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Cancer: Thyroid cancer bone metastases and high morbidity rates

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Abstract

Skeletal-related events (SREs) are important measures of morbidity and mortality in patients with solid tumour bone metastases. The high rate of SREs in patients with differentiated thyroid cancer bone metastases reported by Farooki *et al.* indicates that routine use of antiresorptive therapy in these patients could result in reduced SREs.

Bone metastases are common in patients with advanced solid malignancies, including thyroid cancer. Skeletal complications resulting from bone metastases represent an important source of morbidity and mortality in these patients. To measure the effect of skeletal complications related to bone metastases objectively and determine the benefit of antiresorptive bone therapy, these complications have been defined as skeletal-related events (SREs). These SREs include pathological fractures, spinal cord compression, need for external beam radio-therapy or surgery for symptom control, and hypercalcaemia.

Agents that inhibit osteoclast activity, such as bisphosphonates and the RANKL inhibitor denosumab, reduce the number and time to development of SREs in studies in patients with solid tumour bone metastases.^{1,2} The use of these antiresorptive agents is standard practice in the management of patients with bone metastases from breast and prostate cancer, but is less well defined in patients with thyroid cancer. Although approximately 44% of patients with metastatic differentiated thyroid cancer have bone metastases,³ limited data are available regarding the rate of SREs in these patients and, therefore, the need for antiresorptive therapy within the context of their cost and potential toxicities is not well characterised.

Farooki *et al.* sought to better define the morbidity of bone metastases in a relatively large cohort of patients with differentiated thyroid cancer and bone metastases treated at the Memorial Sloan-Kettering Cancer Center over a 52 year period.⁴ In this retrospective study, the authors identified 245 patients with differentiated thyroid cancer who had bone metastases and sufficient medical data. They determined the occurrence of the first SRE after initial diagnosis of bone metastasis and subsequent SREs until follow-up or death.

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Competing interests

The authors declare no competing interests.

The researchers report that 78% (192 of 245) of patients developed an SRE either concurrent with diagnosis of the initial bone metastasis (51%; 97 of 192) or during the follow-up period (49%; 95 of 192). Of the 95 patients who developed an SRE during the follow-up period, the median time from diagnosis of bone metastasis to an SRE was 5 months (ranging 1 month to 9.2 years). Of those with an SRE, 64% (121 of 192) developed multiple SREs. The median time to the development of a second SRE was 10.7 months after the initial SRE (ranging 0–14 years). Moreover, mortality was significantly higher in patients with bone metastases who developed a single (68% mortality) or multiple (79% mortality) SREs than those who did not have an SRE (42% mortality). The median time from first SRE to final follow-up or death was 1.9 years (ranging 0–19.8 years).

Although 22% of patients received at least one dose of intravenous bisphosphonate therapy, the investigators could not determine if the rate of SREs was reduced or delayed in these patients. However, when the authors excluded the 54 patients who received at least one dose of a bisphosphonate, they found that the results were unaltered, with 74% developing at least one SRE. By contrast, a retrospective single-institution study by Orita *et al.* reported fewer SREs in patients treated with zoledronic acid.⁵ In their series of 50 patients with differentiated thyroid cancer and bone metastases treated over 38 years, Orita *et al.* found that 14% of the 22 patients treated with zoledronic acid developed SREs, whereas 50% of the 28 patients not treated with zoledronic acid developed SREs. However, the most common forms of SREs (need for radiation therapy or surgery for bone metastases) were not included in these analyses, which render the results of this study uninterpretable with regard to the prevention of SREs by zoledronic acid.

In the study by Farooki *et al.*, patients with bone metastases who developed SREs did not differ significantly in age at diagnosis, sex or sites of metastatic disease from those who did not develop SREs. As one would expect, however, patients who did not have an SRE were more likely to have classic papillary thyroid cancer than other aggressive histologic subtypes of thyroid cancer. 28 patients had radioiodine-positive disease that was not identifiable by other imaging modalities (nonstructural metastases). None of these patients had SREs. In fact, when these patients were excluded from the analysis, 88% of patients with bone metastases visible on cross-sectional imaging ended up having an SRE. Interestingly, 46% of first SREs occurred in patients with either one or two skeletal lesions, suggesting that widespread bony disease is not necessary for the development of SREs.

The percentage of SREs occurring in patients with differentiated thyroid cancer with bone metastases reported in the study by Farooki and co-workers is similar to that reported for patients with breast cancer and bone metastases,⁶ and is higher than that reported for patients with bone metastases of prostate or lung cancer.⁷ Importantly, the patients in the study by Farooki *et al.* were selected among those cared for in routine clinical practice, and unlike for breast, prostate, and lung cancer staging, it is not standard of care to screen or stage all patients with advanced differentiated thyroid cancer for bone metastases. Routine screening for bone metastases in advanced differentiated thyroid cancer could uncover far more cases of asymptomatic indolent bony disease.

Furthermore, although the study reports that the cohort of patients had differentiated thyroid cancer, 24% of the patients had poorly differentiated thyroid cancer, which is known to have a much more aggressive course.⁸ An inherent weakness of this study, as acknowledged by the authors, is the potential selection bias of patients with more aggressive disease and, therefore, at high risk of developing an SRE, given that the cohort studied is from a specialist referral centre.

Regardless of the study limitations, the data presented here are important, and highlight the fact that patients with thyroid cancer and bone metastases are at high risk of skeletal complications. This risk is particularly high for those with structurally visible disease on cross-sectional imaging and those with histologic subtypes other than classic papillary thyroid cancer.

Antiresorptive agents are FDA approved for all patients with solid tumour bone metastases to prevent SREs. However, probably the rarity of bone metastases in differentiated thyroid cancer (2–13%)⁹ and the previous lack of data regarding rates of SREs in patients with thyroid cancer and bone metastases have resulted in the undertreatment of these patients with antiresorptive therapy.

Clinical trials of antiresorptive agents in patients with thyroid cancer and bone metastases are clearly necessary to determine which agent is most effective, the proper duration of therapy, and which patients will benefit from the treatment. However, given the known efficacy of antiresorptive agents at decreasing SREs in patients with other solid tumour bone metastases and the high rate of SREs reported by Farooki *et al.*,⁴ we believe that patients with thyroid cancer and bone metastases visible on imaging (other than radioiodine imaging or bone scan alone) should be strongly considered for treatment with a bisphosphonate or the RANKL inhibitor denosumab, unless a clear contraindication exists. Ideally, such patients should be enrolled in clinical trials that compare the efficacy of antiresorptive therapies for the prevention of SREs.

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