Clinical Study

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Prognostic factors of bone metastasis from DTC

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Early prognostic factors at the time of diagnosis of bone metastasis in patients with bone metastases of differentiated thyroid carcinoma

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Abstract

Objective: Bone is the second most common site of distant metastases from differentiated thyroid cancer (DTC). Patients with bone metastases were associated with poor clinical outcomes; however, their clinical courses are heterogeneous. The aim of this study is to evaluate early prognostic factors of patients with bone metastases from DTC at the time of diagnosis of bone metastasis.

Methods: This retrospective study included 93 patients with bone metastases from DTC. We defined ‘Pre-RAIT group’ as patients whose bone metastases were detected before initial RAIT. The ‘post-RAIT group’ was defined as patients whose bone metastases were detected after initial RAIT or during the follow-up period.

Results: Median age was 55.4 years, and 55 patients (59%) had papillary thyroid cancer. Patients in the pre-RAIT group (n = 32) demonstrated significantly poorer overall survival (OS) (HR = 1.86, P = 0.04) than those in the post-RAIT group. There was no significant difference in the OS according to the initial RAI avidity among all patients (P = 0.18). RAI-avid bone metastases had better OS only in the pre-RAIT group (HR = 0.23, P = 0.01) but not in the post-RAIT group. In the post-RAIT group, older age (>45 years), elevated serum thyroglobulin (Tg) level (>250 ng/mL), and the presence of skeletal-related events (SREs) were significantly associated with poor OS. RAI avidity was not a significant prognostic factor in the post-RAIT group (P = 0.33).

Conclusions: Patients whose bone metastases were diagnosed before initial RAIT demonstrate a poorer prognosis. RAI avidity is an early prognostic indicator in the pre-RAIT group. Old age, higher serum Tg levels, and SRE are associated with poor survival outcomes in the post-RAIT group.

Introduction

Patients with differentiated thyroid carcinoma (DTC) usually demonstrate a good prognosis with a 10-year survival rate of over 80–95% (1, 2). Distant metastasis of DTC was known to occur in 5–25% of patients and is the main cause of cancer-related death (3, 4). After the lungs, bone is the second most common site of distant metastases from thyroid cancer (5). The management and risk stratification of patients with bone metastasis from DTC are important because of the effects on quality of life and increased mortality rate (6, 7, 8, 9). Bone metastases can result in clinically significant morbidities, including pathological fracture, severe pain, immobility,
neurological deficits, and deteriorated quality of life (5, 10). A recent study reported that 78% of thyroid cancer patients with bone metastases developed at least one skeletal-related event (SRE) during median 4.9 years of follow-up period, and mortality was significantly higher in patients with bone metastases who developed SREs (10). However, an SRE itself is not a useful early prognostic parameter because follow-up is needed to confirm SREs.

Most previous studies categorize metastatic lesions as synchronous or metachronous (5, 9, 11, 12). Synchronous metastasis is defined as the presence of a distance metastasis at the time of, or within a few months of, the initial diagnosis and includes patients whose metastatic lesions were found on the initial post-therapeutic whole-body scan (WBS) (RxWBS) after radioactive iodine (RAI) therapy (RAIT). Metachronous metastasis is defined as distant metastasis found during the follow-up. However, patients who have no symptoms or SRE and just detected bone metastasis by initial RAIT demonstrate excellent responses to RAIT and much better survival than patients who demonstrate bone metastasis before the initial RAIT (5, 13). Furthermore, patients who demonstrate bone metastasis through an initial RAIT often include bone metastasis with no structural correlation, which is known to have no prognostic significance (14). This might be the reason why synchronous/metachronous categories have been reported as inconclusive prognostic factors. Patients who undergo an initial lobectomy must be categorized as metachronous if they have metastatic DTC. However, these patients are also heterogeneous in terms of the presentation of bone metastasis.

I-131 uptake in RxWBS has been found in more than two-thirds of patients with distant metastases of DTC (4). The RAI avidity of metastatic lesions has also been found to have a significant impact on survival in DTC patients with distant metastasis, and the survival of patients with RAI-avid distant metastases was shown to be significantly better than patients with RAI-non-avid distant metastases (3, 6, 8, 15, 16, 17). RAI uptake by metastatic cancer cells provides a biological marker for differentiation and is an intrinsic property of these cancer cells.

In this study, we evaluated the early prognostic factors at the time of diagnosis of bone metastasis that can predict the survival of patients with bone metastasis from a DTC. We focused on the prognostic impact of the time difference in the diagnosis of bone metastases whether bone metastases were detected before or after an initial RAIT. We also evaluated the importance of RAI avidity according to the timing of the diagnosis of a bone metastasis.

**Patients and methods**

**Definition**

We defined the ‘pre-RAIT group’ as patients whose bone metastases were clinically detected before an initial RAIT. The ‘post-RAIT group’ was defined as patients whose bone metastases were detected on therapeutic WBS after initial RAIT or by another method during the follow-up period. Patients were also categorized by RAI uptake in metastatic bony lesions in RxWBS at the initial RAIT (RAI-avid group vs RAI-non-avid group). SRE was defined as when any of the following conditions developed (10): (i) spinal cord compression, (ii) pathological fracture, (iii) external beam radiation or surgery to control pain or prevent impending fracture, and (iv) hypercalcemia of malignancy as previously reported.

**Patients**

We retrospectively reviewed patients who were diagnosed with bone metastasis from DTC who received follow-up examinations at Asan Medical Center between 1994 and 2013. We enrolled 93 patients with bone metastasis from DTC. All patients in our study series (except two cases) underwent RAIT for remnant ablation or therapeutic purposes. This study was approved by the institutional review board of Asan Medical Center, Seoul, Korea.

The diagnosis of bone metastasis was made according to the following criteria: (i) pathological results of a metastatic bone lesion, (ii) radiiodine uptake, regardless of structural bone lesion, and (iii) if the bony lesion was not confirmed by pathology or radioiodine avidity, at least two repetitive positive findings were noted on imaging (including X-ray, CT, MRI, 18F-fluorodeoxyglucose positron-emission tomography/computed tomography, and bone scan) or one imaging finding was found with an elevated serum thyroglobulin (Tg) level.

**RAIT and follow-up protocols**

Patients who were not diagnosed with bone metastases at the time of the initial RAIT received 1.11–5.55 GBq (30–150 mCi) as the remnant ablation therapy according to their initial surgical staging. A high fixed dose of I-131 (7.4 GBq, 200 mCi) was administered to patients who were diagnosed with metastases before the initial RAIT.

All patients underwent RAIT after thyroxine withdrawal for 5–6 weeks, and RxWBS images were obtained at 2 days and 5–7 days after administration of I-131.
RAI avidity was evaluated by two experienced nuclear physicians (J. S. R. and J. J. L.) and classified as RAI-avid and RAI-non-avid. Patients with RAI uptakes on RxWBS in metastatic lesions were classified as having RAI-avid tumors. Patients without visible RAI uptakes on RxWBS or with uptake in <10% of multiple metastatic lesions were defined as having RAI refractory tumors (18). All patients were treated with thyroxine to suppress thyroid-stimulating hormone and received a regular follow-up with physical examinations and serum thyroglobulin and/or diagnostic imaging studies every 3–6 months.

Statistical analysis
Continuous variables are expressed as the means (± s.d.) or median with interquartile range and categorical variables as numbers (percentage). Continuous variables were compared using Student’s t-test or Wilcoxon rank-sum test. Comparisons between each group according to the categorical variables were performed using Fisher’s exact test (two sided). Survival curves were constructed using Kaplan–Meier methods, and the log-rank test was used to evaluate the differences in survival between groups. A Cox proportional hazards model with hazard ratios (HRs) and 95% confidence intervals (CIs) were used to evaluate the risk of death. In multivariate analysis, we have included the prognostic factors that were significantly associated with overall survival in univariate analysis. R (version 3.0) and the R libraries prodlim, car, Cairo, and survival were used to analyze data and draw graphs (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org). All P values were two sided, and P<0.05 was considered statistically significant.

Results
Clinical characteristics of DTC patients with bone metastasis
A total of 93 patients with bone metastases from DTC (30 male and 63 female patients) were enrolled in this study for median 6.7 years of follow-up period. The mean age of the patients was 52.5±14.5 years, and 38 patients (41%) had follicular thyroid carcinoma (FTC). The median primary tumor size was 3.0 cm (interquartile range (IQR) = 2.0–5.0), and 39 of 80 patients (49%) had cervical LN metastases; 24 patients (26%) had symptoms associated with bone metastases, and 47 patients (51%) had SREs (Table 1).

Patients were classified according to the detection time of the bone metastasis and placed in the pre-RAIT group (n=32) or post-RAIT group (n=61). Majority of patients in the pre-RAIT group (n=32) were symptomatic at initial presentation or had SRE. However, they also included

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and pathological features of the patients with bone metastases from a differentiated thyroid carcinoma according to the time of diagnosis of bone metastases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Total (n=93) 52.5±14.5</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>30 (32)</td>
</tr>
<tr>
<td>Initial TT/completion</td>
<td>78 (84)</td>
</tr>
<tr>
<td>Pathology (follicular)</td>
<td>38 (41)</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>3.0 (IQR 2.0–5.0)</td>
</tr>
<tr>
<td>Tumor size (&gt;4cm)</td>
<td>25/76 (33)</td>
</tr>
<tr>
<td>Cervical LN metastasis</td>
<td>39/80 (49)</td>
</tr>
<tr>
<td>RAI avidity at initial RAI</td>
<td>56/91 (62)</td>
</tr>
<tr>
<td>Multiple bone metastasis</td>
<td>70 (75)</td>
</tr>
<tr>
<td>Multiple organ metastases other than bone</td>
<td>62 (67)</td>
</tr>
<tr>
<td>Symptomatic bone metastasis</td>
<td>24 (26)</td>
</tr>
<tr>
<td>Stimulated Tg (ng/mL)</td>
<td>281 (IQR 32.9–2225)</td>
</tr>
<tr>
<td>Stimulated Tg (&gt;250ng/mL)</td>
<td>40/78 (51)</td>
</tr>
<tr>
<td>SRE</td>
<td>47 (51)</td>
</tr>
<tr>
<td>Operation</td>
<td>21 (23)</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>35 (38)</td>
</tr>
<tr>
<td>Systemic chemotherapy</td>
<td>12 (13)</td>
</tr>
</tbody>
</table>

LN, lymph node; Post-RAIT, group of patients whose bone metastases were accidentally detected by therapeutic whole-body scan after initial RAIT or by other method during follow-up; Pre-RAIT, group of patients whose bone metastases were clinically detected before initial RAIT; RAI, radioactive iodine; RAIT, radioactive iodine treatment; SRE, skeletal-related event; stimulated Tg, stimulated serum thyroglobulin level at initial RAI; Tg, thyroglobulin; TT, total thyroidectomy.
incidental finding of bone metastasis before initial RAIT. The post-RAIT/RAI-avid group (n = 32) was defined as the metastatic bony lesion that was detected by initial RAIT. Among the post-RAIT/RAI-non-avid group (n = 29), half of bone metastases were detected incidentally by imaging modality for other metastatic lesion work-up or by post-additional therapeutic WBS image after I-131 therapy for other metastasis during median 3.8 years of follow-up period (0.4–14.1 years). Of these patients, seven showed RAI uptake by bony lesion in additional RxWBS, which was RAI-non-avid in initial remnant ablation scan and 12 patients performed imaging work-up for metastatic lesion because of persistently high serum thyroglobulin level. Only three patients presented as symptomatic bony lesion or SRE.

The clinicopathological characteristics of the study patients are summarized in Table 1. The patients in the pre-RAIT group were significantly older than the patients in the post-RAIT group (P = 0.02). There were significantly more patients with FTC, symptomatic bone metastasis, and SREs in the pre-RAIT group in comparison with the post-RAIT group. The initial serum-stimulated Tg levels were significantly higher in the pre-RAIT group in comparison with the post-RAIT group (P < 0.01). There were no significant differences in sex, initial surgical extent, primary tumor size, presence of multiple bone metastases, or other organ metastases between the two groups. Fifty-six patients (62%) had RAI-avid bone metastases at the initial RAIT. Of the 30 patients in the pre-RAIT group, 24 (80%) had RAI-avid bone metastases, whereas 32 of 61 patients (52%) in the post-RAIT group demonstrated RAI avidity (P = 0.02).

There were a total of 47 (51%) cases of SRE. Among them, 28 patients presented SRE with initial diagnosis of bone metastasis, and 19 patients presented SRE during median 4.8 years (0.1–17.2) of follow-up periods. The median SRE-free survival was 2.9 and 5.4 years in the pre-RAIT and post-RAIT groups respectively.

Majority of patients (n = 82) performed therapeutic second RAIT during the follow-up. Local therapies such as surgery, external radiation, and radiofrequency ablation were performed in 21, 35, and four patients respectively; 12 patients underwent systemic chemotherapy.

**Overall survival of DTC patients with bone metastasis**

The 5-year and 10-year survival rates of the patients with bone metastases were 77.1 and 46.6% respectively (Fig. 1A). The patients in the pre-RAIT group demonstrated poorer survival than the patients in the post-RAIT group (HR = 1.86; 95% CI = 1.02–3.39; P = 0.04; Fig. 1B), even though they had more patients with RAI-avid bone metastases. There were no significant differences in OS according to RAI avidity in these study patients (P = 0.17; Fig. 1C). There were no differences in OS between patients with synchronous metastasis and those with metachronous metastasis (HR = 1.03; 95% CI = 0.55–1.93; P = 0.93, Fig. 1D). The pathological subtype (PTC or FTC) was not a significant factor associated with OS (P = 0.08).

**Clinicopathological features associated with OS in patients with bone metastases in the pre-RAIT group and post-RAIT group**

We evaluated the prognostic factors associated with OS in both the pre-RAIT (Table 2) and the post-RAIT (Table 3) groups because the baseline characteristics of these two groups were different. In the pre-RAIT group, the RAI avidity of the bone metastases was a significant prognostic factor associated with a better OS (P = 0.01; Fig. 2A). By multivariate analysis, only RAI avidity was found to be an independent prognostic factor associated with OS (HR = 0.23; 95% CI = 0.08–0.71; P < 0.01). However, other clinicopathological variables such as age, sex, pathological subtype, cervical LN metastases, presence of multiple bone metastases, other organ metastases, and SREs were not significantly associated with OS in the pre-RAIT group (Table 3).
In the post-RAIT group, there were no significant differences in the OS according to RAI avidity ($P=0.33$; Fig. 2B). Age above 45 years old was a marginally non-significant factor associated with OS ($P=0.05$; Fig. 2C) by univariate analysis; however, an older age was an independent negative prognostic indicator by multivariate analysis (HR = 15.63; 95% CI = 2.38–102.44; $P<0.01$; Table 3). The serum-stimulated Tg level at the initial RAIT was a significant prognostic factor associated with OS in the post-RAIT group according to both univariate and multivariate analyses (HR = 3.68; 95% CI = 1.19–11.40; $P=0.02$; Fig. 2D and Table 3). The presence of SRE was a marginally non-significant factor associated with OS ($P=0.06$; Fig. 2E); however, SRE was independently associated with poor OS by multivariate analysis (HR = 4.43; 95% CI = 1.38–14.28; $P=0.01$; Table 3). No other clinicopathological factors were associated with OS by multivariate analysis.

**Table 2** Prognostic factors associated with the overall survival of patients who detected bone metastases before the initial RAIT (pre-RAIT group).

**Table 3** Prognostic factors associated with the overall survival of patients who detected bone metastases after initial RAIT (post-RAIT group).
Discussion

In this study, we subcategorized patients into the pre-RAIT and post-RAIT groups according to the timing of a bone metastasis diagnosis. The clinical and pathological characteristics of the study patients in these groups were quite different. Therefore, we evaluated the prognostic factors for these subjects with bone metastases from DTC in each group. Patients who were diagnosed with bone metastasis before RAIT (pre-RAIT group) demonstrated more RAI-avid bone metastases. However, the patients in this group demonstrated significantly poorer prognostic factors in comparison with those in the post-RAIT group. The baseline characteristics of the pre-RAIT group indicated a more extensive tumor burden, such as higher serum-stimulated Tg levels, a more symptomatic presentation, or SREs, in comparison with the post-RAIT group. Therefore, the timing of diagnosis of bone metastases could be an important prognostic indicator that predicts the survival of DTC patients.

The TSH-stimulated serum Tg level is known to be associated with the disease volume in DTC patients (15, 19, 20). A higher stimulated serum Tg level at the time of the detection of distant metastasis is known to be a significant predictor of poor outcomes (15, 21). In this study, the serum-stimulated Tg levels were significantly higher in the pre-RAIT group than in the post-RAIT group. These findings suggest that the clinical characteristics of the patients in these two groups are quite different. In the post-RAIT group, a highly stimulated serum Tg level was an independent prognostic factor associated with the survival of patients with bone metastases.

In the pre-RAIT group, RAI avidity at the initial RAIT was the only independent prognostic indicator of a better OS. Patients in this group tended to have more extensive bone metastases, and the therapeutic effects of RAIT, as represented by the initial RAI avidity, were a critical determinant of the prognosis. However, RAI avidity was not associated with the survival of patients in our post-RAIT group. Patients in this group had a higher proportion of PTCs, more cervical LN metastases, and lower stimulated serum Tg levels in comparison with the pre-RAIT group. In the post-RAIT group also, seven patients who were initially classified with RAI-non-avid metastases demonstrated meaningful RAI uptake on RxWBS after the second high-dose RAIT. We could not detect RAI uptake in the bone metastases because of the relatively larger remnant thyroid tissues in these seven patients. Even though we focused on the prognostic factors at the time of diagnosis of bone metastasis in this study, the changes in RAI avidity could be considered during the follow-up of patients with distant metastases. Moreover, caution must be exercised when interpreting the results of the initial RxWBS if the remnant thyroid tissues are relatively larger. The disease status after the initial treatment of DTC patients should therefore be reassessed, as shown by a previously reported dynamic risk stratification system (22, 23). When considering these patients as RAI-avid, RAI avidity was found to be a significant prognostic factor in the 93 patients (data not shown).

In the post-RAIT group, patients with a SRE at the time of diagnosis of bone metastasis were rare and most developed SRE during the follow-up period. SRE was an independent prognostic factor associated with poorer survival. Development of SRE could be an only modifiable
risk factor to improve survival. It is well known that potent anti-resorptive agents such as zoledronic acid and denosumab provide benefits for the treatment and prevention of skeletal complications in patients with multiple myeloma and breast and prostate cancers (24, 25, 26). Recently, several reports have also described the efficacy of bisphosphonate for treating bone metastasis from thyroid cancer (27, 28, 29). In this study cohort, we administered monthly zoledronic acid to ten patients for primarily preventive purposes. However, we could not determine whether there had been a better initial SRE-free survival in those patients because of their small number and a selection bias (data not shown). Further studies are needed to assess the long-term effects and safety of the initial potent anti-resorptive therapies for the treatment of bone metastasis from DTC (10).

Our study had an inherent limitation because of its retrospective design. There was no uniform protocol for the management after initial RAIT for patients with bone metastases of DTC. There were a relatively small number of study subjects with bone metastases. We also consider selection bias of a tertiary referral center. We usually used a fixed-dose approach for patients with distant metastases of DTC. We could not analyze disease-specific survival because there were a few patients whose cause of death could not be identified. Nonetheless, this was the first study to evaluate survival of patients according to the timing of a bone metastasis diagnosis. This study suggested the clinical relevance to classify bone metastases as pre-RAIT/post-RAIT in patients with DTC.

In summary, we conclude from our current findings that patients whose bone metastases are diagnosed before initial RAIT (pre-RAIT group) demonstrate a poorer prognosis than those diagnosed after an initial RAIT (post-RAIT group). The RAI avidity of the initial RAIT is an early indicator of outcomes than those diagnosed after an initial RAIT (post-RAIT group). This study suggested the clinical relevance to classify bone metastases as pre-RAIT/post-RAIT in patients with DTC.

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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