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ORIGINAL ARTICLE

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Clinical outcomes and prognostic factors in patients with no less than three distant organ system metastases from differentiated thyroid carcinoma

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Abstract

Objectives For patients with differentiated thyroid carcinoma (DTC), distant metastases are commonly identified in the lungs and bones. However, they are relatively rare in other distant organs, such as the liver, kidneys, or brain. The aim of the current study was to describe the clinical outcomes and evaluate the prognostic factors of patients with no less than three different distant organ system metastases from DTC.

Methods This study retrospectively identified 717 patients diagnosed with DTC with distant metastases between January 2005 and December 2017. Patient response to radioactive iodine (RAI) therapy was monitored by changes in serum thyroglobulin levels and imaging changes. Five-year and 10-year overall survival (OS) rates were calculated by the Kaplan–Meier methods and Cox proportional hazards.

Results Among the 717 participants, 37 (5.16%) patients had no less than three different distant organ system metastases from DTC. Five-year and 10-year OS were 45.9% and 37.8% in patients with three or more distant organ system metastases while 74.5% and 64.9% in individuals with one or two distant organ system metastases, respectively. RAI avidity and RAIR-DTC were main independent prognostic factors influencing the clinical outcomes for both groups of patients. The presence of 3 or more different distant organ system metastases was the only independent prognostic factors for 10-year OS by multivariate analysis.

Conclusions Patients with no less than three distant organ system metastases from DTC had poor prognosis. RAI avidity and RAIR-DTC were main factors influencing overall survival for patients with distant metastases from DTC in both groups.

Keywords Differentiated thyroid carcinoma · Distant metastases · Multiple distant organ system metastases · Radioactive iodine therapy · Overall survival

Introduction

Thyroid carcinoma currently affects 567,000 individuals worldwide; the incidence of differentiated thyroid carcinoma (DTC) has dramatically increased, ranking 9th out of 36 cancers in 185 countries [1–3]. In 2018, the estimated number of new cases of thyroid carcinoma was 53,990 (3.1% of all new cancer cases), whereas the estimated deaths were 2060 (0.3% of all cancer deaths) [4]. Thyroid carcinoma is generally considered to be an indolent tumor with an estimated 5-year survival rate of 98.1% from 2008 to 2014 [4].

The most common site of distant metastases from DTC is the lung, followed by the bone [5, 6]. However, patients with pulmonary and/or bone metastases concurrent with other metastatic sites from DTC, such as the pleura, adrenal gland, ovaries, muscle, or skin, are relatively rare, and most of the documented literatures were case reports [7–9]. The presence of multiple distant organ system metastases from DTC is considered to confer worse clinical outcomes [10]. However, the clinical outcomes

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and prognostic factors of these individuals remained unknown.

Thus, the aim of the present study was as follows: (1) to describe the clinical characteristics of patients with ≥3 different distant organ system metastases from DTC; (2) to evaluate the independent prognostic factors of the study population; and (3) to investigate the clinical outcomes of patients with multiple distant organ system metastases from DTC.

Materials and methods

Study population and selection criteria

The study inclusion criteria were as follows: (1) all patients admitted with the diagnosis of DTC and confirmed with distant metastases from DTC by ^{131}I-SPECT/CT or ^{18}F-FDG PET/CT scans were considered for inclusion; (2) all patients underwent total thyroidectomy and radioactive iodine therapy; and (3) the serum thyroglobulin of these patients increased continuously. Since this study was a retrospective one, the institutional review board of our hospital approved this study, and the requirement to obtain informed consent was waived. Among the 717 patients with distant metastases from DTC who underwent radioactive iodine therapy after a total thyroidectomy, 44 patients were excluded from the current study according to the following criteria: (1) 18 DTC patients had unavailable survival data during the follow-up period; (2) 14 individuals were accompanied with other malignant tumors that might have also lead to distant metastases; (3) 7 patients had poor-differentiated thyroid carcinoma confirmed by pathological examinations after initial surgery; (4) 5 patients had an undetectable stimulated serum Tg (sTg) level because of high serum TgAb levels during the follow-up period.

Diagnostic criteria for patients with multiple distant organ system metastases

The diagnostic criteria of the current study were as follows: (1) multiple distant organ system metastases in this study were defined as patients with distant metastases of three different organ systems from DTC; (2) age at diagnosis were defined as the age when patients were confirmed of no less than three different distant organ system metastases after initial radioactive iodine therapy; (3) each patient had a clinical history of radioactive iodine therapy after a total thyroidectomy; (4) metastatic sites with positive ^{131}I uptake could be confirmed by continuously elevated serum Tg levels, positive findings on therapeutic ^{131}I whole-body scan and multiple distant organs involvement confirmed by ^{131}I-SPECT/CT scans; and (5) metastatic sites with negative ^{131}I uptake were discovered by continuously elevated serum thyroglobulin levels and positive findings confirmed by ^{18}F-FDG PET/CT scans. According to these diagnostic criteria, 37 patients with three or more distant organ system metastases were selected as "Group A". The remaining 636 individuals with no more than two distant organ system metastases were divided into "Group B". The classification of different groups was conducted when all medical records and imaging findings was retrospectively analyzed by the end of the follow-up period. That is to say, whether the patient was diagnosed as DTC with three or more distant organ system metastases by ^{18}F-FDG PET/CT scans before initial radioactive iodine therapy, or distant metastases were discovered during follow-up (delayed distant metastases) and further developed into multiple (≥3) distant organ system metastases by the end of the follow-up period, all the above patients would be classified into "Group A".

In addition, the definition of patients who are refractory to radioactive iodine therapy from differentiated thyroid carcinoma (RAIR-DTC or RR-DTC) was those with no RAI uptake on metastatic lesions, or ≥1 lesion with no RAI uptake, or a progression of lesions with RAI uptake [11]. Moreover, lymph node metastases were not considered as one metastatic site in this study. Otherwise, each group of patients were subdivided into three subgroups, namely, Subgroup 1, which included patients with pulmonary metastases but without bone metastases, Subgroup 2, which included patients with bone metastases but without pulmonary metastases, and Subgroup 3, which included patients with both pulmonary and bone metastases. The study flow chart for the patient population included in the current study is presented in Fig. 1.

Treatment of multiple distant organ system metastases from DTC and follow-up

Radioactive iodine (RAI) treatment and follow-up

All patients included in the current study withdrew thyroid hormone medication and had a low-iodine diet for 2–4 weeks before RAI treatment. Before receiving the oral dose of radioactive iodine, each patients in our institution took several conventional examinations, such as stimulated serum thyroglobulin, thyroid stimulating hormone, thyroglobulin antibody, neck ultrasound, ^{99m}TC-MDP whole-body bone scan, chest X-ray, and CT scans. The initial oral dose of RAI therapy for patients with distant metastases was approximately 5.6–7.4 GBqs (150–200 mCi) in our institution. After taking radioactive iodine oral dose administration for 4 days, ^{131}I-whole-body scans (^{131}I-WBS) were performed for each patient. According to the outcomes of the ^{131}I-WBS, individuals were classified as either the non-^{131}I avid group or the ^{131}I avid group. For patients from the ^{131}I avid group, ^{131}I-SPECT/CT scans were performed to

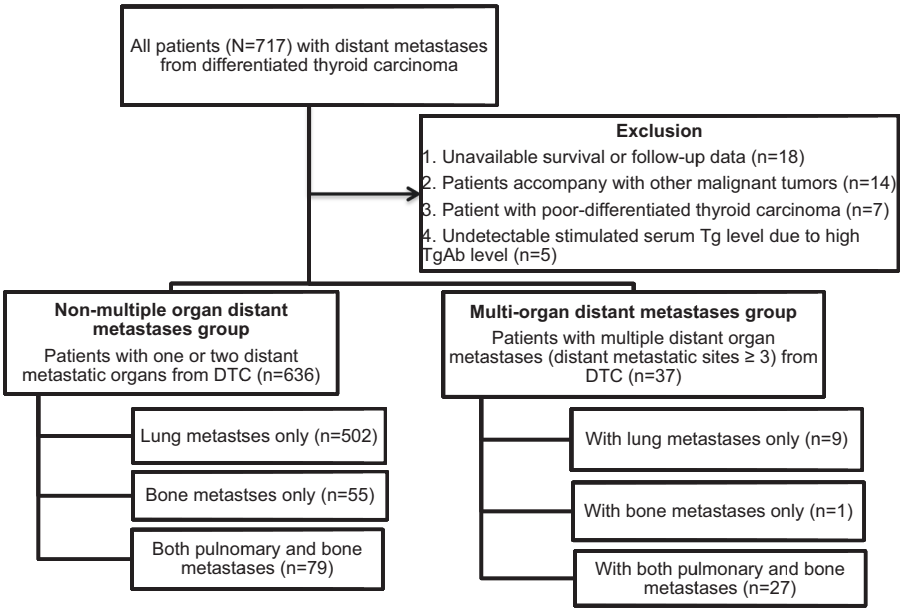

Fig. 1 The flow chart for participates included in the current study

detect the exact metastatic sites. If the patient had continuously elevated serum thyroglobulin without a positive finding by ^{131}I-WBS, ^{18}F-FDG PET-CT was performed to exclude metastatic lesions. The follow-up period of the included study population ranged from 0.9 to 23.7 (3.94 ± 4.53) years. According to the metastatic sites, patients were classified as the lung and bone metastases group, or either pulmonary or bone metastases group.

Other treatment strategies for patients with multiple distant organ metastases

If the patients were diagnosed as RAIR-DTC, other treatment strategies may also be tried under the informed consent of the patient. Thus, four patients underwent chemotherapy and seven individuals had external beam irradiation in this study. Moreover, two patients had targeted therapies as the progression of metastatic DTC and confirmed diagnosis of RAIR-DTC.

Evaluation of the response to therapy

The response to therapy in metastatic individuals from DTC was estimated according to changes in serum Tg levels and anatomical changes monitored by imaging. Changes in serum Tg levels was divided into two groups: (a) effective, the serum Tg concentration was reduced by more than 25% compared with pretreatment levels and (b) stable or ineffective, the serum Tg concentration decreased less than 25% compared with pretreatment levels or continuously increased compared with pretreatment levels. The response to therapy on CT scans were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, as follows: (1) complete response (CR), the disappearance of all detectable lesions; (2) partial response (PR), a greater than 30% decrease in the sum of lesion volumes according to the initial volumes of pulmonary nodules; (3) progressive disease (PD), a greater than 20% increase in the sum of pulmonary metastatic lesion volumes or the appearance of more than one new lesion; and (4) stable disease (SD), not enough shrinkage to meet the qualification for PR or insufficient increase to meet the qualification for PD.

Evaluation of prognostic factors and clinical outcomes

Clinical outcomes of the study population were evaluated by a 5-year and 10-year overall survival (OS) rates. The disease status of each patient was recorded at each half year during follow-up as “alive” or “dead”. Univariate analysis of the variables influencing both 5-year and 10-year OS rates was analyzed. Multivariate analysis of the prognostic factors affecting 10-year OS rates was also performed.

Statistical analysis

SPSS statistics software (version 23.0; IBM Corporation, Armonk, NY) was used to perform statistical analysis. Continuous data were presented as median and standard deviation or range, proportions or exact numbers, as appropriate for every variable. The 5-year and 10-year OS rates of each patient in the study group of patients with no less than three distant organ system metastases were evaluated by Kaplan–Meier methods and Cox proportional hazards. Differences between the subgroups were analyzed

by a log-rank test. $p < 0.05$ was considered as statistically significant.

Results

Patient characteristics

The incidence of multiple distant organ metastases among the distant organ metastases patient population was 5.16% (37 of 717). The baseline characteristics and pathological features of patients with nonmultiple distant organ system metastases from DTC and individuals with multiple distant organ system metastases are presented in Table 1. The median age of the 37 patients with ≥3 different distant organ metastases was 53 (range: 19–89) years. Among the study population of the current study, 20 of 37 (54.1%) were under the age of 55, while 17 of 37 (45.9%) were more than 55 years of age. Twenty-nine (78.4%) individuals were confirmed to have papillary thyroid carcinoma by

Table 1 Baseline demographics and clinical characteristics between different groups of patients with and without multiple distant organ metastases

Characteristics	Total	Group A ($N = 37$)	Group B ($N = 636$)	p-Value	Logistic regression analysis univariate	
					OR [95% CI]	p-value
Age at the diagnosis of DM (years)				0.354	0.731 [0.376–1.421]	0.355
≤55	314	20	294			
>55	359	17	342			
Gender				0.021*	2.164 [1.111–4.215]	0.023*
Female	429	17	412			
Male	244	20	224			
Ratio (F: M)	1.8 F: 1 M	1 F: 1.2 M	1.8 F: 1 M			
Tumor diameter (cm)				<0.0001*	0.042 [0.006–0.307]	0.002*
≤4	418	36	382			
>4	255	1	254			
Extra-thyroidal extension				0.016*	0.423 [0.206–0.871]	0.020*
None	344	26	318			
Minimal/gross	329	11	318			
Histology				0.048*	0.455 [0.205–1.012]	0.054
PTC	425	29	396			
FTC	248	8	240			
Metastatic tumor site				0.982	1.009 [0.478–2.128]	0.982
Lung or bone only	183	10	173			
Lung and bone	490	27	463			
Discovery of metastases				0.839	0.916 [0.392–2.138]	0.839
At presentation	119	7	112			
Delayed distant metastases	554	30	524			
Number of thyroid surgery				0.556	0.820 [0.422–1.591]	0.557
1	296	18	278			
>1	377	19	358			
RAI therapy activity, mCi				/	/	/
Range	100–2200	150–2200	100–1800			
Median	500	600	500			
RAI avidity				0.027*	0.461 [0.228–0.930]	0.031
No	140	13	127			
Yes	533	24	509			
RAIR-DTC				0.336	0.708 [0.349–1.434]	0.338
Yes	404	25	379			
No	269	12	257			
Chemotherapy				0.008*	4.162 [1.333–12.994]	0.014*
No	651	33	618			
Yes	22	4	18			
External beam irradiation				0.096	2.050 [0.866–4.852]	0.103
No	601	30	571			
Yes	72	7	65			

DM distant metastases, *SD* standard deviation, *RAI* radioactive iodine, *PTC* papillary thyroid carcinoma, *FTC* follicular thyroid carcinoma, *RAIR-DTC* radioactive iodine refractory differentiated thyroid carcinoma

pathological results, and 8 (21.6%) patients were diagnosed with follicular thyroid carcinoma. Every patient in the study population had a total thyroidectomy, and 19 of the 37 (51.4%) patients with multiple distant organ system metastases had no less than two surgeries for disease recurrence or remnant lesions. The number of patients with no, minimal or gross extra-thyroidal extension were 26 (70.3%), 3 (8.1%) and 8 (21.6%), respectively. However, sex, tumor diameter, extra-thyroidal extension, and patients with or without chemotherapy showed significant differences between Group A and Group B.

Among the 37 patients included in the current study, the most common metastatic sites were the lungs (36 of 37, 97.3%), followed by bone (27 of 37, 73.0%), kidneys (13 of 37, 35.1%), liver (10 of 37, 27.0%), muscle (8 of 37, 21.6%), adrenal gland (6 of 37, 16.2%), brain (6 of 37, 16.2%), pleura (5 of 37, 13.5%), skin (3 of 37, 8.1%), soft tissue (3 of 37, 8.1%), trachea (2 of 37, 5.4%), pancreas (2 of 37, 5.4%), and ovaries (1 of 37, 2.7%).

Changes in serum thyroglobulin levels

In this study, the response evaluation to radioactive iodine therapy and disease progression was conducted by monitoring the changes in the serum thyroglobulin levels and imaging changes. Among the 37 patients in Group A, the median initial stimulated serum thyroglobulin levels was 2617 (ranged from 296.7 to 50,000) ng/ml. Eleven (11 of 37, 29.7%) patients had dropped serum thyroglobulin levels after radioactive iodine therapy, while 25 (25 of 37, 67.6%) individuals had continuously elevated serum thyroglobulin levels, or their serum thyroglobulin remained at high levels before and after RAI therapy. Otherwise, approximately 60.1% (382 of 636) patients had dropped serum thyroglobulin levels after RAI therapy, while the other 39.9% (254 of 636) individuals suggested poor response to RAI therapy considering changes in serum thyroglobulin levels.

Response to RAI therapy monitored by imaging changes

According to 2015 ATA guidelines, the response to therapy in metastatic patients should be monitored by imaging. Among the 37 patients in Group A, numbers of patients with CR, PR, SD, PD to RAI therapy was 0, 8.1% (3 of 37), 10.8% (4 of 37), and 81.1% (30 of 37), respectively, according to RECIST v1.1. While for patients in Group B, counts of individuals with CR, PR, SD, and PD was 16.7% (106 of 636), 43.7% (278 of 636), 33.2% (211 of 636) and 6.4% (41 of 636), respectively.

Survival analysis for participants between Group A and B

For patients with three or more distant organ system metastases from DTC in Group A, the 5-year OS rates are 45.9% and the 10-year OS rates are 37.8%. In addition, for patients with one or two distant organ system metastases from DTC in Group B, the 5-year and 10-year OS rates are 74.5% and 64.9%, respectively. Survival analysis regarding the 5-year OS rates of patients with distant metastases from DTC between Group A and B is statistically significant (p-value = 0.008; Log-rank value = 6.942). Similarly, survival analysis regarding the 10-year OS rates of individuals with distant metastases from DTC between Group A and B is also statistically significant (p-value = 0.036; Log-rank value = 4.380). Moreover, comparison of the OS rates for patients with distant metastases from DTC between Group A and B by Cox's proportional hazards model (p-value = 0.00001) are presented in Fig. 2.

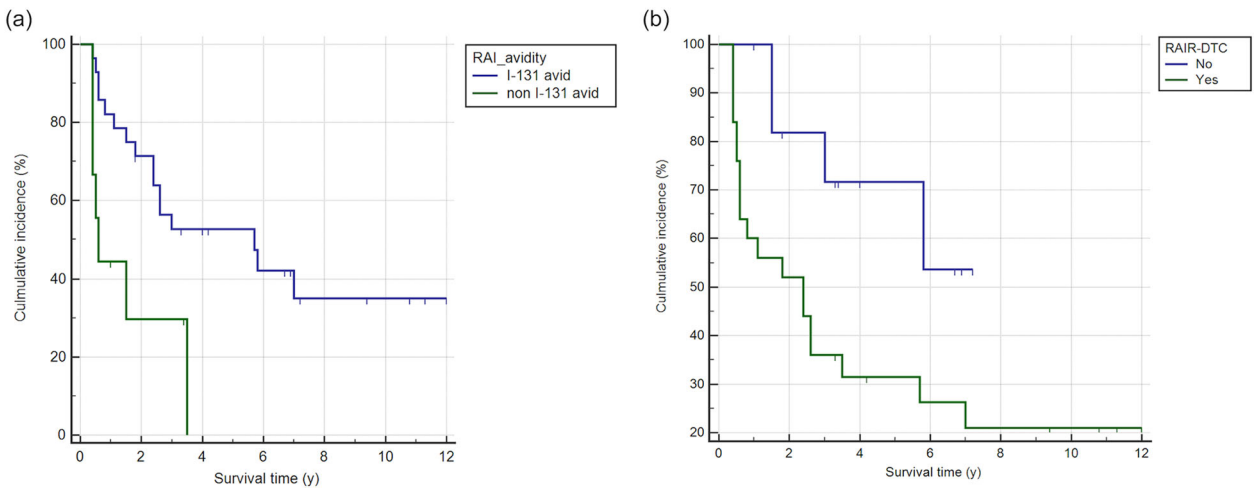

Fig. 2 Comparison of overall survival rates between patients in Group A and Group B by Cox's proportional-hazards regression

Prognostic factors for patients between Group A and B

Prognostic factors which may influencing the 5-year and 10-year OS rates for patients with distant metastases from DTC between Group A and B are presented in Tables 2 and 3. Univariate analysis suggest that RAI avidity and RAIR-DTC may significantly associated to the 5-year OS rates in both Group A and Group B patients. However, prognostic factors significantly associated to OS at univariate analysis including number of thyroid surgery, RAI avidity and RAIR-DTC for patients with three or more distant organ system metastases from Group A. Otherwise, only RAI avidity and RAIR-DTC were significant prognostic factors for Group B patients. In addition, the clinical outcomes and survival curves of patients with no less than three different distant organ system metastases from DTC are presented in Fig. 3. Nevertheless, multivariate analysis of prognostic factors for all patients with distant metastases from DTC in both Group A and Group B by Cox's proportional hazards model are shown in Table 4. RAIR-DTC (p-value = 0.011) and the presence of three or more distant organ system metastases (p-value = 0.00001) are independent prognostic factors regarding 5-year OS rates. Moreover, the results of multivariate analysis underlining that the presence of no less than three different distant organ systemic metastases is the only independent prognostic factors for 10-year OS rates (p-value = 0.0002).

Discussion

The current study describes a group of patients with no less than three different distant organ system metastases from differentiated thyroid carcinoma, which has helped to fill the knowledge gap regarding the different definitions of multiple organ metastases from DTC from previous literature [10]. Our study focused on different parts from the previous documented study, which evaluated the impact of multi-organ distant metastases (MODM) from single organ distant metastases (SODM), and found that MODM were associated with a poorer survival rather than individuals with SODM [10]. Multi-organ distant metastases was generally considered as disease with multiple organ involvement, however, in the previous literature, the authors compared MODM with SODM, and included those with bone and pulmonary metastases or only two organ metastases [10]. Only a few patients had DTC with rare distant organ metastases except the lungs and bone in a published literature [10]. In the current study, our study population mainly focused on patients with no less than three different distant organ system metastases from DTC. In addition, this study evaluated the distribution and characteristics of different distant metastatic sites including the rare distant organ system metastases from DTC.

The current study, included 37 patients with no less than three distant organ system metastases from DTC in Group A and 636 patients with one or two distant organ system metastases in Group B. According to the 2015 ATA guidelines, patients with tumor diameter >4 cm and with gross ETE will be divided into T3 or T4 stage, and these kinds of patients tended to demonstrate poorer clinical outcomes [12]. As DTC with multi-organ (≥3) distant metastases was quite rare, only 37 patients were involved in Group A. Thus, the relatively small sample of Group A and different baseline characteristics such as gender, histology, tumor diameter and ETE may not be comparable enough as in Group A and Group B patients. Otherwise, as distant metastases was a strong presentation of aggressive disease for patients with DTC [13], thus, the influence of distant metastases, even multi-organ distant metastases may offset the impact of tumor diameter and ETE for patients with DTC. This study found that RAI avidity and RAIR-DTC were significantly associated with both 5-year and 10-year OS among patients in both Group A and Group B, while previously documented literature determined that a serum Tg level >30 ng/ml at the time of first distant metastases may be a high risk of having MODM [3, 10]. In addition, comparison of the OS rates for patients with distant metastases from DTC between Group A and B by Cox's proportional hazards model (p-value = 0.00001) also suggested that the presence of three or more distant organ metastases was the only independent prognostic factors for 10-year OS rates.

As reported in a recent study, the overall incidence of thyroid cancer has increased by 3% every year from 1974 to 2013, and both the incidence rate and mortality of thyroid carcinoma has increased for advanced-stage papillary thyroid carcinoma [14]. Papillary thyroid carcinoma was seen in approximately 74–80% of all thyroid neoplasms [7]. Distant metastases develop in approximately 4–15% of patients with DTC, mainly in the bones and lungs [15–19]. However, the incidence data of patients with three or more distant organ metastases from DTC are currently unknown. In the current study, the incidence of multiple distant organ metastases from DTC was 5.16% (37 of 717) among patients with DTC and distant metastases. Thus, patients with no less than three distant organ system metastases from DTC seemed to be quite rare among the DTC patient population.

The most common sites of distant metastases from DTC were the lungs and bones. Other metastases sites were also reported previously, such as the liver, brain, pancreas [18, 20–22]. In this study, the most common metastases site from patients with multiple distant organ metastases from DTC was the lungs, followed by bone, kidneys, liver,

Table 2 Prognostic factors influencing 5-year overall survival rates for patients with distant metastases from DTC between Group A and Group B

Variable	Group A					Group B				
	Patient number	No. of deaths (5 years)	5-year overall survival rate (%)	Log-rank value	*p*-Value[a]	Patient number	No. of deaths (5 years)	5-year overall survival rate (%)	Log-rank value	*p*-Value
Age at the diagnosis of DM (years)				0.004	0.947				0.688	0.407
≤55	20	11	45.0			294	69	76.5		
>55	17	9	47.1			342	93	72.8		
Gender				1.061	0.303				<0.0001	0.993
Female	17	8	52.9			412	105	74.5		
Male	20	12	40.0			224	57	74.6		
Tumor diameter (cm)				0.871	0.351				1.402	0.236
≤4	36	20	44.4			382	89	76.7		
>4	1	0	100.0			254	73	71.3		
Extra-thyroidal extension				0.001	0.970				0.993	0.609
None	26	14	46.2			318	74	76.7		
Minimal	3	1	66.7			191	52	72.8		
Gross	8	5	37.5			127	36	71.7		
Histology				0.196	0.658				0.979	0.322
PTC	29	16	44.8			396	94	76.3		
FTC	8	4	50.0			240	68	71.7		
Metastatic site				0.286	0.593				0.236	0.627
Lung or bone metastases	10	6	40.0			173	41	76.3		
Lung and bone metastases	27	14	48.1			463	121	73.9		
Number of thyroid surgery				1.759	0.185				0.203	0.652
1	18	11	38.9			278	74	73.4		
>1	19	9	52.6			358	88	75.4		
RAI avidity				6.762	0.009[a]				35.667	<0.0001[a]
No	13	8	38.5			127	69	45.7		
Yes	24	12	50.0			509	93	81.7		
RAIR-DTC				5.041	0.025[a]				15.151	0.0001[a]
No	12	3	75.0			379	69	81.8		
Yes	25	17	32.0			257	93	63.8		
Chemotherapy				0.159	0.690				0.030	0.862
No	33	17	48.5			618	157	74.6		
Yes	4	3	25.0			18	5	72.2		
External beam irradiation				0.001	0.977				0.010	0.918
No	30	16	46.7			571	145	74.6		
Yes	7	4	42.9			65	17	73.8		
Total	37	20	45.9			636	162	74.5		

DTC differentiated thyroid carcinoma, *DM* distant metastases, *PTC* papillary thyroid carcinoma, *FTC* follicular thyroid carcinoma, *RAI* radioactive iodine, *RAIR-DTC* refractory to radioactive iodine therapy from differentiated thyroid carcinoma

[a]Statistical significance (p-Value < 0.05)

Table 3 Prognostic factors influencing 10-year overall survival for patients with distant metastases from DTC between Group A and Group B

Variable	Group A					Group B				
	Patient number	No. of deaths (10 year)	10-year survival rate (%)	Log-rank value	*p*-Value[a]	Patient number	No. of deaths (10 year)	10-year survival rate (%)	Log-rank value	*p*-Value
Age at the diagnosis of DM (years)				0.216	0.642				1.961	0.161
≤55	20	12	40.0			294	91	69.0		
>55	17	11	35.3			342	132	61.4		
Gender				0.148	0.701				0.430	0.512
Female	17	11	35.3			412	139	66.3		
Male	20	12	40.0			224	84	64.3		
Tumor diameter (cm)				0.012	0.912				0.486	0.486
≤4	36	22	38.9			382	128	66.5		
>4	1	1	0			254	95	62.6		
Extra-thyroidal extension				0.003	0.960				0.753	0.686
None	26	16	38.5			318	104	67.3		
Minimal	3	2	33.3			191	71	62.8		
Gross	8	5	37.5			127	48	62.2		
Histology				0.034	0.853				0.863	0.353
PTC	29	17	41.4			396	131	66.9		
FTC	8	6	25.0			240	92	61.7		
Metastatic site				0.016	0.900				2.355	0.125
Lung or bone metastases	10	6	40.0			173	49	71.7		
Lung and bone metastases	27	17	37.0			463	174	62.4		
Number of thyroid surgery				4.328	0.038[a]				0.572	0.449
1	18	14	22.2			278	104	62.6		
>1	19	9	52.6			358	119	66.8		
RAI avidity				6.762	0.009[a]				10.423	0.001[a]
No	13	9	30.8			127	68	46.5		
Yes	24	14	41.7			509	155	69.5		
RAIR-DTC				4.447	0.035[a]				23.512	0.0001[a]
No	12	4	66.7			379	91	76.0		
Yes	25	19	24.0			257	132	48.6		
Chemotherapy				0.015	0.901				2.238	0.135
No	33	20	39.4			618	212	65.7		
Yes	4	3	25.0			18	11	38.9		
External beam irradiation				0.228	0.633				0.023	0.880
No	30	19	36.7			571	201	64.8		
Yes	7	4	42.9			65	22	66.2		
Total	37	23	37.8			636	223	64.9		

DTC differentiated thyroid carcinoma, *DM* distant metastases, *PTC* papillary thyroid carcinoma, *FTC* follicular thyroid carcinoma, *RAI* radioactive iodine, *RAIR-DTC* refractory to radioactive iodine therapy from differentiated thyroid carcinoma

[a]Statistical significance (p-Value < 0.05)

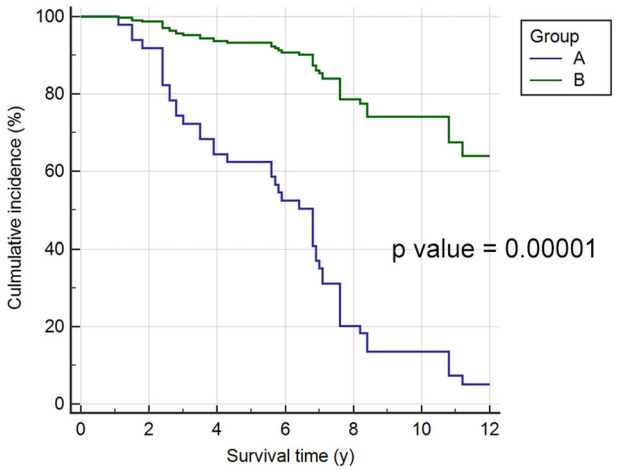

Fig. 3 Overall survival rates for patients with distant metastases from DTC by **a** RAI avidity and **b** RAIR-DTC

muscle, adrenal gland, brain, pleura, skin, soft tissue, trachea, pancreas and ovaries. In addition, distant metastases were correlated to lower survival and literatures have reported that for individuals with distant metastases from DTC, loss of RAI avidity showed an important role in clinical outcomes [23]. In the current study, RAI avidity and RAIR-DTC were two important independent factors correlated with clinical outcomes in both Group A and Group B patients, which was similar to the previous reported literature.

In order to successfully identify suitable treatment regimens, physicians should have the ability to judge the prognosis of individuals with distant metastatic lesions from DTC and consider the characteristics of the patient's tumor burden and baseline condition, as well as know the basic knowledge of radioiodine therapy, targeted treatment and redifferentiation strategies for patients with distant

Table 4 Multivariate analysis of prognostic factors of 5-year and 10-year overall survival rates from all patients with distant metastases from DTC using Cox's proportional hazards model

Prognostic factors	5-year overall survival rates			10-year overall survival rates		
	Risk ratio	95% CI	*p*-Value[a]	Risk ratio	95% CI	*p*-Value
Age at the diagnosis of distant metastases (year)		[0.813–3.003]	0.182		[0.604–2.167]	0.681
≤55	1			1		
>55	1.563			1.144		
Gender		[0.664–2.341]	0.494		[0.752–2.517]	0.303
Female	1			1		
Male	1.247			1.376		
Histology		[0.523–2.547]	0.725		[0.740–2.823]	0.283
PTC	1			1		
FTC	1.154			1.446		
Metastatic site		[0.834–4.153]	0.131			
Lung or bone metastases with other distant metastases	1			1	[0.652–2.974]	0.395
Lung and bone metastases with other distant metastases	1.861			1.393		
Number of thyroid surgery		[0.418–1.762]	0.678		[0.797–3.285]	0.185
1	1			1		
>1	0.858			1.618		
RAI avidity		[0.369–1.641]	0.512		[0.423–1.453]	0.784
No	1			1		
Yes	0.778			0.784		
RAIR-DTC		[1.258–5.923]	0.011[a]		[0.638–2.569]	0.490
No	1			1		
Yes	2.730			1.280		
Group		[0.060–0.376]	0.00001[a]		[0.174–0.571]	0.0002[a]
A	1			1		
B	0.150			0.315		

CI confidence interval, *PTC* papillary thyroid carcinoma, *FTC* follicular thyroid carcinoma, *RAI* radioactive iodine, *RAIR-DTC* refractory to radioactive iodine therapy from differentiated thyroid carcinoma

[a]Statistical significance (p-Value < 0.05)

metastatic lesions from DTC [24]. Radioactive iodine therapy is one of the treatment strategies for treating distant metastases from DTC [25–27]. Recent documented literature reported that RAI therapy could significantly decrease the overall mortality (HR 0.10; $p = 0.02$) [28]. However, liver metastases showed poor ^{131}I-avidity, which was confirmed by previous reported literature [29]. In a previous study, all pediatric patients (under the age of 18 years) were RAI avid and 77 RAI therapies were given for patients with MODM ($M = 2.4$ per patient) [10]. As our institution is one of the largest radioactive iodine therapy center in China, more patients tended to have radioactive iodine therapy. Whenever the post-therapeutic ^{131}I-whole-body scan was negative or indicated that all the metastatic lesions had no ^{131}I-avid, RAI treatment would be stopped. For patients with negative ^{131}I-avidity but whose disease status was kept stable, follow-up was conducted monthly. For patients with a progressive disease, other treatment strategies were undertaken, including chemotherapy, external beam irradiation, tyrosine kinase treatment and/or redifferentiation treatment for metastasized DTC [24].

Differentiated thyroid carcinoma, which is known as an indolent tumor, generally had good prognosis. However, patients with distant metastases from DTC have varied clinical outcomes, ranging from 25 to 70% by 10 years after the diagnosis of DTC or the identification of distant metastases [5, 10, 23, 30–32]. In the current study, the 5-year OS rates are 45.9% and the 10-year OS rates are 37.8% for patients with three or more distant organ system metastases from DTC in Group A. In addition, for patients with one or two distant organ system metastases from DTC in Group B, the 5-year and 10-year OS rates are 74.5% and 64.9%, respectively. However, as reported by a previous literature, for MODM patients, the 5-year OS rate was only 15.3% [10]. The difference between our data and the documented literature was probably because most patients went to our institution for radioactive iodine therapy, and at least part of their metastatic sites were initially ^{131}I-avid. As ^{131}I-avidity was a significant prognostic factors identified by our study, this was a possible reason for better clinical outcomes of our study population. In our previous study, for patients with bone metastases from DTC, the 5- and 10-year OS rates were 86.5 and 57.9%, respectively [33]. For patients with pulmonary metastases from DTC as reported in another previous study, the 5-year and 10-year OS rates were 69.7 and 38.1% for those without ^{131}I-avidity, and 87.0 and 69.2% for patients with ^{131}I-avidity, respectively [8]. In the current study, the 5-year and 10-year OS rates were 38.5% and 30.8% among patients without ^{131}I-avidity, and 50.0% and 41.7% for patients with ^{131}I-avidity, respectively. Thus, patients with multiple distant organ system metastases had a poorer prognosis than patients with bone or pulmonary metastases in our institution. Moreover, the comparison of OS rates for patients with distant metastases from DTC between Group A and Group B by Cox's proportional hazards model (p-value $= 0.00001$) also suggested that the presence of three or more distant organ metastases was the only independent prognostic factors for 10-year OS rates. These results suggested that other than RAI avidity and RAIR-DTC, the presence of three or more distant organ system metastases may be a significantly important factors for patients with metastasized differentiated thyroid cancer.

Our study had the following limitations: First, as this study was a retrospective one, the researchers could hardly avoid the selection bias at either the patient or physician level. Second, the relatively small study population may not be sufficiently representative. Third, pathological results have not been obtained for each metastatic lesion because it is not ethical. Finally, the clinical practice was complicated and variable, resulting in difficulty in setting a control group or using the double-blinded method to conduct the entire research. Although the management of this patient population can be challenging, but a multidisciplinary approach may be helpful to improve the clinical outcomes. A prospective cohort study by a multidisciplinary method with a larger study population are needed for further research.

In conclusion, the incidence of no less than three different distant organ system metastases from DTC was rare. Except for the common metastatic sites such as the lungs and bones, other distant organs can also be involved, for example, the pancreas, pleura, skin, brain and muscle. RAI avidity and RAIR-DTC were significant prognostic factors influencing OS rates. Patients with no less than three different distant organ system metastases had poorer clinical outcomes compared with individuals with one or two distant organ system metastases. The presence of three or more distant organ system metastases may be an important prognostic factor for patients with metastasized differentiated thyroid carcinoma.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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