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The efficacy of radioactive iodine for the treatment of well-differentiated thyroid cancer with distant metastasis

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Objective **Radioactive iodine (^{131}I) has been used as a treatment for high-risk well-differentiated thyroid cancer after thyroidectomy. The aim of this study was to evaluate the long-term follow-up results after using high accumulated doses of ^{131}I (>600 mCi) for the treatment of well-differentiated thyroid cancer.**

Patients and methods **In this study, we retrospectively evaluated prospectively enrolled patients with well-differentiated thyroid cancer who were treated and followed up in Chang Gung Memorial Hospital in Linkou and Keelung, Taiwan. All the patients underwent thyroidectomy between 1979 and 2016.**

Results **For our study, 228 patients with papillary and follicular thyroid carcinoma with distant metastases were enrolled. Of the 228 patients, 71 (31.1%) received ^{131}I therapy with an accumulated dose of at least 600 mCi. Forty-four died because of disease-specific mortality (DSM) after a mean follow-up of 10.6 ± 6.3 years. Compared with the patients in the DSM group, which included 27 survival cases, patients who were younger, and those with a multifocal tumor, more extensive thyroidectomy, and papillary thyroid carcinoma showed better prognosis. The DSM group included a higher percentage of patients who developed a secondary primary cancer after receiving a diagnosis of thyroid cancer than the survival group (18.2 vs. 3.7%). However, the difference did not reach statistical significance ($P = 0.075$).**

Conclusion **^{131}I provided an effective therapeutic modality for well-differentiated thyroid cancer patients with distant metastasis. After a mean of follow-up 10 years, more than 60% of cases resulted in DSM when high accumulated ^{131}I doses were administered. *Nucl Med Commun* 39:1091–1096 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Keywords: cancer-specific mortality, radioactive iodine, thyroglobulin, total thyroidectomy

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Introduction

Radioactive iodine (^{131}I) has been used as an adjuvant treatment for high-risk, well-differentiated thyroid cancer after thyroidectomy for residual or recurrent thyroid cancer [1,2]. Decreasing the use of ^{131}I for the treatment of low-risk thyroid cancer may be necessary owing to the controversial effects of this treatment on well-differentiated thyroid cancer [3,4]. Until now, we lacked sufficient information on the long-term follow-up results of high accumulated ^{131}I doses (>600 mCi) in patients with well-differentiated thyroid cancer.

Most patients with well-differentiated thyroid cancer have good prognoses following appropriate treatment. A 90% remission rate can be achieved after receiving treatments that include thyroidectomies and postoperative ^{131}I therapies [5]; however, recurrence occurs in 15–20% of patients with well-differentiated thyroid cancer during the follow-up period [6,7]. The occurrence of distant metastases is a sign of a poor prognosis for most cases [8]. The aim of this study was to perform a long-term follow-up investigation of patients with well-differentiated thyroid cancer who were treated with ^{131}I ablation and to determine the treatments and prognostic factors that are associated with disease-specific mortality (DSM).

Patients and methods

Study participants

The study was a retrospective analysis of prospectively enrolled patients with well-differentiated thyroid cancer who were treated and followed up in the Chang Gung Memorial Hospital, in Linkou, Taiwan. All patients were treated with thyroidectomy between 1979 and 2016. In our center, most patients with well-differentiated thyroid cancer with tumor sizes of at least 1 cm were treated with total thyroidectomy. After thyroidectomy, tumors were staged on the basis of the Union for International Cancer Control tumor-node-metastasis criteria (6th ed.) [9]. The pathological classification of all thyroid carcinoma tissues was performed according to the WHO criteria [10].

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Postoperative thyroid remnant ablation was recommended for patients with high-risk papillary and follicular thyroid cancers, 4–6 weeks after surgery, and the ^{131}I ablation dose for most patients was 1.1–3.7 GBq (30–100 mCi). A whole-body scan (WBS) was performed 1 week after ^{131}I administration using a dual-head gamma camera (Dual Genesys; ADAC, Milpitas, California, USA) equipped with a high-energy collimator as described previously [11]. The L-T_4 treatment was then initiated to decrease thyroid stimulating hormone levels without inducing clinical thyrotoxicosis. Patients in whom the ^{131}I uptake foci extended beyond the thyroid bed were diagnosed with persistent disease with distant metastases. Patients with lung or bone metastasis were administered increased therapeutic ^{131}I doses at 5.6–7.4 GBq (100–200 mCi), and hospital isolation was arranged at doses that exceeded 1.1 GBq. A WBS was performed1 week after the administration of the higher therapeutic ^{131}I dose.

Recurrent disease included locoregional or distant metastases and was diagnosed using diagnostic or therapeutic ^{131}I scans or other imaging techniques such as ultrasonography, computed tomography (CT), MRI, and PET-CT (metastases may or may not have been cytologically proven). Recurrent tumors were not included if they were diagnosed postoperatively, with diagnostic or therapeutic ^{131}I scans, or if they were nonresectable. In contrast, persistent disease was diagnosed postoperatively, through diagnostic or therapeutic ^{131}I scans and/or other imaging studies, and these analyses included patients with nonresectable thyroid cancer. For the analysis of the therapeutic outcomes, all data on therapeutic outcomes were censored at the end of 2014. Patients were classified into the DSM, nonremission, and remission groups. The DSM group comprised patients who died of thyroid cancer and the remission group comprised patients with negative ^{131}I WBS results and no evidence of local or distant metastasis upon noninvasive examination.

Serum thyroglobulin (Tg) levels were measured using an immunoradiometric assay (CIS Bio International, Paris, France), and the detection limit of the Tg kit was 0.5 ng/ml. The functional sensitivity of this assay was assessed in our laboratory and was found to be 1.2 ng/ml. Tg antibody levels were measured using a competitive radioimmunoassay (Biocode, Liège, Belgium). The analytical sensitivity of this assay was 6 IU/ml.

Unpaired *t*-tests were used to compare continuous data between groups. Categorical data were compared using χ^2 or Fisher's exact tests for small data sets. We calculated the DSM rates for patients who died from thyroid cancer. The follow-up period was defined as the time from the date following surgery and the first ^{131}I ablation to the date of DSM. Survival rates were calculated using the Kaplan–Meier method and compared using log-rank tests [12]. A multivariable Cox proportional hazard regression model was used to estimate the mortality risk. All statistical analyses were carried out using SPSS, version 17.0 statistical software (SPSS Inc., Chicago, Illinois, USA). A P value less than 0.05 was defined as statistically significant in all tests. The Chang Gung Medical Foundation Institutional Review Board (104-3901B) approved this study. The requirement for informed consent was waived because of the retrospective nature of this study.

Results

A total of 228 patients with papillary and follicular thyroid carcinomas with distant metastases were enrolled into our study (Table 1). The 228 patients included 151 patients with papillary thyroid carcinoma and 77 patients with follicular thyroid carcinoma. The mean age of these patients was 54.1 ± 14.9 years, and 155 (68.0%) of the patients were women. Among the 228 patients, 122 were diagnosed with persisted disease with distant metastases at the time of thyroidectomy and ^{131}I remnant ablation. The other 106 patients with distant metastases were diagnosed 6 months after thyroidectomy during the follow-up period.

Seventy-one (31.1%) of the 228 patients received ^{131}I therapy, with an accumulated dose of at least 600 mCi.

Table 1 Clinical features of recurrent papillary or follicular thyroid cancer with distant metastasis

Clinical characteristics	Patients [*n* (%)]
All patients (*N*)	228
Sex (female)	155 (68.0)
Age at diagnosis [mean ± SD (range) (median)] (years)	54.1 ± 14.9 (11–85) (55)
Tumor size [mean ± SD (range) (median)] (cm)	4.0 ± 2.9 (0.2–20.0) (3.5)
Preablation Tg [mean ± SD (range) (median)] (ng/ml)	3207.8 ± 12 436.0 (0.0–141 970.0) (95.5)
Multifocality	51 (22.4)
Extent of thyroidectomy	
Total	174 (76.3)
Less than total	54 (23.7)
Histology	
Papillary	151 (66.2)
Follicular	77 (23.7)
Clinical stage	
Stage I	30 (13.2)
Stage II	28 (12.3)
Stage III	48 (21.1)
Stage IV	122 (53.5)
TNM stage	
Stage I	35 (15.4)
Stage II	37 (16.2)
Stage III	23 (10.1)
Stage IV	133 (58.3)
Site of metastasis	
Lung	88 (38.6)
Others	43 (18.9)
Multiple	97 (42.5)
Postoperative ^{131}I accumulative dose (mCi)	
< 100	16 (7.0)
≤ 100 and <600	141 (61.8)
≥ 600	71 (31.1)
Follow-up period [mean ± SD (range) (median)] (years)	8.3 ± 7.0 (0.3–35.9) (5.9)
Overall mortality	144 (63.2)
Disease-specific mortality	135 (59.2)
Disease free	4 (1.8)
Secondary cancer after thyroid cancer	14 (6.1)

Tg, serum thyroglobulin; TNM, tumor-node-metastasis.

Among the 228 patients, 88 (38.6%) had lung metastases only and 97 (42.5%) had multiple organs metastases. After a mean follow-up duration of 8.3 ± 7.0 years, 135 (59.2%) patients experienced DSM. Only four (1.8%) patients were diagnosed as being disease free at the end of the follow-up period. In addition, 14 (6.1%) patients developed secondary primary cancer after the thyroid cancer operation. These included three lung, one nasopharyngeal, one gastric, one colon, one bone sarcoma, one giant cell tumor, one malignant fibrous histosarcoma, one brain anaplastic astrocytoma, one ovarian, one prostate, one renal transitional, and one pituitary anaplastic cancer.

Of the 71 patients who underwent ^{131}I treatments with at least 600 mCi ^{131}I, 44 experienced DSM after a mean follow-up interval of 10.6 ± 6.3 years (Table 2). Compared with the DSM group, with 27 surviving patients, younger patients, and patients with multifocal tumor, more extensive thyroidectomy, and papillary thyroid carcinoma presented better prognoses in the univariate statistical analysis. Only one of the 71 patients was treated until remission. The DSM group showed a higher percentage of secondary primary cancer after thyroid cancer diagnosis compared with the survival group (18.2 vs. 3.7%); however, this difference was not statistically significant ($P = 0.075$). In addition, the multivariate analysis with a Cox proportional hazards regression model showed that patient age differed significantly between the survival and mortality groups (Table 3).

Of the 71 patients, 45 were diagnosed with papillary thyroid carcinomas (Table 4). On comparing the clinical features between patients with papillary and follicular thyroid carcinomas, among the patients with follicular thyroid carcinoma cohort, there was a higher number of women, and patients with larger tumor sizes, less lymph

Table 2 Clinical features of recurrent and distant metastatic papillary or follicular thyroid cancers that were treated with postoperative ^{131}I accumulative dose of at least 600 mCi in terms of the disease-specific mortality or survival

Clinical characteristics	Total number of patients	DSM	Survival[a]	*P* value
Patient number (*N*)	71	44	27	
Sex (female) [*n* (%)]	46 (64.8)	28 (63.6)	18 (66.7)	0.795
Age at diagnosis (mean ± SD) (years)	51.3 ± 12.5	53.9 ± 10.9	47.1 ± 13.7	0.025
Mean tumor size (mean ± SD) (cm)	4.0 ± 3.0	4.6 ± 3.6	3.1 ± 1.6	0.061
Preablation Tg (mean ± SD) (ng/ml)	2542.4 ± 6524.5	2635.8 ± 6909.6	2388.0 ± 5828.7	0.881
Multifocality [*n* (%)]	17 (23.9)	6 (13.6)	11 (40.7)	0.009
Extent of thyroidectomy [*n* (%)]				
Total	57 (80.3)	32 (72.7)	25 (92.6)	0.041
Less than total	14 (19.7)	12 (27.3)	2 (7.4)	
Histology [*n* (%)]				
Papillary	45 (63.4)	23 (52.3)	22 (81.5)	0.013
Follicular	26 (36.6)	21 (47.7)	5 (18.5)	
Clinical stage [*n* (%)]				
Stage I	7 (9.9)	2 (4.5)	5 (18.5)	0.281
Stage II	7 (9.9)	5 (11.4)	2 (7.4)	
Stage III	18 (25.4)	12 (27.3)	6 (22.2)	
Stage IV	39 (54.9)	25 (56.8)	14 (51.9)	
TNM stage [*n* (%)]				
Stage I	12 (16.9)	4 (9.1)	8 (29.6)	0.032
Stage II	14 (16.9)	7 (15.9)	7 (25.9)	
Stage III	4 (5.6)	4 (9.1)	–	
Stage IV	41 (57.7)	29 (65.9)	12 (44.4)	
Site of metastasis [*n* (%)]				
Lung	21 (29.6)	10 (22.7)	11 (40.7)	0.106
Others or multiple	50 (70.4)	34 (77.3)	16 (59.3)	
Follow-up period (mean ± SD) (years)	11.6 ± 6.5	10.6 ± 6.3	13.2 ± 6.5	0.104
Postoperative ^{131}I accumulative dose (mean ± SD) (mCi)	1013.2 ± 426.2	990.1 ± 378.4	1050.9 ± 492.0	0.566
Disease free [*n* (%)]	1 (1.4)	–	1 (3.7)	0.199
Secondary cancer after thyroid cancer [*n* (%)]	9 (12.7)	8 (18.2)	1 (3.7)	0.075

DSM, disease-specific mortality; TCA, thyroid carcinoma; Tg, serum thyroglobulin; TNM, tumor-node-metastasis.
[a]Include one case in which the cause of death was not TCA.

Table 3 Multivariate analysis by Cox proportional hazards regression model for survival and mortality

				95% Confidence interval	
	β Coefficient	*P* value	Hazard ratio	Lower bound	Upper bound
Age at diagnosis	0.048	0.0191	1.049	1.008	1.092
Histology (papillary/follicular TCA)	0.057	0.8689	1.058	0.540	2.072
Thyroid operative method (less total/total thyroidectomy)	0.069	0.8518	1.072	0.518	2.215
Multifocality (no/yes)	0.447	0.3649	1.563	0.595	4.108
TNM stage (SI/SII/SIII/SIV)	0.043	0.8321	1.044	0.699	1.560

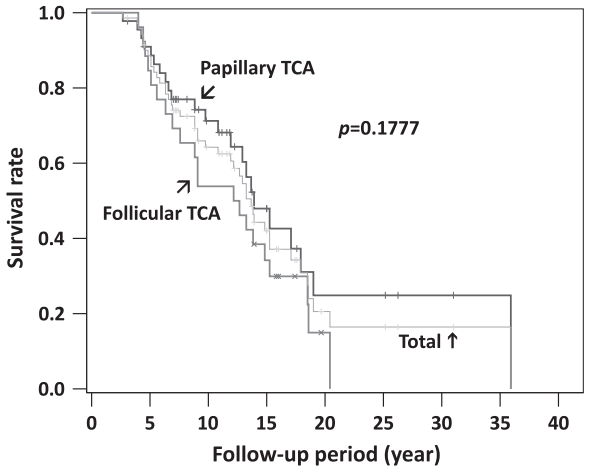
TCA, thyroid carcinoma; TNM, tumor-node-metastasis.

Table 4 Clinical features of patients with recurrent and distant metastatic papillary or follicular thyroid cancers who were treated with postoperative ^{131}I accumulative dose ≥ 600 mCi

Clinical characteristics	Total patients	Papillary	Follicular	*P* value
Patient number (*N*)	71	45	26	
Sex [*n* (%)] (female)	46 (12.7)	25 (55.6)	21 (80.8)	0.032
Age at diagnosis (mean ± SD) (year)	51.3 ± 12.5	49.6 ± 13.5	54.3 ± 9.8	0.136
Tumor size (mean ± SD) (cm)	4.0 ± 3.0	3.4 ± 2.1	5.4 ± 4.3	0.027
Preablation Tg (mean ± SD) (ng/ml)	2542.4 ± 6524.5	2876.3 ± 7160.7	1954.7 ± 5167.6	0.579
Multifocality [*n* (%)]	17 (23.9)	16 (35.6)	1 (3.8)	0.003
Extent of thyroidectomy [*n* (%)]				
Total	57 (80.3)	39 (86.7)	18 (69.2)	0.075
Less than total	14 (19.7)	6 (13.3)	8 (30.8)	
Clinical features of the 1st operation [*n* (%)]				
Lymph node metastasis	7 (9.9)	7 (15.6)	–	0.034
Soft tissue invasion	18 (25.4)	12 (26.7)	6 (23.1)	0.738
Distant metastasis	39 (54.9)	22 (48.9)	17 (65.4)	0.178
TNM stage [*n* (%)]				
Stage I	12 (16.9)	10 (22.2)	2 (7.7)	0.061
Stage II	14 (16.9)	10 (22.2)	4 (15.4)	
Stage III	4 (5.6)	4 (8.9)	–	
Stage IV	41 (57.7)	21 (46.7)	20 (76.9)	
Site of metastasis [*n* (%)]				
Lung	21 (29.6)	17 (37.8)	4 (15.4)	0.046
Others or multiple	50 (70.4)	28 (62.2)	22 (84.6)	
Follow-up period (mean ± SD) (years)	11.6 ± 6.5	11.7 ± 7.1	11.5 ± 5.3	0.907
Postoperative ^{131}I accumulative dose (mean ± SD) (mCi)	1013.2 ± 426.2	1026.0 ± 452.9	991.1 ± 374.6	0.744
Overall mortality [*n* (%)]	45 (63.4)	24 (53.3)	21 (80.8)	0.021
Disease-specific mortality [*n* (%)]	44 (62.0)	23 (51.1)	21 (80.8)	0.013
Disease free [*n* (%)]	1 (1.4)	1 (2.2)	–	0.444
Secondary cancer after thyroid cancer [*n* (%)]	9 (12.7)	7 (15.6)	2 (7.7)	0.337

Tg, serum thyroglobulin; TNM, tumor-node-metastasis.

Fig. 1



Disease-specific survival rates for the patients in the three groups: papillary thyroid carcinoma, follicular thyroid carcinoma, and total patients. TCA, thyroid carcinoma.

node metastases, less lung metastases, and higher DSMs and total mortality than the papillary thyroid carcinoma cohort.

Figure 1 shows the disease-specific survival rates of the patients in the three groups: papillary thyroid carcinoma, follicular thyroid carcinoma, and total patients. The disease-specific survival rates, which were compared using the Kaplan–Meier method with log-rank tests, of the total patient, papillary thyroid carcinoma, and follicular thyroid carcinoma groups were 86.3, 88.6, and 80.8% at 5 years; 64.2, 68.1, and 53.8% at 10 years; and 16.4, 24.9, and 0% at 20 years, respectively. The DSM was not significantly different between the papillary and the follicular thyroid carcinoma groups ($P = 0.1777$) (Fig. 1).

Discussion

Distant metastasis of well-differentiated thyroid cancer is not unusual during treatment, which may be diagnosed on the presentation of thyroid cancer or during follow-up [13–15]. Unlike other malignancies, ^{131}I is the first choice for papillary and follicular thyroid carcinomas with distant metastases, unless they lose the ability to trap iodine [16]. Our study showed that ^{131}I therapy was effective for controlling distant metastases of patients with well-differentiated thyroid cancer over a long-term follow-up period of 10 years. However, in our study, the remission rate was low. During treatment, the balance between the ^{131}I effective dose and possible side effects from the accumulated ^{131}I dose needs to be considered.

A recent Asian survey showed that different ^{131}I dose ranges were used in patients with low-risk thyroid cancer, which was probably because the enrolled physicians considered ^{131}I dose elevation on the basis of clinicosocial factors that were beyond the pre-existing guidelines [17]. Postoperative high serum Tg level, inadequate information on lymph node involvement, and histopathology reporting were the major factors for elevated ^{131}I dose. There remains no consensus on the dose and timing of

^{131}I for patients with thyroid cancer after thyroidectomy [17–20]. In contrast, low-dose ^{131}I ablation was not found to produce significantly different responses or long-term outcomes in patients with small papillary thyroid carcinomas who had microscopic extrathyroid extensions and cervical lymph node metastases [19]. In contrast to the observations in the low-risk group, low-dose ^{131}I therapy after thyroidectomy appears to be insufficient for Korean patients with intermediate-risk, well-differentiated thyroid carcinoma [21]. For patients with distant metastases, the use of high ^{131}I therapy doses allowed a more consistent conclusion to be drawn [7,22]. Dosimetry that was calculated using images taken 2, 3, and 7 days after radioiodine seems to be more appropriate for patients with thyroid cancer, especially for pediatric patients with distant metastases [23,24]. In our study, a high ^{131}I dose was used for patients with distant metastases immediately following thyroidectomy. The ^{131}I dose timing did not seem to interfere with disease outcomes of patients with well-differentiated thyroid cancer [25].

In our study group, follicular thyroid carcinoma had higher DSM rates than papillary thyroid carcinoma, although Kaplan–Meier survival curves showed no statistically significant difference between the two groups. Compared with papillary thyroid carcinoma, follicular thyroid carcinoma may be diagnosed and treated later, which is in accordance to the larger observed tumor sizes [26,27]. More advanced distant follicular thyroid carcinoma metastases were found in our study. This is because, unlike papillary thyroid carcinoma, it is difficult to diagnose follicular thyroid carcinoma with preoperative fine-needle aspiration cytology [28].

During the long-term follow-up of patients with well-differentiated thyroid cancer, a secondary primary cancer diagnosis other than thyroid was not unusual [29,30]. In clinical practice, the differential diagnosis between distant metastasis and secondary primary cancer is important for further treatment. In our study, 6.1% of patients with papillary and follicular thyroid cancer with distant metastases developed secondary primary cancer during the follow-up period. In our previous study, patients with well-differentiated thyroid carcinoma and metachronous secondary primary cancer had worse prognoses than patients without secondary primary cancer [31]. In this study, the DSM of patients with secondary primary cancer was not affected by treatments with ^{131}I doses over 600 mCi.

Conclusion

Patients with well-differentiated thyroid cancer with distant metastases have poor prognoses after long-term follow-up. ^{131}I is an effective therapeutic modality for patients with well-differentiated thyroid cancer with distant metastases. After further follow-up, over a mean period of 10 years, more than 60% of patients experienced DSMs when high accumulated ^{131}I doses were administered.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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