Pulmonary metastases in differentiated thyroid cancer: efficacy of radioiodine therapy and prognostic factors

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Abstract

Context: Data from a large cohort of patients with pulmonary metastases from differentiated thyroid cancer (DTC) were retrospectively analyzed.

Objective: To assess the effect of radioiodine therapy and investigate the prognostic factors of survival for patients with pulmonary metastasis secondary to DTC.

Methods: A total of 372 patients with pulmonary metastasis from DTC treated with ^{131}I entered the study. According to the results of ^{131}I whole-body scan (WBS), pulmonary metastases were classified as ^{131}I -avid and non- ^{131}I -avid. For patients with ^{131}I -avid lung metastases, treatment response was measured by three parameters: serum thyroglobulin (Tg) levels, chest computed tomography (CT) and post-therapeutic ^{131}I -WBS. Overall survival was calculated by the Kaplan–Meier method. Factors predictive of the outcome were determined by multivariate analyses.

Results: Among patients demonstrating ^{131}I -avid pulmonary metastases (256/372, 68.8%), 156 cases (156/256, 60.9%) showed a significant decrease in serum Tg levels after ^{131}I therapy and 138 cases (138/229, 60.3%) showed a reduction in pulmonary metastases on follow-up CT. A complete cure, however, was only achieved in 62 cases (62/256, 24.2%). Multivariate analysis showed that only age, the presence of multiple distant metastases and pulmonary metastatic node size were significant independent variables between the groups of ^{131}I -avid and non- ^{131}I -avid.

Conclusion: This study indicated that, most ^{131}I -avid pulmonary metastases from DTC can obtain partial or complete remission after ^{131}I therapy. Younger patients (<40 years old) with only pulmonary metastases and small ('fine miliatic' or micronodular) metastases appear to have relative favorable outcomes. Patients who do not respond to ^{131}I treatment have a worse prognosis.

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Introduction

Differentiated thyroid cancer (DTC) is most commonly confined to the thyroid gland with or without involvement of regional lymph nodes because of its typical slow-growing pattern. Distant metastases are an uncommon event in DTC and a wide range in prevalence (4–23%) has been reported (1, 2, 3, 4, 5, 6). Lungs are the most frequent site of distant metastasis in DTC and the resulting respiratory failure may be the most common cause of death. About 50% of patients with such metastases die within 10 years (7). Postoperative ablation therapy with

^{131}I is a mainstay of treatment in such cases, in conjunction with complete surgical resection of the thyroid and thyrotropin (TSH) suppression with thyroxine (T_4). According to iodine-concentrating capacity (8), pulmonary metastases are classified as ^{131}I -avid and non- ^{131}I -avid. ^{131}I therapy is only recommended for patients with ^{131}I -avid lung metastases, and there is no obvious benefit for those with non- ^{131}I -avid metastases. Thus, the characteristics and prognosis differ between the two groups. However, few previous investigations have

Clinical Study	H-J Song and others	Lung metastases and DTC	173:3	400
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discussed the efficacy of radioiodine therapy and prognostic factors of ^{131}I -avid and non- ^{131}I -avid lung metastases separately.

Serum thyroglobulin (Tg) level is a useful prognostic factor after radioactive iodine ablation and its measurement is included in the follow-up DTC patients according to the guidelines of the British Thyroid Association and the American Thyroid Association (9, 10). Conventional chest X-ray is routinely used for diagnosis and follow-up of DTC patients with pulmonary metastases. However, pulmonary metastases are more often encountered in patients with papillary carcinoma and their radiological size is usually <1 cm and frequently below the spatial resolution of the chest X-ray. Chest computed tomography (CT) is preferred over chest X-rays and it enhances the diagnostic accuracy in most patients with normal chest X-ray findings (11). Thus, it is useful for the detection of pulmonary metastases of DTC and is able to measure the node size of metastases accurately.

In this study, data from a large cohort of patients with pulmonary metastasis from DTC treated and managed at the same institution were retrospectively analyzed. We aimed to: i) assess the therapeutic effects of radioiodine treatment on ^{131}I -avid pulmonary metastases by the change of Tg level and node size; ii) investigate the prognostic factors related to ^{131}I -avid pulmonary metastases; iii) compare the significant factors that affect the ability of ^{131}I uptake between patients with ^{131}I -avid and non- ^{131}I -avid pulmonary metastases and iv) evaluate the overall survival (OS) and the variables influencing survival.

Subjects and methods

Patients

From January 1997 to December 2013, 4681 patients with DTC were treated at our institution and 372 (372/4681, 7.95%) who had lung metastases yielded the final cohort with the average age of 54.25 ± 16.08 years (range, 12–86 years). Primary thyroid cancers were papillary in 288 patients and follicular in 84. Only pulmonary metastases were involved in 298 patients while 74 patients also had distant metastases to other organs.

Diagnostic criteria for DTC pulmonary metastases

Definitive cytological or pathologic confirmation was not possible in all patients; therefore, diagnosis of pulmonary metastases was based on clinical and postoperative or follow-up chest CT findings, diagnostic or therapeutic ^{131}I whole-body scan (WBS) and serum Tg levels. A patient

satisfying the following criteria was considered to have pulmonary metastases: i) pathological results confirmed; ii) pulmonary ^{131}I uptake on ^{131}I -WBS + pulmonary node(s) on chest CT + elevated serum Tg level; iii) pulmonary ^{131}I uptake on ^{131}I -WBS + normal chest CT + elevated serum Tg level or iv) no pulmonary ^{131}I uptake on ^{131}I -WBS + pulmonary nodes on chest CT + elevated serum Tg level.

According to the results of ^{131}I -WBS, pulmonary metastases were classified as ^{131}I -avid (functioning pulmonary metastases) and non- ^{131}I -avid (non-functioning pulmonary metastases). According to the chest CT results, patients were divided into three categories: i) included patients with negative chest CT but ^{131}I uptake on ^{131}I -WBS, defined as 'fine miliatic'; ii) included patients with micronodular pulmonary metastases, defined radiologically as ≤ 1 cm in diameter and iii) included patients who had macronodular pulmonary metastases, defined radiologically as > 1 cm in diameter. According to the discovery time, pulmonary metastases were defined as initial (found at the time of or within 6 months after thyroidectomy) and developed (found 6 months or more after thyroidectomy).

Procedures for radioiodine therapy

Two hundred and seven (55.65%) patients received unilateral total and contralateral subtotal thyroidectomy and total thyroidectomy was performed in 165 (44.35%) cases. The patients achieved a sufficient hypothyroid state clinically with a serum TSH level > 30 $\mu\text{IU/ml}$. All patients were instructed to follow a low-iodine diet for at least 2 weeks. The dose of ^{131}I was 3.7–7.4 GBq (100–200 mCi). Conventional measurements, including free tri-iodothyronine, free T_4 , TSH, Tg, Tg antibody (TgAb), neck ultrasonography and chest CT scan were performed before ^{131}I administration. Tg and TgAb were measured by RIA (from 1997 to 1999) and chemiluminescence (from 1999 to 2013). All patients underwent conventional CT for examination of metastatic lesions without the use of contrast media in order not to affect the radioiodine therapy. The CT images were obtained with 7 mm slice thickness starting from the apex of the lungs. All CT images were obtained with the patient in the supine position. Patients were evaluated in terms of metastatic pulmonary lesions and the lesions were classified according to size. Levothyroxine (L-T_4) therapy was replaced 48 h later and post-therapeutic ^{131}I -WBS was carried out 5 days after ^{131}I administration. Post-treatment ^{131}I -WBS was obtained in the anterior and posterior projections

Clinical Study	H-J Song and others	Lung metastases and DTC	173:3	401
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with a large field-of-view gamma camera equipped with a high-energy (peak energy centred on 360 keV with a 20% energy window), parallel-hole collimator (Hawkeye Millennium VG, GE Medical Systems, Milwaukee, WI, USA). In patients with ^{131}I -avid metastases on ^{131}I -WBS, additional treatments with ^{131}I were given 4–12 months later. In cases with considerable residual thyroid tissue, even post-therapeutic WBS may fail to show ^{131}I concentration in the lungs owing to significant neck uptake (12), therefore, ^{131}I therapy was discontinued in patients with non- ^{131}I -avid lung metastases after residual thyroid tissue was completely ablated.

Evaluation of changes in serum Tg level

After at least two courses of ^{131}I therapy, changes in Tg level were classified into three types: effectiveness (biochemical relief (BR)), stabilization and ineffectiveness according to our previously study (13). i) Effectiveness: compared with pretreatment, the serum Tg levels exhibited a reduction of $\geq 25\%$; ii) stabilization: compared

with pretreatment, the serum Tg decreased or increased by $< 25\%$ and iii) ineffectiveness: compared with pretreatment, the serum Tg increased by $\geq 25\%$.

Evaluation of changes in chest CT images

Chest CT responses were assessed using Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) as follows: i) complete response (CR), disappearance of all lesions; ii) partial response (PR), $\geq 30\%$ decrease in the sum of lesions diameters, taking as reference the baseline sum diameters; iii) progressive disease (PD), $\geq 20\%$ increase in the sum of lesion diameters or appearance of greater than or equal to one new lesions is also considered progression and iv) stable disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Criteria for complete cure

Complete cure was defined by all the following criteria: no evidence or minimal visual evidence of ^{131}I concentration on ^{131}I -WBS in the chest region; no evidence of residual disease

Table 1 Changes of serum Tg for 256 DTC patients with ^{131}I -avid lung metastases after ^{131}I therapy: univariate statistical analysis.

Factors	No. of patients	Effective	Stable	Ineffective	χ^2	P
Age ^a					4.595	0.032
0–19	18 (7.03%)	10	6	2		
20–39	112 (43.75%)	71	26	15		
40–59	86 (33.59%)	57	16	13		
≥ 60	40 (15.63%)	18	7	15		
Gender					5.323	0.021
Male	95 (37.11%)	65	20	10		
Female	161 (62.89%)	91	35	35		
Pathological type					1.668	0.434
Papillary	193 (75.39%)	114	45	34		
Follicular	63 (24.61%)	42	10	11		
Operation method					2.475	0.115
Lobectomy or subtotal thyroidectomy	140 (54.69%)	81	29	30		
Total thyroidectomy	116 (45.31%)	75	26	15		
Time of lung metastasis					0.059	0.806
Initial	39 (15.23%)	23	11	5		
Developed	217 (84.77%)	133	44	40		
Tg level ^b					99.860	< 0.0001
< 100	41 (16.02%)	30	2	9		
100–1000	141 (55.08%)	87	28	26		
> 1000	74 (28.90%)	39	25	10		
Metastatic site					14.088	0.0002
Lung and lung + lymph node	197 (76.95%)	126	50	21		
Lung + bone and lung + other organs ^c	59 (23.05%)	30	5	24		
CT results					4.749	0.029
Positive	229 (89.45%)	136	48	45		
Negative	27 (10.55%)	20	7	0		
Total	256	156	55	45		

Tg, thyroglobulin.

^aAge at discovery of lung metastases.

^bTg level following L-T₄ withdrawal (ng/ml).

^cBrain in one patient, parapharyngeal in eight patients, liver in one patient, kidney in two patients and soft tissue in two patients.

Clinical Study	H-J Song and others	Lung metastases and DTC	173:3	402
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Table 2 Multivariate analysis of response factors of ^{131}I therapy.

Factors	Changes in serum Tg			Imaging changes of lung metastases		
	Adjusted odds ratios	95% CI	P value	Adjusted odds ratios	95% CI	P value
Age (≥ 40 / < 40)	1.414	1.040–1.934	0.027	1.422	1.051–1.923	0.022
Gender (females/males)	0.742	0.446–1.233	0.248	1.483	0.890–2.470	0.130
Time of lung metastasis (initial/developed)				0.766	0.468–1.255	0.290
Tg level ^a	1.264	0.856–1.867	0.239	1.375	0.948–1.995	0.093
Site (lung combined with other organs ^b metastases/only lung)	2.562	1.443–4.549	0.001	1.575	0.890–2.785	0.118
Node size ^c	2.553	1.111–5.865	0.027	4.464	1.863–10.697	0.0008

^aTg level following L-T₄ withdrawal (ng/ml).^bBrain in one patient, parapharyngeal in eight patients, liver in one patient, kidney in two patients and soft tissue in two patients.^cNode size: for serum Tg group, CT was positive/negative; for anatomical imaging group, CT was nodule $> 1/\leq 1$ cm.

on chest CT; and undetectable serum Tg or ≤ 10 ng/ml in the hypothyroid status and in the absence of TgAb.

Statistical analysis

SPSS version 17.0 and SAS version 13.0 were used for statistical analyses. All data are expressed as mean $\pm$ s.d.,

proportions or absolute numbers. All the factors that may have affected serum Tg and anatomical imaging in the pulmonary metastases were analyzed by univariate analysis and confirmed by the χ^2 test. Binary logistic regression analysis was used to determine which factors contributed to the outcome of ^{131}I therapy response. Kaplan–Meier survival analysis was applied to evaluate

Table 3 Changes of anatomical imaging for 229 DTC patients with ^{131}I -avid lung metastases after ^{131}I therapy: univariate statistical analysis.

Factors	No. of patients	CR	PR	SD	PD	χ^2	P
Age ^a						6.109	0.013
0–19	14 (6.11%)	3	4	7	0		
20–39	99 (43.23%)	20	43	31	5		
40–59	76 (33.19%)	14	36	24	2		
≥ 60	40 (17.47%)	1	17	14	8		
Gender						5.058	0.024
Male	86 (37.55%)	14	49	20	3		
Female	143 (62.45%)	24	51	56	12		
Pathological type						0.993	0.802
Papillary	175 (76.42%)	30	76	59	10		
Follicular	54 (23.58%)	8	24	17	5		
Operation method						0.038	0.845
Lobectomy or subtotal thyroidectomy	132 (57.64%)	23	57	43	9		
Total thyroidectomy	97 (42.36%)	15	43	33	6		
Time of lung metastasis						13.100	0.0003
Initial	33 (14.41%)	15	11	5	2		
Developed	196 (85.59%)	23	89	71	13		
Tg level ^b						4.114	0.042
1–100	37 (16.16%)	11	13	9	4		
100–1000	121 (52.84%)	25	51	36	9		
> 1000	71 (31.00%)	2	36	31	2		
Metastatic site						8.044	0.004
Lung and lung + lymph node	175 (76.42%)	28	93	43	11		
Lung + bone and lung + other organs ^c	54 (23.58%)	10	7	33	4		
Node size (cm)						15.801	< 0.0001
≤ 1	212 (92.58%)	36	96	74	6		
> 1	17 (7.42%)	2	4	2	9		
Total	229	38	100	76	15		

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

^aAge at discovery of lung metastases.^bTg level following L-T₄ withdrawal (ng/ml).^cBrain in one patient, parapharyngeal in eight patients, liver in one patient, kidney in two patients and soft tissue in two patients.

Clinical Study	H-J Song and others	Lung metastases and DTC	173:3	403
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Table 4 Comparison by univariate statistical analysis between the groups of DTC patients with ^{131}I -avid and non- ^{131}I -avid lung metastases.

Factors	No. of patients	^{131}I -avid	Non- ^{131}I -avid	χ^2	P
Age ^a				43.639	<0.0001
0–19	19 (5.11%)	18	1		
20–39	129 (34.68%)	112	17		
40–59	141 (37.90%)	86	55		
≥ 60	83 (22.31%)	40	43		
Gender				0.420	0.516
Male	134 (36.02%)	95	39		
Female	238 (63.98%)	161	77		
Pathological type				1.927	0.165
Papillary	288 (77.42%)	193	95		
Follicular	84 (22.58%)	63	21		
Operation method				0.304	0.581
Lobectomy or subtotal thyroidectomy	207 (55.65%)	140	67		
Total thyroidectomy	165 (44.35%)	116	49		
Time of lung metastasis				9.724	0.002
Initial	43 (11.56%)	39	4		
Developed	329 (88.44%)	217	112		
Metastatic site				5.112	0.024
Lung and lung + lymph node	298 (80.11%)	197	101		
Lung + bone and lung + other organs ^b	74 (19.89%)	59	15		
Node size (cm)				11.501	0.0003
CT-negative	28 (7.53%)	27	1		
≤ 1	313 (84.14%)	212	101		
> 1	31 (8.33%)	17	14		
Total	372	256	116		

^aAge at discovery of lung metastases.

^bFor ^{131}I -avid group: brain in one patient, parapharyngeal in eight patients, liver in one patient, kidney in two patients and soft tissue in two patients; for non- ^{131}I -avid group: brain in two patient, parapharyngeal in two patients, liver in one patient, kidney in one patient and soft tissue in one patient.

the effect of different variables on survival and the differences between the groups were compared using the log-rank test. Multivariate analysis was performed to assess the relationship between survival time and several variables simultaneously. For analyses of this type, Cox proportional hazards model was used. A *P* value <0.05 was considered to indicate statistical significance.

Results

Characteristics of patients with pulmonary metastases

There were 372 enrolled patients with a predominance of females (male=134, female=238 and male:female

ratio=1:1.78). The ratio was lower than that observed in the general series of DTC patients, which means that pulmonary metastases are relatively more frequent in male patients. The mean age at diagnosis was 54.25 ± 16.08 years (range, 12–86 years) and the mean follow-up period was 59.48 ± 40.41 months. The initial pulmonary metastases were detected in 43 patients and the remaining 329 patients were diagnosed at follow-up (developed pulmonary metastases). Chest CT showed that pulmonary metastases were negative in 28 (28/372, 7.53%) patients, micronodular (≤1 cm) in 313 (313/372, 84.14%) patients and macronodular (>1 cm) in 31 (31/372, 8.33%) patients. ^{131}I -avid pulmonary metastases

Table 5 Multivariate analysis between the groups of DTC patients with ^{131}I -avid and non- ^{131}I -avid lung metastases.

Factors	Adjusted odds ratios	95% CI	P value
Age (≥40/<40)	2.494	1.865–3.350	<0.0001
Time of lung metastasis (initial/developed)	1.028	0.644–1.641	0.909
Site (lung combined with other organs metastases ^a /only lung)	2.203	1.260–3.850	0.005
Nodule size (>1/≤1 cm)	6.335	3.269–12.278	<0.0001

^aFor ^{131}I -avid group: brain in one patient, parapharyngeal in eight patients, liver in one patient, kidney in two patients and soft tissue in two patients; for non- ^{131}I -avid group: brain in two patient, parapharyngeal in two patients, liver in one patient, kidney in one patient and soft tissue in one patient.

Clinical Study	H-J Song and others	Lung metastases and DTC	173:3	404
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was observed in 256 (256/372, 68.82%) patients and non-¹³¹I-avid pulmonary metastases was found in 116 (116/372, 31.18%) patients. The median cumulative radioiodine dose was 18.315 GBq (495 mCi) with a range of 3.7–86.95 GBq (100–2350 mCi). A single dose was given to 37 patients, two doses to 61 patients and greater than or equal to three doses to the remaining 274 patients.

Changes in serum Tg level after ¹³¹I therapy

Changes in serum Tg in 256 DTC patients with ¹³¹I-avid pulmonary metastases after radioiodine therapy are shown in Table 1. ¹³¹I therapy was effective in 156 patients (BR, effective rate, 60.9%) and the average serum Tg varied from 683 (range, 17–6957) to 311 (range, 0–1407) ng/ml. Stabilization of Tg was seen in 55 patients (stable rate, 21.5%) after ¹³¹I therapy and the average serum Tg varied from 791 (range, 27–8027) to 692 (range, 15–8395) ng/ml. Treatment was ineffective in 45 patients (ineffective rate, 17.6%) and the average serum Tg increased from 847 (range, 19–15 955) to 1301 (range, 26–20 475) ng/ml.

Univariate analysis showed that changes in serum Tg were influenced by age, sex, the initial Tg level, combination with other distant metastases and

pulmonary node size (*P* values 0.0321, 0.0210, <0.0001, 0.0002 and 0.0293 respectively). Multivariate analyses revealed that age, combination with other distant metastases and pulmonary node size had a significant impacts on Tg changes (*P* values 0.0270, 0.0013 and 0.0272 respectively; shown in Table 2). Significantly decreased serum Tg (BR) and favorable efficacy were observed in patients who were aged <40 years, only had pulmonary metastases and 'fine miliaric' nodes (negative chest CT).

Changes in chest CT after ¹³¹I therapy

Of the 229 pulmonary metastases patients with positive chest CT findings, only 38 achieved CR (16.6%), 100 PR (43.7%), 76 SD (33.2%) and 15 had PD (6.5%). Univariate analyses of the factors influencing the changes of CT are shown in Table 3. Age, sex, time of lung metastases, initial Tg level, combination with other distant metastases and pulmonary node size were significantly associated with CT changes (*P* values 0.0134, 0.0245, 0.0003, 0.0425, 0.0046 and <0.0001 respectively). Multivariate analyses revealed that age <40 years and node size <1 cm had favorable effect on CT changes (*P* values 0.0223 and 0.0008; Table 2).

Table 6 Survival for patients with lung metastatic differentiated thyroid cancer.

Factor	No. of patients	5-year survival rate (%)	10-year survival rate (%)	15-year survival rate (%)	Univariate <i>P</i> value	Multivariate <i>P</i> value	Hazard ratio (95% CI)
Age (years)					<0.0001	0.00015	
<40	130 (50.78%)	90.7	79.5	66.9			1
≥40	126 (49.22%)	77.6	59.2	32.7			1.7 (1.2–2.6)
Gender					NS		
Males	95 (37.11%)	81.7	67.6	55.8			
Females	161 (62.89%)	85.3	72.2	62.9			
Pathological type					NS		
Papillary	193 (75.39%)	88.0	73.6	60.4			
Follicular	63 (24.61%)	80.5	69.2	58.8			
Time of lung metastasis					NS		
Initial	39 (15.23%)	86.9	73.3	64.8			
Developed	217 (84.77%)	89.5	75.4	62.3			
Metastatic site					<0.0001	<0.0001	
Lung and lung + lymph node	197 (76.95%)	90.0	73.6	60.9			1
Lung + bone and lung + other organs	59 (23.05%)	45.9	34.3	17.2			2.3 (1.7–3.6)
Node size (cm)					<0.0001	<0.0001	
Negative	27 (10.55%)	100.0	90.9	75.8			1
≤1	212 (82.81%)	88.5	68.9	50.1			1.9 (1.1–3.4)
>1	17 (6.64%)	59.2	30.6	0			3.5 (2.1–5.8)
¹³¹ I					<0.0001	<0.0001	
Yes	256 (68.82%)	87.0	69.2	56.2			1
No	116 (31.18)	69.7	38.1	20.9			2.1 (1.3–3.2)

CI from multivariate analysis; NS, not significant.

Patients who achieved complete cure

Sixty-two patients achieved complete cure after radioiodine therapy for pulmonary metastases. Mean age was 30 years old (range, 12–56 years). Fifty-eight patients had pulmonary metastases only and the remaining four patients had single bone metastases, which were treated with surgery and external radiotherapy. Serum Tg level measured after withdrawal of L -T₄ treatment were undetectable in 39 patients and <10 ng/ml in the remaining 23 patients. Complete cure occurred in 24 patients with a negative chest CT examination at discovery of pulmonary metastases, 36 with micronodular metastases and two with macronodular metastases. The mean cumulative dose of ^{131}I administered to the 62 patients was 11.248 GBq (304 mCi), six with <7.4 GBq (200 mCi), 40 with 7.4–14.8 GBq (200–400 mCi), 13 with 14.8–22.2 GBq (400–600 mCi) and only three with a cumulative activity >22.2 GBq (600 mCi). Three of these 62 patients have relapsed during follow-up period.

Patients with no ^{131}I uptake

A total of 116 patients had non-functioning pulmonary metastases. Fifteen of these patients had multiple organ involvement. The non-functioning lung metastases occurred late (found 6 months or more after thyroidectomy) in 112 patients. The proportion of patients older than 40 years was much higher (non- ^{131}I -avid vs ^{131}I -avid=84.5% vs 49.2%).

After univariate analysis between the patients with ^{131}I -avid and non- ^{131}I -avid pulmonary metastases (Table 4), the significant factors related to the ability of ^{131}I uptake were age, pathological type, time of discovery lung metastases, combination with other distant metastases and node size. After multivariate analysis (Table 5), only age, combination with other distant metastases and node size remained significant for ^{131}I uptake.

Survival rate and prognostic survival factors

The survival rate and prognostic survival factors are listed in Table 6. Survival rate in ^{131}I -avid patients was 87.0% at 5 years, 69.2% at 10 years and 56.2% at 15 years. In non- ^{131}I -avid patients, survival rate was 69.7% at 5 years, 38.1% at 10 years and 20.9% at 15 years (Fig. 1). For ^{131}I -avid patients, the univariate analysis showed that survival rate was affected by age, combination with other distant metastases and pulmonary node size (P value <0.0001 for all the factors). Prognostic variables were

strongly inter-related. After adjusting for other significant factors, Cox's regression analyses showed that the three variables remained significant for survival (P values 0.00015, <0.0001 and <0.0001 respectively).

The survival rate at 10 years was 79.5% in patients aged <40 years and 59.2% in patients older than 40 years (Fig. 2). For patients with only lung metastases, the survival rate at 10 years was 73.6%, which was significantly higher than patients with multiple organ metastases (for whom the 10-year survival rate was 34.3%; Fig. 3). The 10-year survival rate of 90.9% in patients with negative chest CT was higher than the 68.9% survival rate observed in patients with micronodular metastases ($\leq 1\text{cm}$) and the 30.6% observed in those with macronodular metastases (>1cm) (Fig. 4).

Discussion

We studied a large number of DTC patients with pulmonary metastases. We assessed the effect of radioiodine therapy and investigated the prognostic factors for survival for DTC patients with pulmonary metastases. A few studies have looked primarily at the clinical management and outcome of patients with DTC presenting with lung metastases (1, 2, 3, 4, 8, 11, 12, 14, 15). Our study differed from earlier investigations in three regards: i) we included a larger patient sample; ii) when evaluating the effect of radioiodine therapy, we explored only the patients with ^{131}I -avid pulmonary metastases and the factors that affected

Figure 1

Overall survival for patients with lung metastases by ^{131}I -avid and non- ^{131}I -avid.

Figure 2

Overall survival for patients with lung metastases by age at diagnosis.

^{131}I uptake were discussed for non- ^{131}I -avid lung metastases and iii) the parameters of Tg level and chest CT were selected as an evaluation index and discussed.

For patients with non- ^{131}I -avid (radioiodine-refractory) pulmonary disease, the benefit of radioiodine therapy was very limited. It was not appropriate for evaluation of the efficacy of ^{131}I therapy in these patients. Loss of radioiodine avidity is associated with a poor outcome. Several studies have reported that DTC patients with ^{131}I -avidity have longer survival rates than those with non- ^{131}I -avid pulmonary metastasis (15, 16, 17, 18). In agreement with the previous studies, our patients with non- ^{131}I -avid disease had a 10-year OS rate of 38.1% compared to 69.2% for ^{131}I -avid metastases ($P < 0.0001$). We further investigated the factors related to ^{131}I uptake. After univariate and multivariate analyses, age > 40 years ($P < 0.0001$), combination with other distant metastases ($P = 0.0056$) and macronodular lesions ($P < 0.0001$) were independently significant predictors for non- ^{131}I -avid pulmonary metastases.

Numerous studies have been performed on the diagnostic value of serum Tg measurement and have found that it is a highly sensitive means of detecting metastases (19). Moreover, Tg level was an independent prognostic indicator for disease-free remission and death (20, 21). It was thought that the serum Tg level under TSH elevation ($> 30 \text{ mU/l}$) was the most reliable indicator for persistent or recurrent disease. Therefore, the change in

serum Tg levels (after the withdrawal of L-T4 over the course of 3–4 weeks) was considered to be a prognostic indicator to assess the efficacy of ^{131}I therapy for pulmonary metastases. We found a significant decrease in serum Tg (BR) in 156 patients (60.9% effective rate). Multivariate analyses revealed that age ≤ 40 years, only lung metastases and 'fine miliatic' nodes (negative chest CT) were the favorable factors. These corresponded well with the favorable prognostic factors of OS and suggested that decreased serum Tg indicates the effectiveness of radioiodine therapy. However, serum Tg was only reliable if TgAb was undetectable, otherwise serum Tg level could have been falsely lowered (21). Thus, patients with positive antibodies were excluded from the study. The size of pulmonary metastases was usually $< 1 \text{ cm}$, which was below the spatial resolution of chest X-ray. Chest CT could enhance the diagnostic accuracy in most patients with normal chest X-ray and had an additive effect to ^{131}I -WBS and Tg level (11). According to nodule size on chest CT, pulmonary metastases were divided into three categories: i) normal ($n = 27$); ii) micronodular ($\leq 1 \text{ cm}$, $n = 212$) and iii) macronodular ($> 1 \text{ cm}$, $n = 17$). The significance of this classification was that it was related to radioiodine efficacy. Micronodular pattern of lung metastases was invariably related to good ^{131}I uptake, while macronodular metastases frequently showed poor ^{131}I uptake (14). In our study, multivariate analyses revealed that patients with node size $< 1 \text{ cm}$ had a favorable

Figure 3

Overall survival for patients with lung metastases by sites of metastasis.

Figure 4

Overall survival for patients with lung metastases by pulmonary node size.

response on changes in CT imaging ($P=0.0008$, $OR=4.464$, 95% CI, 1.863–10.697). Complete remission following ^{131}I therapy always occurred in patients with micronodular metastases, especially for ‘fine miliaric’ nodes. The 10-year survival rate was significantly higher in category 1 (90.9%) patients, lower in category 2 (68.9%) and only 30.6% in category 3 patients.

In our cohort, for patients with ^{131}I -avid pulmonary metastases, the 5-, 10- and 15-year OS rates were 87.0, 69.2 and 56.2% respectively. This corresponded with the result of those reported in the previous studies (8, 15, 22, 23, 24). Cox’s regression analysis showed that the three variables, including age, combination with other distant metastases and pulmonary node size, were significant predictor for survival (P values 0.00015, <0.0001 and <0.0001 respectively). Age is known to be an independent prognostic factor for mortality in DTC (14, 25, 26), and the mortality risk increases with age. In our series, survival rate at 10 years was 79.5% in the patients younger than 40 years of age, while it was only 59.2% in the patients older than 40 years. Although pulmonary metastases with ^{131}I uptake may be stable for several years or decades, all metastases should be treated at an early stage. Favorable responses have been observed in patients with small metastases. Previously, Casara *et al.* (14) showed that micronodular metastasis susceptible to ^{131}I therapy had a good prognosis, whereas macronodular metastasis of non- ^{131}I -avid lesions had a poor prognosis. As in our study, patients with normal chest CT can achieve a CR with radioiodine alone

for long periods of time. Macronodular metastases frequently show poor ^{131}I uptake (14/31, 45.2%) and poor survival rate (10-year, OS=30.6%).

Limitations

First, our study was retrospective. During the long study period, a few clinical data were missing, which might have caused bias in the data selection. Second, in the diagnosis of lung metastasis in non- ^{131}I -avid patients, the histopathological confirmation was not always possible, particularly in patients with small (‘fine miliaric’ or micronodular) lesions. Therefore, they were clinically diagnosed based on their CT images and elevated Tg levels. However, we cannot completely rule out the possibility of other conditions, such as incidental primary lung cancers or benign lung diseases such as inflammation.

Summary

In conclusion, our study indicated that most ^{131}I -avid pulmonary metastases from DTC can obtain partial or complete remission after ^{131}I therapy. Younger patients (<40 years old) with only pulmonary metastases and small (‘fine miliaric’ or micronodular) metastases appear to have relative favorable outcomes. In contrast, patients with non- ^{131}I -avid pulmonary metastases who do not respond to radioiodine treatment have a worse prognosis, and ^{131}I treatment should be abandoned and other treatment modalities used when tumour progression has been documented.

Declaration of interest

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

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Author contribution statement

H-J Song, Z-L Qiu and Q-Y Luo conceived and designed the paper. H-J Song, C-T Shen and W-J Wei collected the data. H-J Song and Z-L Qiu analyzed the data. H-J Song wrote the paper.

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