

NOTE

Prognosis and prognostic factors of differentiated thyroid carcinoma after the appearance of metastasis refractory to radioactive iodine therapy

Yasuhiro Ito^{1), 2)}, Akira Miyauchi¹⁾, Mitsuru Ito³⁾, Tomonori Yabuta¹⁾, Hiroo Masuoka¹⁾, Takuya Higashiyama¹⁾, Mitsuhiro Fukushima¹⁾, Kaoru Kobayashi¹⁾, Minoru Kihara¹⁾ and Akihiro Miya¹⁾

¹⁾Department of Surgery, Kuma Hospital, Kobe 650-0011, Japan

²⁾Clinical Trial Management Center, Kuma Hospital, Kobe 650-0011, Japan

³⁾Department of Internal Medicine, Kuma Hospital, Kobe 650-0011, Japan

Abstract. Differentiated thyroid carcinomas (DTCs) are generally indolent, but few therapeutic strategies are available after a metastatic recurrence that is refractory to radioactive iodine (RAI) therapy. Molecular-target therapy has shown promising results for DTCs with RAI-refractory recurrence. However, not all RAI-refractory recurrences are progressive, and even those that are progressive may not be immediately life-threatening. Here we investigated the prognosis and prognostic factors of 74 DTC patients (52 females, 22 males) in whom RAI-refractory metastases appeared. The five-year and 10-year cause-specific survival (CSS) rates of the 74 patients (8–82 yrs of age; median age at the detection of metastases, 61 yrs) were 95% and 70%, respectively, and the older patients (≥ 60 yrs, $n=38$) and male patients were significantly more likely to die of carcinoma. Also in multivariate analysis, older age (≥ 60 years) and male gender were independent predictors of carcinoma-related death. Taken together, our data indicate that RAI-refractory metastases of older patients and male patients are more progressive than those of other patients. Further studies are necessary to clarify the appropriate indications for molecular-target therapy for RAI-refractory and progressive metastases.

Key words: Differentiated thyroid carcinoma, Metastasis, RAI-refractory, Prognosis

DIFFERENTIATED THYROID CARCINOMAS (DTCs) are most often papillary (TPCs) and follicular carcinoma (TFCs). DTCs generally have an indolent character and show good prognoses if appropriate early treatment is performed, such as surgery (except for low-risk papillary microcarcinoma) [1], radioactive iodine (RAI) ablation (although RAI is not common in Japan) and thyroid-stimulating hormone (TSH) suppression. However, DTCs occasionally show metastasis to distant organs or become locally too advanced to resect surgically. For such cases, RAI therapy has been the first line of therapy, but if metastatic lesions become refractory to RAI, the therapeutic options are

very limited, which worsens the prognosis [2–4].

A novel and promising therapeutic option, molecular-target therapy, was recently introduced for patients with RAI-refractory DTC metastases. Clinical trials testing this therapy are ongoing [5], and one molecular-target agent, sorafenib [6], has been approved by the U.S. Food and Drug Administration (FDA). However, the appropriate indications for molecular-target therapy have not yet been established. Moreover, molecular-target agents have shown various adverse effects and are very costly. In addition, not all RAI-refractory recurrences are progressive or life-threatening, and it is thus far from acceptable to use molecular-target agents for all patients with RAI-refractory metastases.

In the present study, we investigated the prognosis and prognostic factors of DTC patients with RAI-refractory metastases as the first step to address the treatment issues described above.

Submitted Apr. 19, 2014; Accepted May 12, 2014 as EJ14-0181
Released online in J-STAGE as advance publication May 27, 2014

Correspondence to: Yasuhiro Ito, M.D., Ph.D., Department of Surgery, Clinical Trial Management Center, Kuma Hospital, 8-2-35, Shimoyamate-Dori, Chuo-ku, Kobe 650-0011, Japan.

E-mail: ito01@kuma-h.or.jp

Patients and Methods

Patients

We enrolled 74 patients who were treated with RAI (13–150 mCi) between November 1997 and December 2012 after total thyroidectomy for DTC (62 TPCs, 11 TFCs, and one TPC+TFC) to treat distant or unresectable local metastases or to investigate their sensitivity to RAI, and who showed no uptake of the RAI to the lesions. Sixty-seven patients were administered a therapeutic dose (≥ 100 mCi) and the remaining 7 were administered a tested dose (≤ 50 mCi) of RAI. The patients' (52 females and 22 males) median age at the detection of metastases was 61 yrs (8–82 yrs). All these patients underwent initial surgery at Kuma Hospital, and metastases were detected in 29 (40%) before a total or completion total thyroidectomy. Metastatic lesions were detected on various imaging studies: roentgenography, CT scan, MRI, and PET-CT. None of these patients showed RAI uptake to metastatic lesions. The organs where DTC metastasized were lung in 66 patients, bone in 12 patients, and distant lymph nodes or local lesions in 14 patients. Fourteen patients showed metastases in more than one organ.

Patients with persistent disease but without metastases detectable on imaging studies and those with coexisting thyroid malignancies other than TPC and TFC were excluded from the series. Patients whose metastases initially showed RAI uptake but became RAI-refractory during repeated RAI therapy were also excluded.

The follow-up period ranged from 7 to 172 months (median 67 months), and to date, 12 patients have died of thyroid carcinoma.

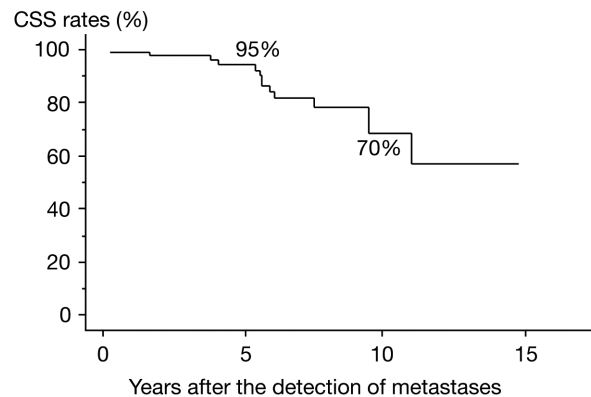
Statistical analyses

We used the Kaplan-Meier method and log rank test to analyze time-dependent variables, with StatView-J 5.0 software. A p -value less than 0.05 was regarded as significant. A Cox-hazard regression model was used for the multivariate analysis.

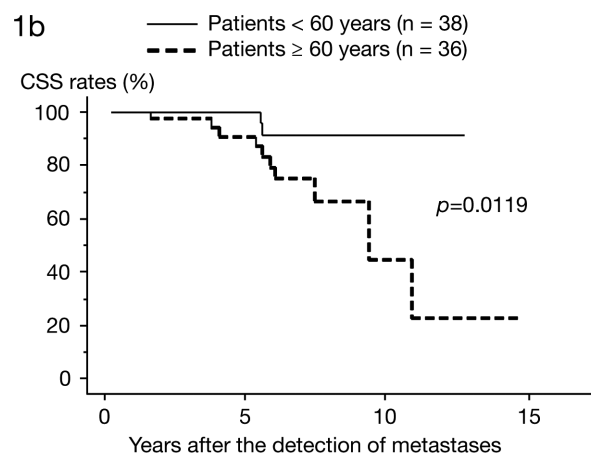
Results

As shown in Fig. 1a, the 5-year and 10-year cause-specific survival (CSS) rates after the detection of metastases were 95% and 70%, respectively. The patients' age at the detection of metastases (≥ 60 yrs vs. < 60 yrs; $p=0.0119$) and their gender ($p=0.0147$) was significantly linked to the CSS after the detection of metastases (Fig. 1b, c).

1a



1b



1c

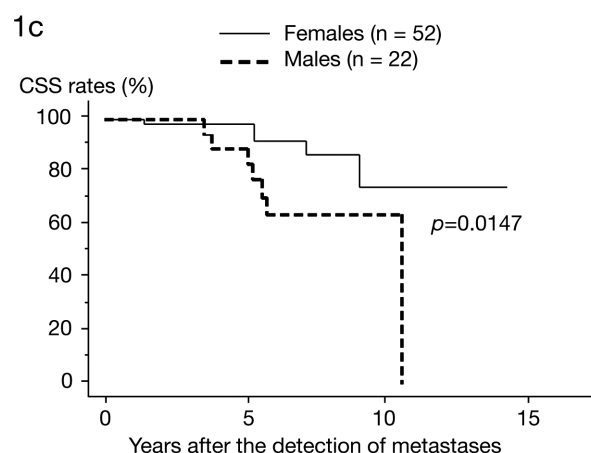


Fig. 1 a: Kaplan-Meier curve for the CSS of the 74 patients with RAI-refractory metastases who underwent initial surgical treatment at our hospital. b: Comparison of the CSS between the 38 patients ≥ 60 yrs and the 36 patients < 60 yrs. c: Comparison of the CSS between the 52 female patients and 22 male patients.

The patients' age, tumor size, significant extrathyroid extension (Ex) and clinical node metastasis (N) at the initial surgery were not related to the CSS of the patients (data not shown).

Table 1 provides the results of the multivariate analysis of these patients' background and clinicopathological features. Male gender and age at the detection of metastasis (≥ 60 yrs) were revealed as independent prognostic factors of CSS after the detection of metastases.

Discussion

In this study, we demonstrated that age ≥ 60 yrs significantly affected the CSS of patients after the detection of DTC recurrence refractory to RAI. Age is an important prognostic factor and was adopted by the UICC TNM classification system [7], AMES [8], and MACIS [9]. We also found that advanced age was a significant predictor of carcinoma-related death of the TPC and TFC patients [10, 11]. Miyauchi *et al.* demonstrated that persistent disease was more likely to be seen in M0 TPC patients ≥ 60 yrs and < 40 yrs than those aged 40–59 yrs, but short thyroglobulin doubling time (Tg-DT) (< 2 yrs), which is the most important dynamic prognostic factor [12], was much more frequently observed in their patients ≥ 60 yrs compared to young and middle-aged patients [13]. These findings suggest that recurrence in older patients is more progressive and harder to control than that in young patients, which is consistent with our present findings.

In contrast, the prognosis of patients < 60 yrs was excellent in our series even after the appearance of RAI-refractory metastases. We speculate that the RAI-refractory metastases of patients ≥ 60 yrs are more progressive than those of young patients.

We also observed that, in the subset of patients who underwent initial surgical treatment at our hospital, the male patients were more likely to die of carcinoma than the female patients. This finding was not detected in our entire series, possibly because for the patients who underwent initial treatment at other hospitals, the treatment history varied. We previously demonstrated that male gender had a moderate prognostic impact on TPCs and TFCs [10, 11]. However, our present findings suggest that RAI-refractory metastases of male patients are significantly more progressive and life-threatening than those of female patients. It might thus be advisable to consider patient gender when the indications for molecular-target therapy for RAI-refractory

Table 1 Multivariate analysis for CSS after the detection of RAI-refractory metastasis in 74 DTC patients

Variables	p-value	Hazard ratio (95% *CI)
Age at recurrence ≥ 60 yrs	0.0135	8.498 (1.555–46.427)
Male gender	0.0231	5.435 (1.261–23.256)
Significant extrathyroid extension	0.7996	1.195 (0.303–4.717)
Age at initial surgery ≥ 60 yrs	0.1640	0.334 (0.071–1.566)
Tumor size > 4 cm	0.2005	0.453 (0.107–1.910)
Clinical node metastasis	0.8757	1.126 (0.255–4.975)

*CI, confidence interval

and progressive metastases are being established.

In this study, we did not enroll patients whose metastases initially showed RAI uptake but became RAI-refractory during repeated RAI therapy, in order to simplify the data analysis; this is a limitation of the study. Further investigations are needed to compare the outcomes of such patients with those of patients who were RAI-resistant at the first administration.

Molecular-target agents are very costly, and their use often produces various adverse events such as skin conditions, hepatic failure and interstitial pneumonia, some of which are life-threatening. Our preliminary study showed that RAI-refractory metastases in older patients and male patients are more progressive than those of other patients. However, the appropriate patient population for molecular-target therapy among patients with progressive and RAI-refractory metastases remains a matter of debate. DTCs generally have a more prolonged course than other solid carcinomas such as carcinoma of the liver and kidney, even though DTC metastases refractory to RAI appear and even progress. The use of molecular-target agents for all patients with progressive and RAI-refractory metastases may constitute overtreatment. The indications for molecular-target therapy might depend on the balance among the effects of the therapy, the rates of adverse events, and the cost. As indicated above, patients with short (< 2 yrs) Tg-DT are likely to die of carcinoma [12], a finding that could be helpful to decide the indication for molecular-target therapy. Similarly, short tumor-DT, which definitely reflects the promptness of carcinoma progression, should be useful for this purpose. Further studies regarding this issue are needed to identify the most appropriate indications for molecular-target therapy.

References

1. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, et al. (2014) Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. *Thyroid* 24: 27-34.
2. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl J, et al. (2006) Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab* 91: 2892-2899.
3. Capdevila J, Argiles G, Rodriguez-Frexinos V, Nunez I, Tabernero J (2010) New approaches in the management of radioiodine-refractory thyroid cancer: the molecular targeted therapy era. *Discov Med* 9: 153-162.
4. Ito Y, Higashiyama T, Takamura Y, Kobayashi K, Miya A, et al. (2010) Clinical outcomes of patients with papillary thyroid carcinoma after the detection of distant recurrence. *World J Surg* 34: 2333-2337.
5. Anderson RT, Linnehan JE, Tongbram V, Keating K, Wirth LJ (2013) Clinical, safety, and economic evidence in radioactive iodine-refractory differentiated thyroid cancer: A systematic literature review. *Thyroid* 23: 392-401.
6. Brose MS, Nutting C, Jarzab B (2013) Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer. The phase III DECISION trial. The 49th annual meeting of the American Society of Clinical Oncology (ASCO) Plenary session Abstract #4.
7. Sobin LH, Gospodarowicz M, Wittekind C, eds. (2010) UICC: TNM classification of malignant tumors, 7th ed. Wiley-Blackwell, New York.
8. Cady B, Rosai R (1988) An expanded view of risk group definition in differentiated thyroid carcinoma. *Surgery* 104: 947-953.
9. Hay ID, Bergstrahl EJ, Goellner JR, Ebersold JR, Grant CS (1993) Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery* 114: 1050-1057; discussion 1057-1058.
10. Ito Y, Kudo T, Kobayashi K, Miya A, Ichihara K, et al. (2012) Prognostic factors for recurrence of papillary thyroid carcinoma in the lymph nodes, lung and bone: analysis of 5,768 patients with average 10-year follow-up. *World J Surg* 36: 1274-1278.
11. Ito Y, Hirokawa M, Higashiyama T, Takamura Y, Miya A, et al. (2007) Prognosis and prognostic factors of follicular carcinoma in Japan: importance of postoperative pathological examination. *World J Surg* 31: 1417-1424.
12. Miyauchi A, Kudo T, Miya A, Kobayashi K, Ito Y, et al. (2011) Prognostic impact of serum thyroglobulin doubling-time under thyrotropin suppression in patients with papillary thyroid carcinoma who underwent total thyroidectomy. *Thyroid* 21: 707-716.
13. Miyauchi A, Kudo T, Kihara M, Higashiyama T, Ito Y, et al. (2013) Relationship of biochemically persistent disease and thyroglobulin-doubling time to age at surgery in patients with papillary thyroid carcinoma. *Endocr J* 60: 415-421.