Skeletal-Related Events due to Bone Metastases from Differentiated Thyroid Cancer

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Background: In oncology, the clinical impact of metastatic bone disease is conveyed via a composite end point termed skeletal-related events (SRE), which encompasses spinal cord compression, pathological fracture, a need for external beam radiation or surgery to bone, and hypercalcemia of malignancy. An appreciation for the high incidence of SRE in other advanced cancers involving the bone has led to the approval of potent antiresorptive agents because they delay the time to the first SRE and decrease the incidence of SRE. The risk and rate of SRE after diagnosis of bone metastasis have not been described in thyroid cancer; antiresorptive agents are not routinely used.

Methods: This was a retrospective review of 245 differentiated thyroid cancer patients with bone metastases identified as part of routine clinical care at Memorial Sloan-Kettering Cancer Center between 1960 and 2011. The occurrence of SRE was recorded from the initial diagnosis of bone metastasis until final follow-up or death.

Results: Seventy-eight percent of patients (192 of 245) either presented with or developed at least one SRE after the diagnosis of metastatic bone disease. The median time from identification of bone metastasis to first SRE was 5 months (excluding the 97 patients in whom first SRE occurred at the time of the bone metastasis diagnosis). Of the patients who sustained an initial SRE, 65% (120 of 192) went on to sustain a second SRE at a median of 10.7 months after the first event. SRE were frequently multiple; 39% (74 of 192) sustained three or more discrete SRE.

Conclusion: Thyroid cancer bone metastases identified as part of routine clinical follow-up frequently cause significant and recurrent morbidity. The incidence of SRE and median time to first SRE in metastatic thyroid cancer to bone are similar to those reported in other solid tumors. Prospective clinical trials to assess the efficacy of antiresorptive agents in this population are needed. (***J Clin Endocrinol Metab*** **97: 2433–2439, 2012)**

Bone metastases occur in 2–13% of all patients with differentiated thyroid cancer (1) and are associated with very poor clinical outcomes (2, 3). In addition to conferring worse survival, the development of bone metastases can also result in clinically significant morbidities including pathological fracture, severe pain, immobility, and deterioration in quality of life. A composite end point known as skeletal-related events (SRE) is used in clinical studies to quantify the morbidity associated with skeletal metastases. Clinical end points that constitute an SRE include the following: 1) spinal cord compression, 2) pathological fracture, 3) external beam irradiation or surgery to control pain or prevent impending facture, and variably 4) hypercalcemia of malignancy (some studies do not include this as an SRE). To obtain approval for pharmacotherapies directed specifically at impacting the morbidity of bone metastases, the U.S. Food and Drug Administration requires evidence of either a reduction in the incidence of SRE or a delay in the median time to the first SRE.

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Abbreviations: CT, Computed tomography; MRI, magnetic resonance imaging; PET, position emission tomography; RAI, radioactive iodine; SRE, skeletal-related event.

In patients with bone metastases from other solid tumors, the risk of developing at least one SRE over an approximately 2-yr period ranges from 48% in non-small-cell lung cancer to 49% in prostate cancer to 68% in breast cancer (4). In a previous publication of 146 thyroid cancer patients with bone metastases from our center, 27% of patients suffered a pathological fracture and 14% developed cord compression (other SRE not reported) (3). Recently a small series of thyroid cancer patients with bone metastases reported that 50% of the patients (14 of 28) not treated with bisphosphonate therapy developed at least one SRE over a 4-yr follow-up period (5). Unfortunately, many patients suffer sequential SRE because a history of an SRE is associated with a 2-fold higher risk of developing a subsequent SRE (6). Furthermore, without antiresorptive therapy, the median time to first SRE in breast cancer is 7 months after identification of a bone metastasis (7).

Based on the results of randomized, placebo-controlled trials, potent antiresorptive agents are the standard of care for treatment and prevention of skeletal complications in patients with multiple myeloma and documented bone metastases from solid tumors. Specific practice guidelines have been established, which incorporate the use of these agents as standard of care (8, 9). SRE end points are vital tools for assessing the efficacy of drug therapy to reduce skeletal morbidity in advanced cancers involving the bone. For example, in breast cancer, randomized, placebo-controlled trials have shown that iv bisphosphonates given on a monthly basis reduce the incidence of first and subsequent SRE and delay the time to first SRE (7, 10, 11). More recently the receptor activator of nuclear factor-κB ligand inhibitor denosumab has shown superiority over zoledronic acid in metastatic breast cancer and castration-resistant prostate cancer in terms of median time to first SRE (12, 13).

Although thyroid cancer has the third highest propensity to spread to the bone behind breast and prostate cancer (6), there is a paucity of data on the risk of skeletal morbidity in this population. Moreover, the management of metastatic bone disease in thyroid cancer has been historically limited to radioiodine ablation, surgical excision, and external beam radiation. American Thyroid Association and the National Comprehensive Cancer Network guidelines endorse consideration of antiresorptive therapy with either a bisphosphonate or denosumab. However, these recommendations are based on small retrospective thyroid cancer series (14, 15) or extrapolation of experience from larger trials of other solid tumors and do not appear to be widely implemented in clinical practice.

With the widespread use and proven efficacy of iv bisphosphonates and denosumab in other solid tumors metastatic to bone, it is critical to have a better understanding of the incidence and natural history of SRE in thyroid cancer patients with skeletal metastases. If thyroid cancer patients with bone metastases develop SRE in a fashion similar to patients with breast, prostate, and lung cancer, it stands to reason that antiresorptive therapies could have a favorable impact on SRE in this specific cohort of patients and might be a highly relevant therapy for physicians treating metastatic thyroid cancer to bone. Therefore, the goal of this study was to better define the morbidity of bone metastases in differentiated thyroid cancer by defining the incidence, onset, and time course of SRE in a large retrospective cohort of patients followed up at a single major medical center.

Patients and Methods

After obtaining institutional review board approval, a retrospective review of electronic medical records at Memorial Sloan-Kettering Cancer Center identified 288 patients with bone metastases from thyroid cancer. This data set included the 145 patients evaluated between 1960 and 1998 previously reported by Pittas *et al.* (3) and an additional 143 patients treated between 1999 and 2011. Patients were excluded from the study for the following reasons: insufficient medical records (n = 18), anaplastic thyroid cancer (n = 11), medullary thyroid cancer (n = 9), and inadequate documentation of bone metastases (n = 5). The remaining 245 patients with bone metastases from thyroid cancer formed the basis for this study.

Bone metastases were diagnosed from reports of chest or skeletal roentgenograms, computed tomography (CT), magnetic resonance imaging (MRI), radioactive iodine (RAI) uptake, or 2-deoxy-2-[18F]fluoro-D-glucose-whole-body position emission tomography (PET) performed as standard of care treatment or as directed by patients' symptoms. Structural bone metastases were defined as evidence on CT, MRI, or PET (and could be either RAI avid or RAI negative) whereas nonstructural bone metastases were defined by RAI uptake without corresponding anatomic evidence on structural imaging. Charts were electronically reviewed for the occurrence of the first SRE after the initial diagnosis of bone metastasis and for the development of subsequent SRE until follow-up or death.

SRE were defined as spinal cord compression, pathological fracture, a need for external beam radiation or surgery to bone, or the development of hypercalcemia of malignancy. Treatment of a single lesion with both radiotherapy and surgery were coded as a single event if both therapies were given within a 30-d window with the SRE coded based on whichever therapy was administered first.

Potential risk factors for the development of an SRE were analyzed including age, histology, the sites of metastatic bone disease, the presence of nonosseous metastases, and the presence of nonstructural bone metastases (defined as bone RAI avidity without structural evidence on CT, MRI, or PET/CT). A history of treatment with iv bisphosphonates was also noted.

Statistical analysis

Continuous data are presented as means and SD with median values. For comparing medians, a nonparametric Mann-Whitney *U* test was used, and for categories we used χ^2 and Fisher's exact tests. Kaplan-Meier curves are used to present SRE-free survival times. Analysis was performed using SPSS software (version 18.0.1: SPSS Inc., Chicago, IL).

Results

The study cohort consists of 245 patients with differentiated thyroid cancer who had bone metastases either identified at the time of initial diagnosis (107 of 245, 44%) or during follow-up (138 of 245, 56%). The median age at diagnosis was 57 ± 15 yr (range 15–80 yr) with 51% being female. The median follow-up duration after diagnosis of thyroid cancer was 4.9 yr (range 0.1–44 yr). The initial bone metastasis was confirmed on structural imaging (*i.e.* x-ray, CT, or MRI) in 89% and was present solely on radioactive iodine scanning without a structural correlate in 11%. At the time the initial bone metastasis was identified, symptoms attributable to the bone lesion (usually pain) were present in 67%. See Table 1 for additional clinicopathological description of the cohort.

Of this cohort of 245 thyroid cancer patients with bone metastases, 78% (192 of 245) developed at least one SRE either concurrent with the identification of the initial bone metastasis (51%, 97 of 192) or during subsequent follow-up (49%, 95 of 192) (see Table 2). Thirty-six percent (71 of 192) had only a single SRE, whereas 64% (121 of 192) developed multiple SRE over time. In the 95 patients in whom the first bone metastasis was not associated with an SRE, the median time between the diagnosis of the bone metastasis and the first SRE was 5 months (range 1 month to 9.2 yr). The major results of the study were unaltered when patients receiving at least one dose of iv bisphosphonates were excluded (n = 54). Of the 191 patients who never received iv bisphosphonates, 74% developed at least one SRE and 44% developed a second SRE.

The median time from first SRE to final follow-up or death was 1.9 yr (range 0–19.8 yr). The mortality was significantly higher in patients with bone metastases who developed either a single (68% mortality) or multiple (79% mortality) SRE compared with those patients who did not develop an SRE (42%, $P < 0.0001$). Patients with bone metastases who developed an SRE were not significantly different with respect to age at diagnosis (55 ± 16 yr *vs.* 55 ± 13 yr), gender (40% male and 60% female *vs.* 49% male and 50% female), sites of metastatic bone disease, or the presence of nonosseous metastases than patients who did not develop an SRE. However, patients who did not develop an SRE were more likely to have a classical papillary thyroid cancer histology rather than one of the other phenotypes (odds ratio 3.8, $P < 0.002$) and more likely to have bone metastases characterized as RAI positive without a structural correlate than to have structural disease (either RAI positive or negative) identifiable on cross-sectional imaging ($P < 0.001$).

None of the 28 patients with nonstructural bone metastases went on to sustain an SRE. Excluding these 28 patients with nonstructural bone metastases, 88% of all patients with structural metastases (192 of 217) went on to sustain an SRE.

In the 192 patients who developed an SRE, at the time of the first SRE, 64% (123 of 192) had distant metastases confined to the bones, 28% (53 of 192) had bone and lung, 7% (13 of 192) had metastatic disease to bone, lung, and other distant sites (*e.g.* brain, skin, skeletal muscle) and

TABLE 1. Clinicopathological description of the cohort

		n
Age at diagnosis, yr (mean ± SD, range)	57 ± 15 (15–80)	245
Gender		
Male	49%	119
Female	51%	126
Histology		
Follicular thyroid cancer	34%	84
Poorly differentiated thyroid cancer	24%	59
Papillary thyroid cancer	19%	46
Hurthle cell carcinoma	13%	31
Follicular variant, papillary thyroid cancer	10%	25
Any distant metastases at diagnosis		
Yes	62%	151
No	38%	94
Bone metastases at diagnosis		
Yes	44%	107
No	56%	138
Characterization of bone metastases		
Structural abnormality	89%	217
RAI uptake without structural correlate	11%	28
Bone metastases symptomatic[a]		
Yes	67%	163
No	33%	80
Bisphosphonate use		
Yes	22%	54
No	78%	191
Final outcome		
Alive	33%	80
Dead	67%	165
Overall duration of follow-up from thyroid cancer diagnosis (yr)		
Median	4.9	245
Range	(0.1–44)	
Duration follow up after detection of first bone metastasis (yr)		
Median	3.4	245
Range	(0.1–20)	

[a] Symptom status was unable to be determined in two patients.

TABLE 2. Description of SRE

		n
Developed at least one SRE (n = 245)		
Yes	78%	192
No	22%	53
RAI avidity of bone lesion causing first SRE		
RAI positive	50%	81
RAI negative	50%	81
Number of bone metastases at time of first SRE (n = 192)		
1	27%	52
2–5	51%	98
6–10	17%	32
>10	5%	10
Number of discrete SRE per patient (n = 192)		
1	36%	71
2	25%	47
3	15%	27
4	11%	22
5	7%	14
6–10	6%	11
First SRE presented concurrent with first bone metastasis identification (n = 192)		
Yes	51%	97
No	49%	95
Type of first SRE (n = 192)		
Radiation therapy	46%	89
Surgery to metastatic site	19%	37
Spinal cord compression	16%	31
Pathological fracture	16%	31
Hypercalcemia	3%	4
Location of First SRE (n = 192)		
Vertebrae	47%	90
Pelvis	18%	35
Hip	10%	20
Other	10%	19
Chest (excluding vertebrae)	9%	17
Skull	6%	11
Developed a second SRE (n = 192)		
Yes	65%	125
No	35%	67
Type of Second SRE (n = 125)		
Radiation therapy	44%	55
Surgery to metastatic site	25%	31
Spinal cord compression	10%	13
Fracture	19%	24
Hypercalcemia	2%	2

1% (three of 192) had bone and other distant sites (see Table 2). Furthermore, at the time of the first SRE, 27% had only a single identifiable metastatic lesion, whereas 51% had two to five discrete bone metastases, 17% had six to 10 lesions, and 5% had more than 10 skeletal metastases [median of three discrete bone metastases (range 1–23)]. The likelihood of developing a second SRE was not statistically different between the 52 patients that presented with only a single bone metastasis at the time of the first SRE and the 140 patients who had multiple bone metastases at the time of the first SRE (57 *vs.* 68%, $P = 0.10$).

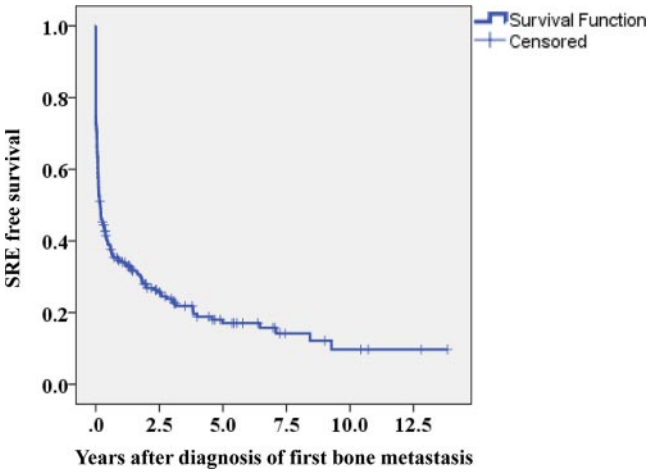

FIG. 1. SRE-free survival from the diagnosis of bone metastasis in all patients (n = 245).

The median follow-up duration after detection of the initial bone metastasis was 3.4 yr (range 0.1–20 yr). The Kaplan-Meier curve in Fig. 1 describes the time course for development of an SRE in our entire bone metastases cohort. Ninety percent of our cohort developed SRE within the first 2 yr of being diagnosed with a bone metastasis, which is consistent with other solid tumors.

In the 125 patients who developed a second SRE, the median time between first and second SRE was 0.9 yr (10.7 months, range 0–14 yr) (see Fig. 2). A comparison of patients who developed a second SRE with those that had only a single SRE revealed no significant differences in gender, histology of the primary tumor, type of SRE, or location of first SRE (data not shown, all $P > 0.05$). Patients diagnosed with a second SRE were younger at the diagnosis of their thyroid cancer (53 ± 13 *vs.* 57 ± 12 yr, $P = 0.04$), were followed up for a longer duration after the

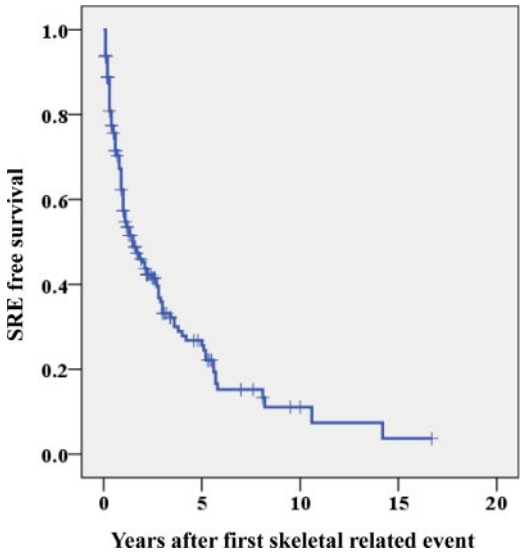

FIG. 2. Subsequent SRE-free survival after development of the first SRE (n = 125).

identification of the first bone metastasis (4.9 ± 3.9 *vs.* 3.3 ± 3.2 yr, $P = 0.04$) and for a longer duration after development of the first SRE (4.4 ± 3.7 *vs.* 2.4 ± 3 yr, $P = 0.03$) than patients who did not have a second SRE identified during the available follow-up period. The longer follow-up period (patients still alive and being actively followed up) likely contributed to the increased detection of second SRE in this cohort.

Discussion

Consistent with other studies, the mortality rate over a 5-yr follow-up period was 67% in this cohort of older patients with bone metastases from thyroid cancer. Strikingly, 78% of these patients with bone metastases developed at least one SRE during follow-up and 49% developed multiple SRE over a 5-yr follow-up period. Forty-six percent of first SRE occurred in patients with either one or two bone metastases, demonstrating that widespread skeletal metastases are not required to develop an SRE. This very high rate of SRE development is on par with what is seen in metastatic breast and prostate cancer and underscores the need for a better understanding of the role of antiresorptive therapy in thyroid cancer patients. It is important to emphasize that the bone metastases found in this study were identified as part of routine clinical care. These findings may or may not be applicable to asymptomatic bone metastases identified by intensive screening or disease detection approaches. Furthermore, these results emphasize the need for an increased focus on the morbidity associated with skeletal metastases in thyroid cancer.

Consistent with other solid tumors, the most common type of SRE is radiation therapy for painful bone lesions or to prevent impending fractures (9, 16). Additionally, 44% of our patients either developed a pathological fracture or required surgery to repair or prevent a pathological fracture. The most common type of fracture was vertebral collapse, which often results in chronic pain and kyphosis. These data point out that the clinical consequences of bone metastases in thyroid cancer are underappreciated: they often cause clinically significant events that require active intervention and that can be expected to detract from quality of life (17, 18). Hypercalcemia was the least common SRE (3%). Although hypercalcemia is not uniformly included in the SRE composite end point, excluding it would not significantly alter our findings.

In approximately 50% of our cohort, the SRE was present at the initial diagnosis of bone metastases. However, in the remaining 50%, an SRE developed a median of 5 months after diagnosis of the first bone metastases. Similarly, a second SRE developed in 65% of patients a median of 10 months after the first SRE. These time intervals are very similar to what is seen in metastatic breast and prostate cancer. Except for a longer duration of follow-up, no clinicopathological feature (age, histology, gender, stage) beyond the development of the first SRE was able to identify patients at risk for subsequent SRE.

SRE were less likely to develop in patients with bone metastases that were from classical papillary thyroid cancer or were identified only by RAI imaging without evidence of structural disease. In fact, none of the patients with nonstructural bone metastases (RAI uptake alone) went on to sustain an SRE. This suggests that either the natural history of these RAI avid lesions is more benign or that the upfront RAI treatment may have facilitated earlier detection and treatment of bone metastases before they became clinically significant. In addition, ^{131}I single-photon emission-CT/CT detection of these nonstructural bone metastases has been shown to alter staging (19) and hence estimates of recurrence and mortality risk. Long-term mortality data are needed to determine whether these nonstructural bone metastases should be considered advanced stage disease; we hypothesize from our data that these patients should not be considered as such.

Although 22% of the patients in this study received at least one dose of an iv bisphosphonate therapy (either zoledronic acid or pamidronate), it was not possible to determine the precise dosing, duration of dosing, or dosing in relationship to SRE for the majority of these patients. Nor was it possible to determine what clinicopathological features or individual physician practice patterns led to the decision to either use or not use bisphosphonates. Therefore, we could not perform any meaningful analysis with regard to the potential impact of bisphosphonate therapy on the incidence of either the primary SRE or subsequent SRE in our cohort. However, a retrospective study from Orita *et al.* (15) compared 22 patients treated with monthly zoledronic acid with 28 untreated patients over mean follow-up periods of 26 and 45 months from the diagnosis of bone metastases, respectively. The group that received monthly iv zoledronic acid therapy experienced significantly fewer SRE (13.4%, three of 22) in comparison with the untreated group (50%, 14 of 28), suggesting zoledronic acid reduced the risk of SRE.

We must also consider the natural history of metastatic thyroid cancer when evaluating the risks and benefits of antiresorptive therapies. Despite the presence of distant metastases, overall survival in thyroid cancer is often much better than that in other cancers. The potential benefit of antiresorptive therapy in reducing SRE must be

weighed against the risks associated with long-term use of potent antiresorptives at approved monthly dosing for advanced cancers involving the bone such as osteonecrosis of the jaw (described for both bisphosphonates and denosumab) and atypical subtrochanteric fractures (described with bisphosphonates) (20). Based on randomized data in other solid tumors demonstrating both a reduction in SRE incidence and an increase in median time to first SRE (7, 11, 16) and on the 78% risk of developing an SRE after clinical identification of a bone metastasis in this retrospective study, it seems reasonable to strongly consider initiating potent antiresorptive therapy at the diagnosis of structurally evident bone metastases in an effort to reduce skeletal morbidity in differentiated thyroid cancer patients. Ideally, prospective, randomized clinical trials should be conducted in differentiated thyroid cancer patients to prove this hypothesis.

Because our center specializes in the multidisciplinary management of advanced thyroid cancer, it is possible that a significant referral bias could influence the rates of SRE reported in this study. This bias would tend to overestimate the incidence of SRE if patients with bone metastases from thyroid cancer who did not experience an SRE were less likely to be referred to our center. In our experience, this does not appear to be the case because we are commonly referred patients who have bone metastases, whether or not they are associated with an SRE.

In summary, skeletal-related events are common and repetitive in patients with bone metastases from thyroid cancer on par with that seen in metastatic breast cancer. The high rate of SRE described in this study emphasizes the need to evaluate, treat, and potentially decrease the high morbidity associated with bone metastases from thyroid cancer. Prospective trials with iv bisphosphonates or denosumab are required to evaluate the potential benefits of such therapies in metastatic thyroid cancer and to better define the optimal duration and frequency of administration.

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