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

Jen-Der Lin, Sheng-Fong Kuo, Bie-Yui Huang, Shu-Fu Lin and Szu-Tah Chen

Objective Radioactive iodine (¹³¹I) 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 ¹³¹I (>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 ¹³¹I 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 ¹³¹I 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 ¹³¹I doses were administered. Nucl Med Commun 39:1091–1096 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

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

Introduction Radioactive iodine (¹³¹I) 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 ¹³¹I 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 ¹³¹I 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 ¹³¹I 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 ¹³¹I 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].
Postoperative thyroid remnant ablation was recommended for patients with high-risk papillary and follicular thyroid cancers, 4–6 weeks after surgery, and the 131I ablation dose for most patients was 1.1–3.7 GBq (30–100 mCi). A whole-body scan (WBS) was performed 1 week after 131I 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-T4 treatment was then initiated to decrease thyroid stimulating hormone levels without inducing clinical thyrotoxicosis. Patients in whom the 131I 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 131I 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 performed 1 week after the administration of the higher therapeutic 131I dose.

Recurrent disease included locoregional or distant metastases and was diagnosed using diagnostic or therapeutic 131I 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 131I scans, or if they were nonresectable. In contrast, persistent disease was diagnosed postoperatively, through diagnostic or therapeutic 131I 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 with distant metastases. Patients with lung or bone metastases were diagnosed using diagnostic or therapeutic 131I scans, or if they were nonresectable. In contrast, persistent disease was diagnosed postoperatively, through diagnostic or therapeutic 131I 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 131I 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 χ2 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 131I 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 persistent disease with distant metastases at the time of thyroidectomy and 131I 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 131I therapy, with an accumulated dose of at least 600 mCi.

| 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] | 32078 ± 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 (33.8)       |
| Clinical stage           |                 |
| Stage I                  | 30 (13.2)       |
| Stage II                 | 28 (12.3)       |
| Stage III                | 48 (21.1)       |
| Stage IV                 | 122 (54.5)      |
| 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 131I accumulative dose (mCi) < 100 | 16 (70) |
| ≤ 100 and <600           | 141 (61.8)      |
| ≥ 600                    | 71 (31.1)       |
| Follow-up period [mean ± SD (range)] (median) [years] | 8.3 ± 7.0 (3.0–35.8) (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 131I treatments with at least 600 mCi 131I, 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

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

| Clinical characteristics | Total number of patients | DSM | Survival | 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±3.8     | 3.1±1.6    | 0.051 |
| Preablation Tg (mean±SD) (ng/ml) | 2542.4±6524.5 | 2635.8±6909.6 | 2388.0±5828.7 | 0.881 |
| Multilocality [n (%)]    | 17 (23.9)                | 6 (13.6) | 11 (40.7) | 0.009 |
| Extent of thyroidectomy [n (%)] | 57 (80.3)          | 32 (72.7) | 25 (92.6) | 0.041 |
| Total                    | 14 (19.7)                | 12 (27.3) | 2 (7.4)    |         |
| Papillary                | 45 (63.4)                | 23 (52.3) | 2 (8.1)    | 0.013 |
| Follicular               | 26 (36.6)                | 21 (47.7) | 5 (18.5)   |         |
| Clinical stage [n (%)]   | 75 (100)                 | 39 (88.4) | 36 (11.6)  |         |
| Stage I                  | 7 (9.9)                  | 4 (8.8)   | 3 (8.3)    | 0.281 |
| Stage II                 | 7 (9.9)                  | 5 (10.6)  | 2 (5.3)    |         |
| Stage III                | 18 (24.5)                | 12 (25.5) | 6 (16.2)   |         |
| Stage IV                 | 39 (54.9)                | 25 (50.0) | 14 (38.1)  |         |
| TNM stage [n (%)]        | 75 (100)                 | 40 (80.0) | 35 (70.0)  |         |
| Stage I                  | 12 (16.0)                | 4 (8.0)   | 8 (16.0)   | 0.032 |
| Stage II                 | 14 (19.2)                | 7 (14.0)  | 7 (14.0)   |         |
| Stage III                | 4 (5.4)                  | 4 (8.0)   | –         |         |
| Stage IV                 | 41 (54.7)                | 29 (58.0) | 12 (24.5)  |         |
| Site of metastasis [n (%)] | 75 (100)              | 40 (80.0) | 35 (70.0)  |         |
| Lung                     | 21 (28.0)                | 10 (20.0) | 11 (22.0)  | 0.196 |
| Others or multiple       | 50 (70.0)                | 34 (68.0) | 16 (32.0)  |         |
| Follow-up period (mean±SD) (years) | 11.6±6.5            | 10.6±6.3   | 13.2±6.5   | 0.104 |
| Postoperative 131I 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.

*Include one case in which the cause of death was not TCA.

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

| β Coefficient | P value | Hazard ratio | 95% Confidence interval |
|---------------|---------|--------------|-------------------------|
| Age at diagnosis | 0.048   | 0.0191 1.049 | 1.008 1.092 |
| Histology (papillary/follicular TCA) | 0.057   | 0.869 1.058 | 0.540 2.072 |
| Thyroid operative method (less total/total thyroidectomy) | 0.069   | 0.851 1.072 | 0.518 2.215 |
| Multilocality (no/yes) | 0.447   | 0.364 1.563 | 0.595 4.108 |
| TNM stage (SI/SII/SIII/SIV) | 0.043   | 0.832 1.044 | 0.699 1.560 |

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

| Clinical features of patients with recurrent and distant metastatic papillary or follicular thyroid cancers who were treated with postoperative $^{131}$I accumulative dose $\geq 600$ mCi |
|---------------------------------------------------------------|
| Total patients Papillary Follicular | $P$ value |
| Patient number ($N$) | 71 | 45 | 26 | 0.032 |
| Sex ($n$ [%]) (female) | 46 (12.7) | 25 (55.6) | 21 (80.8) | 0.136 |
| Age at diagnosis (mean±SD) (year) | 51.3±12.5 | 49.6±13.5 | 54.3±9.8 | 0.027 |
| Tumor size (mean±SD) (cm) | 4.0±3.0 | 3.4±2.1 | 5.4±4.3 | 0.003 |
| 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 | 9 (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 (84.8) | 0.007 |
| Follow-up period (mean±SD) (years) | 11.6±8.5 | 11.7±7.1 | 11.5±5.3 | 0.744 |
| Postoperative $^{131}$I accumulative dose (mean±SD) (mCi) | 1013.2±452.9 | 1025.0±452.9 | 991.1±374.6 | 0.021 |
| Overall mortality ($n$ [%]) | 45 (63.4) | 24 (53.3) | 21 (80.8) | |
| 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.
Conclusions

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 DSNM when high accumulated $^{131}$I doses were administered.

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