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Natural history of bone metastasis in colorectal cancer: final results of a large Italian bone metastases study

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Background: Data are limited regarding bone metastases from colorectal cancer (CRC). The objective of this study was to survey the natural history of bone metastasis in CRC.

Patients and methods: This retrospective, multicenter, observational study of 264 patients with CRC involving bone examined cancer treatments, bone metastases characteristics, skeletal-related event (SRE) type and frequency, zoledronic acid therapy, and disease outcomes.

Results: Most patients with bone metastases had pathologic T3/4 disease at CRC diagnosis. The spine was the most common site involved (65%), followed by hip/pelvis (34%), long bones (26%), and other sites (17%). Median time from CRC diagnosis to bone metastases was 11.00 months; median time to first SRE thereafter was 2.00 months. Radiation and pathologic fractures affected 45% and 10% of patients, respectively; 32% of patients had no reported SREs. Patients survived for a median of 7.00 months after bone metastases diagnosis; SREs did not significantly affect survival. Subgroup analyses revealed that zoledronic acid significantly prolonged median time to first SRE (2.00 months versus 1.00 month, respectively, $P = 0.009$) and produced a trend toward improved overall survival versus no zoledronic acid.

Conclusion: This study illustrates the burden of bone metastases from CRC and supports the use of zoledronic acid in this setting.

Key words: bone metastases, colorectal cancer, zoledronic acid

introduction

Colorectal cancer (CRC) is among the three most common cancers, with an estimated 1.2 million new cases diagnosed worldwide per year [1]. Although CRC is generally more aggressive than breast cancer, mortality rates are notably lower than for other solid tumors such as lung cancer [2]. Before the introduction of modern chemotherapy and targeted treatment options, bone metastases were reported in ~10% to 24% based on clinical and autopsy records of patients with advanced CRC ($N = 118$), and affected patients had limited survival [3]. More recently, a retrospective analysis of 252 patients with colon cancer showed that 5.5% ($n = 14$) of patients had bone metastases at primary diagnosis [4]. Patients with metastatic CRC are now typically treated with 5-fluorouracil and leucovorin and either oxaliplatin or irinotecan (FOLFOX or FOLFIRI), and the anti-vascular endothelial growth factor antibody bevacizumab or the anti-epidermal growth factor receptor antibodies cetuximab or panitumumab are added to these regimens when indicated [5–10].

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With the newer treatment regimens, median survival of >20 months has been reported for patients with advanced CRC [5–10]. However, the increase in overall survival in patients with metastatic cancer increases the likelihood that patients have the time to not only develop bone metastases during the course of their disease but also that the associated bone destruction will manifest within the patient's lifetime, resulting in potentially debilitating sequelae. The acute consequences of bone metastases include skeletal-related events (SREs; defined as pathological fracture, the need for radiotherapy or surgery to bone, spinal cord compression, and hypercalcemia of malignancy) that may undermine patients' function and quality of life [11]. These SREs have been correlated with significant decrements in quality of life and reduced survival [11]. However, despite the potentially devastating implications of bone metastases, there are limited data in the literature about the natural history of bone metastasis in patients with CRC [4, 11–16]. Here, we report the final data of a large Italian multicenter study on the natural history of patients with bone metastases from CRC.

methods

study design

This was a retrospective, observational multicenter study of medical records for patients treated at 16 oncology centers in Italy, who were diagnosed with CRC between November 1985 and May 2009. Data were collected from patients of all ages who received any standard treatment (i.e. not an experimental protocol or trial). All patients had been treated and followed according to the usual practice of their physicians. Only patients with CRC who had at least one bone metastasis during their disease course and who had died of CRC itself or disease-related complications before the start of the study were included. Patients were defined as having bone metastasis if two or more of the following criteria were satisfied: (i) physician reported patient as having bone metastasis; (ii) at least one bone metastasis identified via a positive bone scan; (iii) record of palliative radiation therapy to bone; or (iv) identification of bone metastasis by another assessment, such as standard X-rays, computed tomography (CT) scans, or magnetic resonance imagings of the skeleton.

Data were collected throughout the disease course for all cancer treatments, including surgery, radiation therapy, chemotherapy, and biological therapies. Variables assessed for prognostic correlations included gender, age, primary site, histotype, stage at diagnosis of primary cancer, tumor grade, adjuvant chemotherapy, time to appearance of visceral metastases, number of sites of visceral metastases, number and sites of bone metastases, time to appearance of bone metastases, presence of bone pain, times to first and subsequent SREs (from diagnosis of bone metastasis), SRE types, survival after first SRE, and type and times of bisphosphonate therapy.

statistical analysis

In the univariate model, all the clinical variables were evaluated as predictors for shorter time to bone metastasis, higher risk of skeletal morbidity (i.e. SRE), and shorter time from SRE to death. Patients who did not have a recorded date for a specific event were censored at the date of death. All survival intervals were determined by the Kaplan–Meier product-limit method [17]. The differences in survival according to clinical parameters or treatment were evaluated by the log-rank test [18] and described by the Kaplan–Meier method. Finally, the Cox proportional hazards model was applied to the multivariate survival analysis. All the significant variables in the univariate model were used to build the multivariate model of survival, and median values were derived from whole-month values rather than fractions. Patients included in the analysis were diagnosed with bone metastases after September 1988 and died before July 2009. SPSS software (version 17.00; SPSS, Chicago, IL) was used for statistical analysis. A P value <0.05 was considered statistically significant.

results

patient characteristics

After review of records for >2500 patients who had died from CRC, 264 patients with bone metastases who received zoledronic acid (48%) or no bisphosphonate (12%; unknown 40%) therapy were identified. At the time of chart review, all patients had died from their disease. Most patients had colon cancer, and tumor histology was mostly nonmucinous (Table 1).

characteristics of skeletal metastases

Bone metastases were primarily to the spinal column, with vertebral involvement in 65% of patients. By comparison, 34% of patients had metastatic disease in the hip or pelvis, 26% had metastatic disease in the long bones, and 17% of patients had osseous metastases in other sites (hands, feet, and skull). Of the 264 patients, 114 (43%) had single bone lesions during the course of the disease. Osteolytic lesions were more prevalent than mixed lesions (81% versus 13% of bone lesions, respectively), and mixed lesions were more prevalent than osteoblastic lesions (6%). At the time of diagnosis of bone lesions, the median intensity of pain [visual analogue scale (VAS) score, 0–10] reported by patients was 7.

clinical risk factors

The median time from primary CRC diagnosis to diagnosis of bone metastases was 11.00 months [95% confidence interval (CI) 4.7–13.1 months; Table 2]. In a univariate analysis exploring tumor site, tumor histology, tumor stage, tumor grade, node status, and use of adjuvant chemotherapy as risk factors, only tumor grade showed a significant correlation ($P < 0.001$) with the time to developing bone metastases (Table 2).

The median time to first SRE after the diagnosis of bone metastases was 2.00 months (95% CI 1.04–3.45 months). Radiation to bone was the predominant type of SRE, occurring in approximately half of the patients (Figure 1). Pathologic fracture was the second most common SRE, occurring in ∼10% of patients. Spinal cord compression from metastatic disease induced structural instability of the vertebrae and the requirement for orthopedic surgery occurred at a similar prevalence (6% each). Approximately one-third (32%) of patients with bone metastases from colon cancer did not have a reported SRE. Time to first SRE was significantly shorter for patients with osteolytic lesions (1.00 month versus 2.00 months for osteoblastic, $P < 0.001$). However, the number of bone metastases at presentation did not correlate with time to first SRE ($P = 0.109$) regardless of lesion type (i.e. osteolytic,

Table 1. Patient demographics and baseline disease characteristics

Characteristic	Patients, *n* (%) (*N* = 264)	No ZOL[a] (*N* = 31)	ZOL (*N* = 126)	Unknown (*N* = 107)
Tumor site				
Colon	163 (62)	21 (68)	78 (62)	62 (60)
Rectum	98 (37)	9 (29)	47 (37)	42 (39)
Unknown	3 (1)	1 (3)	1 (<1)	1 (<1)
Tumor histology				
Nonmucinous	174 (66)	24 (77)	95 (75)	55 (51)
Mucinous	56 (21)	7 (23)	31 (25)	18 (17)
Unknown	34 (13)	0	0	34 (32)
Tumor grade				
1	10 (4)	1 (3)	4 (3)	5 (5)
2	119 (45)	20 (65)	74 (59)	25 (23)
3	91 (34)	10 (32)	48 (38)	33 (31)
Unknown	44 (17)	0	0	44 (41)
Tumor stage				
T1	5 (2)	0	0	5 (5)
T2	22 (8)	2 (6)	12 (10)	8 (7)
T3	153 (58)	17 (55)	64 (51)	72 (67)
T4	54 (20)	NA	NA	NA
Unknown	30 (11)	NA	NA	NA
Nodal status				
N^-	51 (19)	6 (19)	31 (25)	14 (13)
N^+	157 (59)	21 (68)	73 (58)	63 (59)
Unknown	56 (21)	4 (13)	22 (17)	30 (28)
Metastatic status				
M0	104 (39)	12 (39)	50 (40)	42 (39)
M1	122 (46)	13 (42)	52 (41)	57 (53)
Unknown	38 (14)	6 (19)	24 (19)	8 (7)
Adjuvant chemotherapy				
Yes	62 (23)	10 (32)	30 (24)	22 (21)
Stage II	4 (6)	NA	NA	NA
Stage III	58 (94)	NA	NA	NA
No	154 (58)	15 (48)	60 (48)	79 (74)
Unknown	48 (18)	6 (19)	36 (29)	6 (6)
Stage at diagnosis				
Stage I	8 (3)	1 (3)	4 (3)	3 (3)
Stage II	31 (12)	4 (13)	15 (12)	12 (11)
Stage III	65 (25)	10 (32)	30 (24)	25 (23)
Stage IV	122 (46)	15 (48)	60 (48)	47 (44)
Unknown	38 (14)	1 (3)	17 (13)	20 (19)
Number of bone metastases, *n*[b]	NA	35	145	NA
Location of lesion				
Spine	—	13 (37)	65 (45)	—
Pelvis	—	10 (29)	34 (23)	—
Long bone	—	7 (20)	32 (22)	—
Other	—	5 (14)	14 (10)	—
Lesion type				
Osteolytic	—	28 (80)	116 (80)	—
Osteoblastic	—	3 (8)	12 (8)	—
Mixed	—	4 (12)	14 (10)	—
Unknown	—	0	3 (2)	—

[a]Patients were known not to receive any bisphosphonate therapy.
[b]Includes patients who had bone metastases at more than one site. Percentages are based on total number of metastases not number of patients.
Note that percentages may not total 100% because of rounding.
BP, bisphosphonate; N, node; NA, not available; ZOL, zoledronic acid.

osteoblastic, or mixed). Median survival after the first SRE was 4.50 months (95% CI 2.8–5.7 months) in the overall study population.

Table 2. Median time from primary cancer diagnosis to diagnosis of bone metastasis

Baseline characteristics	Patients, *n* (%) (*N* = 264)	Time, months	95% CI	*P* value
Tumor site				
Rectum	163 (62)	12.00	6.8–17.2	0.336
Colon	98 (37)	11.00	8.75–13.25	
Tumor histology				
Nonmucinous	174 (66)	11.00	7.65–14.35	0.069
Mucinous	56 (21)	9.00	6.56–11.44	
Tumor stage[a]				
2	22 (8)	12.00	0–28.96	0.216
3–4	207 (78)	13.00	10.22–15.78	
Tumor grade				
1	10 (4)	33.00	9.76–56.24	<0.001
2	119 (45)	16.00	11.48–20.52	
3	91 (34)	6.00	4.61–7.39	
Nodal status				
N^-	51 (19)	20.00	13–27	0.138
N^+	157 (59)	13.00	10.48–15.52	
Adjuvant chemotherapy				
Yes	62 (23)	23.00	9.43–36.57	0.402
No	154 (58)	20.00	15.26–24.75	
Overall	264 (100)	11.00	4.67–13.06	

[a]At initial diagnosis.
CI, confidence interval; N, node.

The median overall survival after diagnosis of bone metastases was 7.00 months (95% CI 5.75–8.70 months). In univariate analyses (Table 3), osteoblastic lesions ($P = 0.008$) or the presence of only one bone lesion ($P = 0.004$) correlated with longer median survival compared with osteolytic lesions or the presence of two or more bone lesions. Neither the occurrence of SREs ($P = 0.88$) nor use of zoledronic acid ($P = 0.161$) significantly correlated with survival after diagnosis of bone metastases.

bisphosphonate therapy

Of the 264 patients with confirmed bone metastases, 107 did not have data on bisphosphonate use. These patients were excluded, and a subgroup analysis was carried out on the patients with well-documented bisphosphonate treatment history. In this subset, 126 patients had received zoledronic acid (4 mg every 4 weeks via 15-min i.v. infusion, with dose adjustment based on creatinine clearance) and 31 patients had not received an i.v. bisphosphonate.

Baseline demographics and disease characteristics were generally similar between patients receiving zoledronic acid and those not receiving zoledronic acid (Table 1). Patients who received zoledronic acid had a significantly longer time to first SRE than patients who did not receive zoledronic acid (2.00 months versus 1.00 month from diagnosis of bone metastasis, respectively, $P = 0.009$) (Figure 2). Patients who received zoledronic acid had a median overall survival of 10 months (95% CI 8.09–11.91 months), which was a trend toward improved survival, compared with patients who did not receive zoledronic acid, in whom median survival was only 6.00

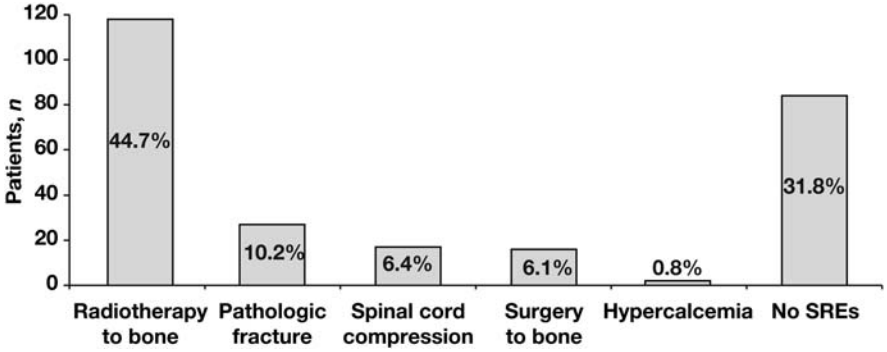

Figure 1. Incidence of skeletal-related events (SREs) occurring in patients with bone metastases from colorectal cancer ($N = 264$) egardless of therapy.

Table 3. Median survival after bone metastasis diagnosis

Variable	Time, months	95% CI	*P* value[a]
Bone metastasis type			
Osteolytic	7.00	5.87–8.13	0.008
Osteoblastic	21.00	5.90–36.11	
Number of bone metastases			
1	9.00	6.34–11.67	0.004
>1	6.00	4.9–7.1	
SREs			
No	7.00	5.43–8.57	0.88
Yes	7.00	5.58–8.43	
Bisphosphonate treatment			
ZOL	10.00	8.09–11.91	0.161
No ZOL	6.00	4.46–7.54	
Overall	7.00	5.75–8.70	

[a]Log-rank test.
CI, confidence interval; SRE, skeletal-related event; ZOL, zoledronic acid.

Figure 2. Comparison of time to first SRE in colorectal cancer patients receiving zoledronic acid ($n = 126$) and those who did not receive zoledronic acid ($n = 31$, $P = 0.009$). SE, standard error; SRE, skeletal-related event; ZOL, zoledronic acid.

months (95% CI 4.46–7.54 months, $P = 0.161$). In multivariate analyses, both osteolytic versus osteoblastic bone metastases [hazard ratio (HR) = 4.92, 95% CI 1.75–13.78, $P = 0.002$] and zoledronic acid versus no bisphosphonate therapy (HR = 0.73, 95% CI 0.48–0.99, $P = 0.046$) were independent factors that correlated with longer time to first SRE.

discussion

This retrospective study was the first multicenter survey to chronicle the natural history of bone metastasis in patients with CRC. Approximately 10% of the >2500 CRC patients in this analysis had bone metastases clearly documented in their medical records. Because of the retrospective nature of the review, only patients with at least one known bone metastasis were evaluated, and some patients with poorly documented bone metastases would not have been identified. Patients with documented bone metastases, but who were alive at study entry, were excluded. Therefore, the incidence of bone metastases from CRC may be higher than the 10% of cases we identified. Historically, the incidence of bone metastases from CRC has been ~6%, but a retrospective analysis (1993–2002) of this patient population found that the rate has increased to 10.4%, likely due to improved survival and the prolonged time patients are at risk for this complication [16]. The incidence of bone metastases from CRC reported here is consistent with this analysis. Furthermore, bone metastases were reported in ~10% to 24%, based on clinical and autopsy records of patients with advanced CRC ($N = 118$) [3]. In a more recent retrospective analysis of positron emission tomography and/or CT scans from 252 patients with colon cancer, 5.5% ($n = 14$) of patients had bone metastases at primary diagnosis [4]. The median time between primary diagnosis and diagnosis of bone metastases was 21 months, and all patients with bone lesions also had visceral metastases [4]. These data may reflect improved early diagnosis of colon cancer in the last decade.

Colorectal cancers are relatively aggressive tumors, and the current study revealed a median time to detection of bone metastases in patients of 11.00 months. With current median survival reports of >20 months for patients with metastatic CRC [5–9, 19], it is likely that many patients may develop bone metastases during the course of their disease and survive for prolonged periods of time at risk for SREs. Better understanding of the natural history may provide insight into which patients should receive additional monitoring for metastasis to bone to allow early treatment to prevent SREs. For example, in the current analysis, tumor grade was found to be predictive for the development of bone metastases from CRC.

This evaluation of the natural history of bone metastasis secondary to CRC suggests that there is a very aggressive

disease course in bone that can result in potentially debilitating SREs within a short time. According to the medical records, the median time to developing the first SRE after diagnosis of bone metastases was only 1.00 month. Therefore, diagnosis of bone metastases in a CRC patient should warrant immediate attention and close follow-up. Patients with bone metastases from CRC may have prolonged negative effects from potentially disabling SREs, illustrated by the median survival after development of bone metastases in our patients of 7.00 months and median survival after onset of first SRE of 4.50 months. Unfortunately, patients' function and quality of life may be reduced by bone metastases and the associated SREs, leading to increased requirements for supportive care, thus creating a considerable burden for patients and the health care system. Common complications from bone metastases in CRC patients are similar to those reported in patients with bone metastases from other solid tumors [11], and the most commonly reported events included severe bone pain requiring palliative radiotherapy to bone, pathologic bone fractures, and spinal cord compression.

This retrospective analysis is consistent with the phase III trials of zoledronic acid in patients with bone metastases from solid tumors, including breast, lung, and prostate cancer [20–22], and is the first study to provide support for zoledronic acid as an effective therapy for the prevention of SREs in patients with bone metastases from CRC. In the current analysis, the median time from diagnosis of bone metastases to the first SRE in patients who received zoledronic acid was approximately double that of patients who received no i.v. bisphosphonate therapy (2.00 months versus 1.00 month, respectively, $P = 0.009$). Although the difference did not achieve statistical significance, patients with bone metastases from CRC who received zoledronic acid showed a trend toward improved overall survival versus patients who did not receive zoledronic acid. Indeed, a population-based case-controlled analysis of 933 pairs of postmenopausal women (patients and controls) showed that bisphosphonate use for treatment of postmenopausal osteoporosis for >1 year was associated with a significant reduction in the relative risk for developing CRC (relative risk = 0.50, 95% CI 0.35–0.71) [23]. Moreover, potential progression-free or overall survival benefits have been reported with zoledronic acid in other advanced cancer settings [24–30]. Some of these analyses suggest that the benefits of zoledronic acid could extend beyond SRE prevention and may have anticancer potential.

Limitations of this study include its retrospective design and missing information. Notably, the missing data may introduce some bias into this trial. Data are missing for tumor stage (12%), nodal status (21%), and metastases (14%). Moreover, data regarding bisphosphonate use were not available for 40% of patients.

Although there are guidelines for use of bisphosphonates in patients with other specific tumors or solid tumors in general, there is little guidance specific for patients with CRC [31–34]. This retrospective analysis of real-world data demonstrates that bone metastases from CRC are typically aggressive and result in the relatively rapid onset of SREs in the majority of patients. Furthermore, the correlative analyses support the use of zoledronic acid for the treatment of patients with bone metastases from CRC to decrease the incidence of SREs and possibly provide survival advantages.

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disclosure

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