residual disease in 33.3% (5/15) of patients, supplementary surgeries were performed to enable the RAIT. At the end of the follow-up, 38 (32.5%) patients received o-RAIT and 79 (67.5%) received m-RAIT with a median of 3 (range 2–7) cycles. In the comparison between o-RAIT and m-RAIT group, as shown in Table 1, the m-RAIT group exhibited younger age at diagnosis (27.1y vs. 33.9y, $P = 0.036$), more local persistent disease before RAIT (34.2% vs. 7.9%, $P = 0.0003$), and more metachronous metastasis (17.7% vs. 2.6%, $P = 0.046$) compared with o-RAIT group.

Overall characteristics of RAIT and its response comparison between o-RAIT and m-RAIT group

The detailed characteristics of RAIT (cycles) and the response to RAIT were shown in Table 2. The median RAIT dose of all patients, and both patients in o-RAIT and m-RAIT group was 5.55 GBq per each RAIT cycle ($P = 0.089$). The median cumulative RAI dose of patients in o-RAIT and m-RAIT group was 5.55 GBq and 14.80 GBq, respectively ($P < 0.0001$). For patients in m-RAIT group, the interval between each RAIT cycle was 6.3 (5.6, 8.2) months. In terms of the response to first RAIT, 58 (49.6%) patients were classified as PR, 48 (41.0%) patients as SD, and 11 (9.4%) patients as PD, the evaluation of o-RAIT and m-RAIT were shown in Table 2. For patients in m-RAIT group, we additionally evaluate the response to their last RAIT, 17 (21.5%) patients were classified as PR, 42 (53.2%) as SD, and 20 (25.3%) as PD. There was no significant difference of the response to the first RAIT between o-RAIT and m-RAIT ($P = 0.947$). However, the last RAIT response of m-RAIT was worse not only than the RAIT response in o-RAIT group ($P = 0.005$), but also than their own first RAIT response ($P = 0.0003$). The changes of the response throughout the first to the last RAIT of same patient were shown in Fig. 2. Totally, 24 (20.5%) patients had PD, including 4 patients in o-RAIT group and 20 patients in m-RAIT group. The median PFS was not reached and the 5-year PFS rate was 76.6%, there was also no significance in PFS between the two groups ($P = 0.121$). With a median follow-up of 61.1 (range 13.0–257.6) months, no patient in our study had OS event.

Risk factors for PD after RAIT

Univariate and multivariate logistic analyses were performed to analyze the risk factors for PD after RAIT in the total cohort (Table 3). The sample size of low-risk and intermediate-risk groups were too limited and initial risk stratification was not included. Univariate analysis showed that age at diagnosis ($P = 0.042$), maximum of primary tumor size ($P = 0.019$), and local persistent disease before RAIT ($P = 0.0001$) were significantly associated with risk of PD after receiving RAIT, while number of RAIT cycles was not ($P = 0.252$).

Table 1 Clinicopathological characteristics of overall cohort and comparison between o-RAIT and m-RAIT group

	Overall ($n = 117$)	o-RAIT ($n = 38$)	m-RAIT ($n = 79$)	P value
Age at diagnosis [median (P_{25}, P_{75})] (years)	29.9 (19.2, 39.4)	33.9 (27.4, 39.9)	27.1 (17.1, 37.2)	0.036
Gender, *n* (%)				0.512
Male	45 (38.5)	13 (34.2)	32 (40.5)	
Female	72 (61.5)	25 (65.8)	47 (59.5)	
Pathological type, *n* (%)				1.000
PTC	114 (97.4)	37 (97.4)	77 (97.5)	
FTC	3 (2.6)	1 (2.6)	2 (2.5)	
Maximum primary tumor size [median (P_{25}, P_{75})] (cm)	2.5 (1.5, 3.5)	2.0 (1.3, 2.8)	2.9 (1.6, 3.7)	0.052
AJCC_T stage, *n* (%)[†]				0.393
T1 + T2	58 (49.6)	21 (55.3)	37 (46.8)	
T3 + T4	59 (50.4)	17 (44.7)	42 (53.2)	
AJCC_N stage, *n* (%)[†]				0.903
N0	8 (6.8)	3 (7.9)	5 (6.3)	
N1a	6 (5.1)	2 (5.3)	4 (5.1)	
N1b	103 (88.0)	33 (86.8)	70 (88.6)	
Initial risk stratification, *n* (%)[‡]				0.168
Low risk	1 (0.9)	1 (2.6)	0 (0.0)	
Intermediate risk	4 (3.4)	0 (0.0)	4 (5.1)	
High risk	112 (95.7)	37 (97.4)	75 (94.9)	
Local recurrence or Persistent disease, *n* (%)[§]				0.0003
Neither	77 (65.8)	34 (89.5)	43 (54.4)	
Local recurrence	10 (8.5)	1 (2.6)	9 (11.4)	
Local persistent disease	30 (25.6)	3 (7.9)	27 (34.2)	
Distant metastatic synchronization, *n* (%)				0.046
Synchronous	102 (87.2)	37 (97.4)	65 (82.3)	
Metachronous	15 (12.8)	1 (2.6)	14 (17.7)	

[†] For patients who underwent multiple surgeries, the AJCC_T stage and AJCC_N stage were determined based on the maximum extent of tumor invasion and lymph node involvement observed across all surgical and postoperative records

[‡] The initial risk stratification of structural disease recurrence was determined according to the 2015 ATA guideline

[§] The appearance of new local lesions after a postoperative disease-free status more than 12 months was defined as local recurrence, presence of ongoing disease since diagnosis within 12 months was considered as local persistent disease. The local recurrence or persistence disease were all diagnosed before RAIT

Abbreviations: *RAIT* radioactive iodine therapy, *o-RAIT* only once RAIT, *m-RAIT* multiple RAITs, *PTC* papillary thyroid cancer, *FTC* follicular thyroid cancer, *AJCC* American Joint Committee on Cancer, *T* tumor, *N* node

Characteristics with a P value < 0.1 for univariate analysis were included in multivariate analysis. Patients over 45 years old (OR 8.477; 95%CI: 1.874–38.355; $P = 0.006$) and had local persistent disease before RAIT (OR 9.143; 95%CI: 2.380–35.127; $P = 0.001$) were identified as independent risk factors for PD after RAIT.

Survival analysis between matched patients from o-RAIT and m-RAIT group

To evaluate the PFS benefits of multiple RAITs and reduce confounders, we performed a PSM and matched the risk factors for PD after RAIT, including age at diagnosis and local persistent disease before RAIT. Considering the patients who received multiple RAITs often have longer therapeutic course, follow-up time was also necessary to be included for matching. Patients from o-RAIT and m-RAIT were matched with 1:1 ratio and we achieved a matched cohort of 31-pair patients with similar baseline characteristics. Notably, survival analysis indicated that there was no significance in PFS between paired patients from o-RAIT and m-RAIT (5-year PFS rate: 83.6% vs. 81.6%, $P = 0.808$) (Fig. 3).

In the subgroup analysis for the matched cohort, patients with age at diagnosis > 45 years old (5-year PFS rate: 37.5% vs. 91.4%, $P = 0.0003$, Fig. 4A), local persistent disease before RAIT (5-year PFS rate: 27.8% vs. 86.0% vs. 100.0%, $P = 0.010$, Fig. 4C) had worse PFS. Patients with maximum primary tumor size > 4 cm also showed worse PFS but the difference was not statistically significant (5-year PFS rate: 66.7% vs. 86.2%, $P = 0.440$, Fig. 4B). Moreover, we further

Table 2 Characteristics of RAIT and its response of overall cohort and comparison between o-RAIT and m-RAIT group

	Overall ($n = 117$)	o-RAIT ($n = 38$)	m-RAIT ($n = 79$)	P value
Median single RAIT cycle dose (GBq)	5.55 (5.55, 6.01)	5.55 (5.00, 5.55)	5.55 (5.55, 6.48)	0.089
Cumulative RAIT dose [median (P_{25}, P_{75})] (GBq)	11.10 (5.55, 16.65)	5.55 (5.00, 5.55)	14.80 (11.10, 20.17)	< 0.0001
Interval between each RAIT cycle (months)	/	/	6.3 (5.6, 8.2)	/
Response to first RAIT, n‡				0.947
PR	58 (49.6)	19 (50.0)	39 (49.4)	
SD	48 (41.0)	15 (39.5)	33 (41.8)	
PD	11 (9.4)	4 (10.5)	7 (8.9)	
Response to last RAIT, n‡				/
PR	/	/	17 (21.5)	
SD	/	/	42 (53.2)	
PD	/	/	20 (25.3)	
5-year PFS rate (%)	76.6	84.8	72.9	0.121

‡ The response classification was based on the updated 2025 edition "Chinese Anti-Cancer Association (CACA) Guidelines for Holistic Integrative Management of Thyroid Cancer", specific descriptions and criteria were shown in the Supplementary Table 1

Abbreviations: *RAIT* radioactive iodine therapy, *o-RAIT* only once RAIT, *m-RAIT* multiple RAITs, *PR* partial response, *SD* stable disease, *PD* progressive disease, *PFS* progression-free survival

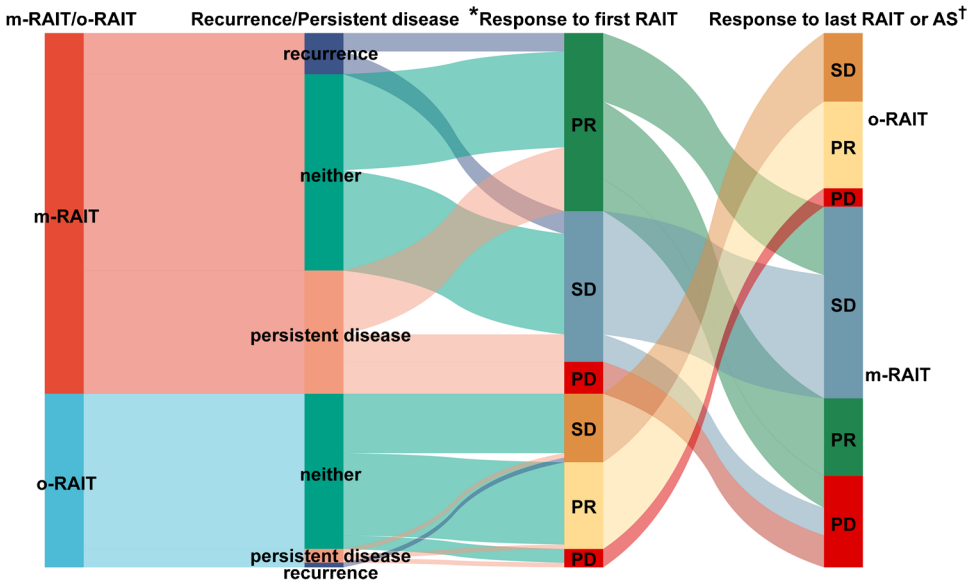

Fig. 2 The Sankey diagram about the response to the first and last RAIT in patients with o-RAIT and m-RAIT. * The response categories were classified based on the 2025 edition "Chinese Anti-Cancer Association (CACA) Guidelines for Holistic Integrative Management of Thyroid Cancer". † The response to last RAIT of m-RAIT group or the response to active surveillance (AS) of o-RAIT group. Abbreviations: RAIT, radioactive iodine therapy; o-RAIT, only once RAIT; m-RAIT, multiple RAITs; PR, partial response; SD, stable disease; PD, progressive disease; AS, active surveillance

compared the PFS between patients received o-RAIT and m-RAIT in subgroup with age > 45 years old (Fig. 4D), maximum tumor size > 4 cm (Fig. 4E), and local persistent local disease (Fig. 4F), and there was no significant difference in each subgroup.

Discussion

RAIT has been the standard postoperative treatment for patients with RAI-avid pulmonary micrometastatic DTC and repeated RAIT has become the common practice in the clinical management of such patients. However, it is noteworthy that few patients could achieve CR despite multiple RAITs and the benefits of multiple RAITs in such patients remain unclear. Moreover, the adverse effects related to multiple RAITs are receiving increasing concern. Therefore, in this retrospective study, we first explore the difference in PFS benefits of RAI-avid pulmonary micrometastatic DTC patients with different RAIT administration cycles (once versus multiple RAIT).

Firstly, we compared the clinicopathological characteristics and RAIT response between o-RAIT and m-RAIT group. Compared with o-RAIT group, m-RAIT exhibited younger age at diagnosis, more local persistent disease before RAIT, and more metachronous metastasis. Notably,

Table 3 Univariate and multivariate logistic analysis of associated risk factors for PD after RAIT ($n = 117$)

Clinicopathological characteristics	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age at diagnosis				
< 45 years old	REF		REF	
≥ 45 years old	3.070 (1.040–9.057)	0.042	8.477 (1.874–38.355)	0.006
Gender				
Male	REF			
Female	1.678 (0.635–4.437)	0.297		
Pathological type				
PTC	REF			
FTC	1.978 (0.172–22.780)	0.584		
Maximum of primary tumor size	1.389 (1.055–1.830)	0.019	1.356 (0.973–1.888)	0.072
AJCC_T stage[†]				
T1 + T2	REF			
T3 + T4	1.856 (0.739–4.663)	0.188		
AJCC_N stage[†]				
N0	REF			
N1a	0.600 (0.041–8.732)	0.708		
N1b	0.768 (0.145–4.084)	0.757		
Local recurrence/Persistent disease[§]				
Neither	REF			
Local recurrence	2.156 (0.389–11.966)	0.380	3.832 (0.511–28.768)	0.191
Local persistent disease	7.547 (2.708–21.031)	0.0001	9.143 (2.380–35.127)	0.001
Distant metastatic synchronization				
Metachronous	REF			
Synchronous	0.741 (0.216–2.542)	0.633		
Multiple RAITs or not	2.881 (0.909–9.132)	0.072	1.570 (0.371–6.639)	0.540
Number of RAIT cycles	1.209 (0.874–1.672)	0.252		
Cumulative RAI dose	1.001 (0.999–1.003)	0.309		

[†] For patients who underwent multiple surgeries, the AJCC_T stage and AJCC_N stage were determined based on the maximum extent of tumor invasion and lymph node involvement observed across all surgical and postoperative records

[§]The local recurrence or persistence disease were all diagnosed before RAIT

Abbreviations: *PD* progressive disease, *RAIT* radioactive iodine therapy, *PTC* papillary thyroid cancer, *FTC* follicular thyroid cancer, *AJCC* American Joint Committee on Cancer, *T* tumor, *N* node, *OR* odds ratio, *CI* confidence interval, *REF* reference

although there was no significance in the first RAIT response between o-RAIT and m-RAIT, while the last RAIT response of m-RAIT was worse when comparing it with both o-RAIT and their own first response. The worse response to the last RAIT in the m-RAIT group suggested that multiple RAITs did not bring additional PFS benefits. The subsequent analysis of risk factors for PD also revealed that older age at diagnosis and local persistent disease before RAIT were independent predictor of PD while the number of RAIT cycles was not, which further indicated o-RAIT may have non-inferior survival benefits compared with m-RAIT. Which is similar to the study by Dinneen et al., who reported that although RAIT was associated with the improved disease-specific survival (DSS) in univariate analysis, it was not an independent predictor of DSS in multivariate analysis [27]. These findings are meaningful to shed light on the reflection of management of RAIT administration in terms of timing and interval, owing to the non-inferior response and the less radiation exposure to patients with only once RAIT.

So far, there has been limited research to address the PFS benefit differences between various RAIT administrations, prospective studies are also difficult to conduct, let alone randomized controlled trials (RCT) given the ethical concerns. PSM, as a commonly used statistical method, which could serve as a robust solution for balancing baseline characteristics in the retrospective observational study, help create comparable groups and partially mimic RCTs [28, 29]. In patients with DTC, who generally have a long DSS, PSM

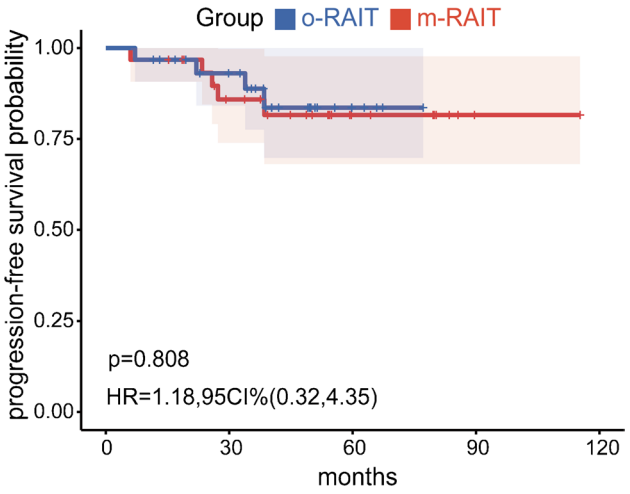

Fig. 3 Kaplan–Meier estimate of progression-free survival of matched o-RAIT and m-RAIT group ($n = 62$). Abbreviations: RAIT, radioactive iodine therapy; o-RAIT, only once RAIT; m-RAIT, multiple RAITs; HR, hazard ratio; CI, confidence interval

may particularly be a feasible way to explore the influence of specific RAIT administration on prognosis. Of which, whether to receive repeat RAIT for patients with RAI-avid pulmonary micrometastases have become the current major concern. It is noteworthy that local persistent disease before RAIT, as an adverse risk factor for conducting multiple RAITs, as well as progression disease after RAIT, we thus take it as a key factor in addition to age at diagnosis and follow-up time for PSM to make the baseline more comparable between the two groups. Of note, in the total matched cohort, the o-RAIT group exhibit non-inferior PFS compared with m-RAIT. Furthermore, in the aggressive subgroups which more likely lead to the decision-making of repeated RAIT, there remain no difference between o-RAIT and m-RAIT, which indicated repeated RAITs may not improve the PFS for such patients and again suggested the "less is more" philosophy of RAIT in clinical practice.

Several reasons may explain the non-inferior PFS performance of o-RAIT. Firstly, patients with RAI-avid pulmonary micrometastatic DTC may keep well-differentiated and indolent nature, which are sensitive to RAIT and tend to carry favorable prognosis, one round RAIT would be sufficient to achieve disease control and maintain SD. Secondly, the repeated TSH stimulation before RAIT administration during multiple RAITs may potentially activate the lesions, even exacerbating disease progression [30, 31], which is also supported by Thies' finding that recurrence and DTC-related

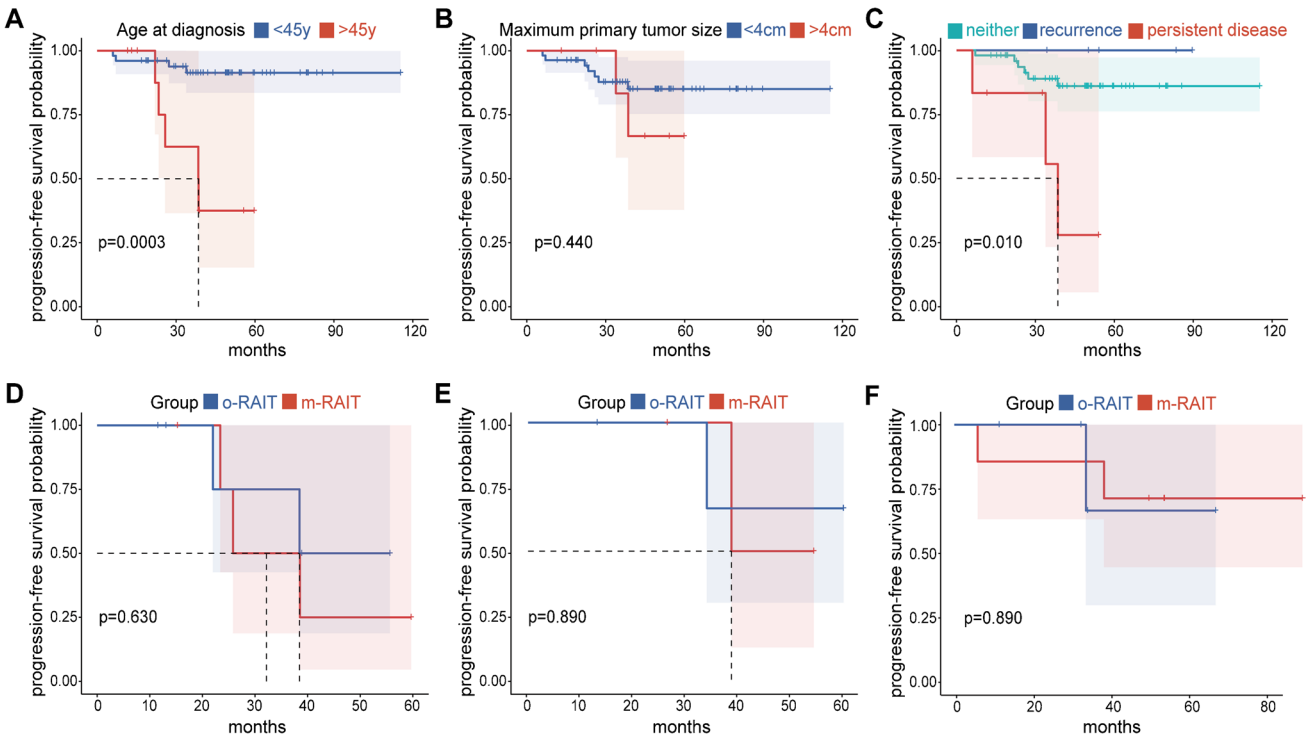

Fig. 4 Kaplan–Meier estimate of progression-free survival of subgroup analysis for the matched cohort. **A** Patients with age at diagnosis > 45 years old versus those < 45 years old; **B** Patients with maximum primary tumor size > 4 cm versus those < 4 cm; **C** Comparison between patients with local recurrence, local persistent disease, and neither; **D** o-RAIT versus m-RAIT in patients with age at diagnosis > 45 years old; **E** o-RAIT versus m-RAIT in patients with maximum primary tumor size > 4 cm; **F** o-RAIT versus m-RAIT in patients with local persistent disease Abbreviations: RAIT, radioactive iodine therapy; o-RAIT, only once RAIT; m-RAIT, multiple RAITs

mortality rates increased with more RAIT administrations in their study with limited metastatic high-risk patients, especially when cumulative dose exceed 600 mCi [32]. Thirdly, the RAI avidity of metastatic lesions may gradually decline along with repeated RAIT, and lead to structural incomplete response as a result of insufficient radiation dose to lesions, which has been observed by Samuel and Sun et al. [33, 34]. From which, a philosophy of "less is more" is suggested for such patients in clinical practice, though the dosimetry estimation they applied may not be exactly practical for micrometastatic DTC.

Apart from the above-mentioned concerns, it is noteworthy that increasing cumulative RAI doses correlate with higher prevalence of adverse effects such as myelosuppression, pulmonary fibrosis, and second primary malignancies [35, 36], and these adverse effects have become the major concerns in clinical decision-making.

Of note, in our study, local persistent disease before RAIT is associated with progression disease after RAIT and worse PFS, which has been supported by multiple studies [23, 37]. Particularly, from Lin et al.'s study, we can see the 10-year DSS rates were relatively low in the local persistent disease patients compared to those with local recurrence (52.5% vs. 85.1%) [38]. Since local persistent disease can be monitored and timely managed to improve the prognosis of these patients [24], therefore, even in patients with distant metastatic DTC, local management remains the important part of long-term dynamic follow-up.

In addition, it is noteworthy that patients with RAI-avid pulmonary micrometastatic DTC tended to be younger, compared with other studies and studies conducted by ourselves [7, 39]. Studies suggested younger age at diagnosis, especially for those under 45 years old, is associated with better prognosis following RAIT in patients with DM-DTC [40, 41], which was support by our analysis that older age at diagnosis was independent risk factors for worse PFS. Hence, based on the prior evidence above, as well as our findings in this study, in patients with RAI-avid pulmonary micrometastases, the methodology of RAIT in terms of timing and interval should be seriously considered by taking the relatively younger age, quite favorable outcome, and radiation exposure risks into account. And the "less is more" strategy with balance between the treatment-associated risks and uncertain survival benefits of RAITs need to be weighed upon the repeated RAIT decision-making.

The limitations of this study included: 1) the single-center and retrospective design, which resulted in a small sample size that may introduce selection bias and restrict the generalizability of our findings, though such RAI-avid pulmonary micrometastatic patients were rarely encountered in clinical practice; 2) the relatively short follow-up period was insufficient to explore the relationship between number of RAIT cycles and long-term outcomes, such as OS. Though biases were inevitable in this retrospective study, we hope our preliminary exploration would provoke further research into the benefits of multiple RAITs in such patients and we look forward to future studies with larger sample size, multicenter design, and longer follow-up to confirm our findings and extend them to more patients.

In summary, the non-inferior survival benefits of once RAIT in this study led to our reflection about the management strategy of patients with RAI-avid pulmonary micrometastatic DTC. Although the therapeutic strategy of "less is more" was more often mentioned in patients with low and intermediate risk DTC [42–45], it also should be tailored throughout in the management of high-risk patients, particularly in those with RAI-avid pulmonary micrometastatic DTC. In such patients, the active surveillance should become the mainstay during the follow-up, and more individualized assessment and risk–benefit balance need to be emphasized for RAIT decision-making.

Conclusion

Once RAIT exhibited non-inferior PFS benefits compared with multiple RAITs for patients with RAI-avid pulmonary micrometastatic DTC, supporting the therapeutic strategy of "less is more."

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00259-025-07339-3.

Acknowledgements This work was supported by the National High Level Hospital Clinical Research Funding (No. 2022-PUMCH-B-072). We thank Zhuan-Zhuan Mu and Yi-Han Zhao for providing guidance for the writing of this manuscript.

Author contributions Yan-Song Lin contributed to the conception, designing, and drafting. The data analysis and the draft of the manuscript was completed by Cong Shi, Di Sun and all other authors give suggestions while drafting the manuscript. All authors read and approved the final manuscript.

Funding This work was supported by National High Level Hospital Clinical Research Funding (2022-PUMCH-B-072).

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

Declarations

Ethics approval The study was approved by the Hospital Ethics Committee of Peking Union Medical College Hospital (JS-2432).

Consent to participate Not applicable.

Consent to publish Not applicable.

Competing interests The manuscript has never been published elsewhere and the authors have nothing to disclose.

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