

# NATURAL HISTORY OF MALIGNANT BONE DISEASE IN RENAL CANCER: FINAL RESULTS OF AN ITALIAN “BONE METASTASES” SURVEY

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## ABSTRACT\*

**Introduction:** Bone metastases are an emerging clinical problem in renal cancer patients as related survival increases. We report the final data of the largest survey for renal cell carcinoma patients.

**Methods:** 398 renal cancer patients with evidence of bone metastases have been included (all were dead at the time of study inclusion). Clinico-pathological data, data on survival and skeletal-related events (SRE), and data on skeletal-related therapies have been collected and statistically analyzed.

**Results:** The survey included 286 males and 112 females with median age: 63 (16-87), 31.4% with bone metastases at initial diagnosis of renal cancer and 31.1% with single bone metastasis. Lesion types were predominantly osteolytic (77%), with lower rates of mixed (14.6%) and osteoblastic (7.6%) metastases. Sites of lesions were spine (65.8%), pelvis (38.4%), long bones (31.6%), other (18.8%). Median time to bone metastases was 8 months (0-288) overall and 24 months (1-288) for patients without bone met at diagnosis. 71.1% of patients had at least one SRE, including pathologic fracture (12.6%), radiotherapy (61.8%), spinal compression (7.6%), bone surgery (14.8%), hypercalcemia (3.2%). Median number of SREs per patient was 1 (0-4); median time to first SRE was 2 months (0-72), to second SRE was 4 months (0-113), to third SRE was 11 months (1-108). Median survival was 12 months patients with at least one SRE was longer than in patients without SREs (14 vs 9 months). According to Memorial Sloan-Kettering Cancer Center (MSKCC) criteria, median time to skeletal disease was 24 months (0-288) in patients with good prognosis, 5 months (0-180) in patients with intermediate prognosis, and 0 months (0-77) in patients with poor prognosis. A total of 168 patients received zoledronic acid (ZOL) until worsening of performance status or death. In comparison with a control group (n = 162) the median time to first SRE was prolonged in the ZOL group (3 months vs 1 month for control; P<0.05). Five cases of ONJ have been diagnosed.

**Conclusions:** The present survey is the largest descriptive study of the natural history of bone disease in renal cancer patients. The effects of biological therapies on bone metastases are discussed.

\*This abstract reports data updates compared with the published abstract.

## INTRODUCTION

- Approximately 30% of patients with renal cell carcinoma (RCC) will develop bone metastases, which influence bone metabolism and place patients at risk for skeletal-related events (SREs; pathological fractures, radiotherapy, spinal cord compression, and hypercalcemia of malignancy)<sup>1</sup>
  - SREs have been correlated with decrements in quality of life and reduced survival in patients with bone metastases<sup>2</sup>
- Systemic treatments for RCC have traditionally included primarily interferon- $\alpha$  and interleukin-2; newer options include antiangiogenic agents and mTOR inhibitors
- Zoledronic acid (ZOL) is the only bisphosphonate approved for the treatment of patients with bone metastases for solid tumors other than breast cancer, to prevent and reduce the risk of SREs<sup>3,4</sup>
- Randomized trials evaluating bisphosphonates (including ZOL) have included only small numbers of patients with RCC, resulting in a lack of robust data<sup>5,6</sup>
  - Among a subset of patients with RCC (n = 74), ZOL reduced the risk of an SRE by 61% vs placebo (HR = 0.394; P = .008)<sup>5</sup>
  - There is a need for more real-world data
- This retrospective database analysis assessed the natural history of bone disease in patients with RCC in a large multicenter Italian study, and evaluated the efficacy of ZOL for reducing SREs in these patients

## METHODS

- Retrospective multicenter study of medical records of 398 patients with RCC treated at different centers in Italy
  - At the time of this study, all patients included had died from RCC
- Patients were identified as having bone metastases if  $\geq 2$  of the following criteria were met:
  - Physician reported patient as having bone metastases
  - $\geq 1$  bone metastasis identified via bone scan
  - Record of palliative radiation therapy to bone, or
  - Identification of bone metastases by another assessment (standard radiography, computed tomography scans, or magnetic resonance imaging of the skeleton)
- All the clinical variables were evaluated as predictors for shorter time to bone metastases, higher risk of skeletal morbidity (ie, SRE) and shorter time from SRE to death
  - Survival intervals were determined using Kaplan-Meier product estimates; differences in survival according to clinical parameters or treatment were evaluated by the log-rank test
  - Cox proportional hazards model was used for the survival analyses
- Medical records were evaluated for SREs and drug safety

## RESULTS

### Patient Characteristics

- The study included 398 patients; the median age was 63 years
  - Patients had predominantly multiple bone metastases
  - Most of the lesions were osteolytic (Table 1)
- 161 patients were treated with ZOL (4 mg every 4 weeks via 15-minute IV infusion, with dose adjustments based on creatinine clearance) and 186 patients were not treated with bisphosphonates

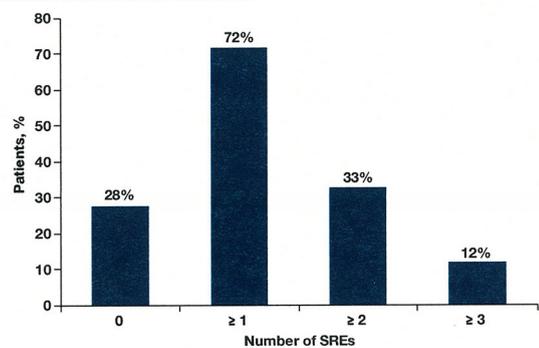
**Table 1. Patient Baseline Demographics (N = 398)**

Characteristic	
Age, y	
Median	63
Range	16-92
Sex, n (%)	
Male	286 (71.9)
Female	112 (28.1)
Tumor histotype, n (%)	
Clear cell	345 (86.7)
Papillary	22 (5.5)
Chromophobe	3 (0.76)
Other	16 (4.03)
Not available	12 (3.01)
Number of bone metastases, n (%)	
1	116 (29)
$\geq 2$	282 (71)
Location of lesion, n (%)	
Spinal column	271 (68.1)
Limb	155 (39)
Long bone	125 (31.4)
Other	68 (17.1)
Lesion type, n (%)	
Osteolytic	316 (79.4)
Osteoblastic	27 (6.8)
Mixed	51 (13.1)
Unknown	3 (0.7)

### Natural History of Skeletal-Related Events (SREs)

- 71.6% patients experienced SREs (Figure 1), and one-third of patients had  $\geq 2$  SREs

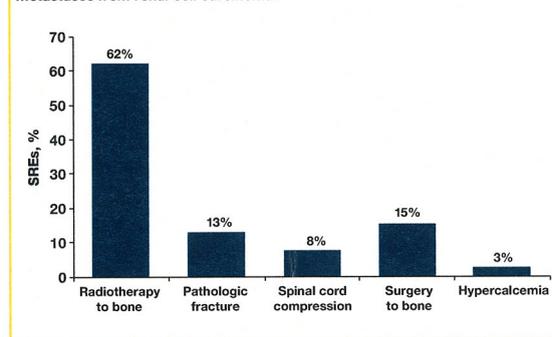
**Figure 1. Skeletal-related events (SREs) are common in patients with bone metastasis from renal cell carcinoma.**



## RESULTS (CONTINUED)

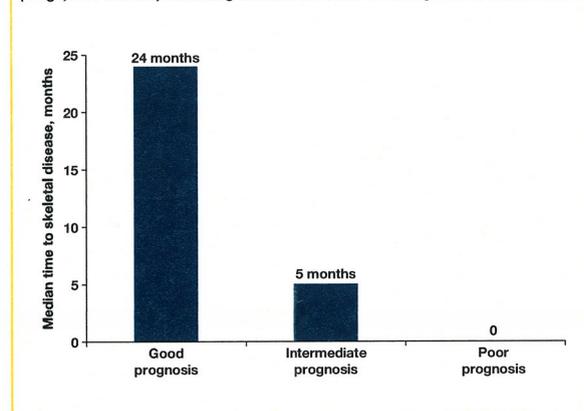
- Radiation to bone was the most common type of SRE, occurring in more than half of the cases (Figure 2)

**Figure 2. Incidence of skeletal-related events (SREs) in patients with bone metastases from renal cell carcinoma.**



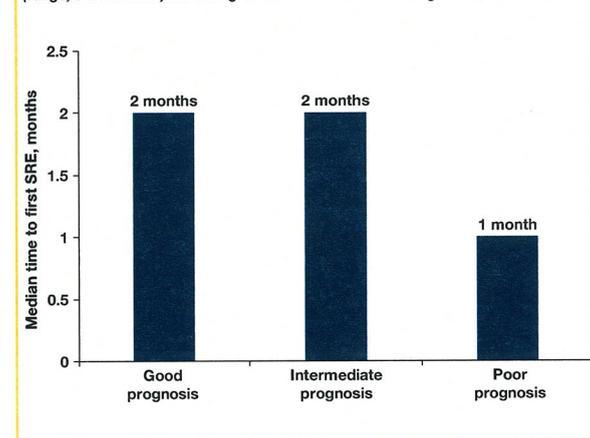
- Median time to diagnosis of bone metastasis varied depending on Memorial Sloan-Kettering Cancer Center (MSKCC) prognosis score (Figure 3)
- Median time to first SRE was also influenced by MSKCC score, albeit to a smaller extent (Figure 4)

**Figure 3. Comparison of time to bone metastases diagnosis for good (range, 0-288 months), intermediate (range, 0-180 months), and poor prognosis (range, 0-77 months) according to Memorial Sloan-Kettering Cancer Center score.**



## RESULTS (CONTINUED)

**Figure 4. Comparison of time to first skeletal-related event (SRE) for good (range, 0-72 months), intermediate (range, 0-26 months), and poor prognosis (range, 0-25 months) according to Memorial Sloan-Kettering Cancer Center score.**



### Efficacy of Zoledronic Acid

- Patients who received ZOL had a median survival of 15 months compared with 7 months in patients who did not receive ZOL (Table 2)
- Median survival was paradoxically shorter in patients with no SREs versus those with  $\geq 1$  SRE, possibly because of competing risks (ie, some patients might have died because of aggressive visceral metastases or other disease complications before they experienced SREs)
- Patients who received ZOL also had a significantly longer time to first SRE than patients who did not receive ZOL (Figure 5)

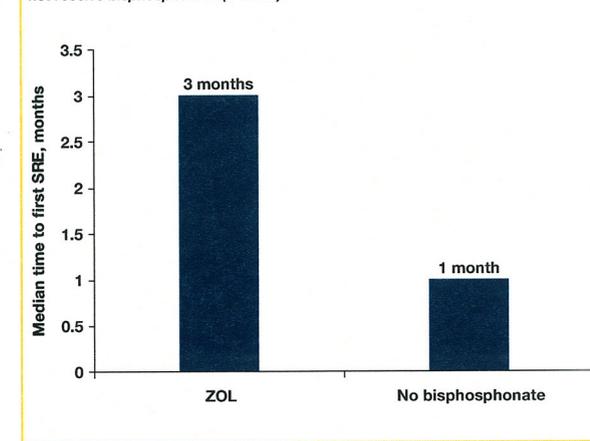
**Table 2. Median Survival After Bone Metastases Diagnosis**

Variable	Time, months	Range
All patients	12	1-178
By SRE history		
Patients with at least 1 SRE	14	1-178
No SRE	9	0-62
After first SRE	10	0-144
By bisphosphonate treatment		
ZOL treated	15	2-120
No bisphosphonate	7	1-178

Abbreviations: SRE, skeletal-related event; ZOL, zoledronic acid.

## RESULTS (CONTINUED)

**Figure 5. Comparison of time to first skeletal-related event (SRE) in patients with renal cell carcinoma receiving zoledronic acid (ZOL) (n = 181) and those who did not receive bisphosphonate (n = 186).**



## CONCLUSIONS

- This retrospective study (N = 398) was the first multicenter survey reporting the natural history of bone metastases in patients with RCC
  - The common SREs in patients with bone metastasis from RCC were similar to those reported for other solid tumors
- More than 70% of patients with RCC in this study had SREs, thereby underlying the importance of early detection and treatment for bone metastases in this setting
  - These data also show that patients with good prognosis remain at risk for SREs; therefore, proactive management of bone metastases is important throughout the RCC disease continuum
- These data confirm and extend prior reports of the beneficial effects of ZOL for reducing SREs in patients with RCC
  - In addition, ZOL-treated RCC patients with bone metastases had longer survival

### References

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