

Management of Painful Bone Metastases: Our Experience According to Scientific Evidence on Palliative Radiotherapy

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Abstract. *Aim: Our aim was to evaluate retrospectively the role of the radiotherapy in the multi-disciplinary management of pain due to bone metastases. Patients and Methods: A total of 305 patients received radiotherapy with or without bisphosphonate and analgesic drugs. Tolerability and efficacy were evaluated using a Numerical Rating Scale, Pain Intensity Difference evaluation scale related to administration of the drug, a 5-point verbal scale of the patients' general impression. Results: We found differences in some patient subgroups: pain reduction was significantly more evident in patients treated with a single-fraction radiotherapy scheme. Overall, 68% of patients experienced an improvement in pain control using concomitant drugs during radiotherapy. Conclusion: Our study underlines the role of radiotherapy in the management of metastatic bone pain. The use of rapid-onset opioids to prevent predictable pain is a crucial step in managing radiotherapy. An interdisciplinary approach is recommended.*

Up to 90% of patients with metastatic cancer experience cancer-related pain. Approximately half or more of these patients may experience pain related to bone metastases. Treatment of such painful metastases may reduce pain intensity and improve the quality of life (1). Pain associated with bone metastases is a common debilitating manifestation of malignancy and its treatment requires a multi-disciplinary approach, requiring both pharmacological and radiation

therapies (RT) (1-4). Therefore, several professionals (radiation oncologist, pain-therapist, oncologist, and palliative care professionals, specialized nurses) should collaborate for a proper care of patients affected by bone metastases (5). This inter-disciplinary approach is also underlined in an Italian law (number 38/2010). In article 5, the law identifies several specialists, including radiation oncologists, that should have specific tasks/duties in the field of palliative care (6). RT has an important role in the management of pain, especially when the pain is caused by bone metastases. Indeed, approximately one half of all prescribed RT is given for palliation of symptoms, including pain (7). According to the Italian law 38/2010, the diagnosis and treatment of pain is mandatory in all clinical settings. Taking into account this point, the aim of the present study was to assess retrospectively the role of the RT in the multidisciplinary management of pain due to bone metastases.

Patients and Methods

In one year, a total of 305 patients were treated in five RT departments in Naples, Italy, for palliative purposes. The total number of treatments was 458. All patients had a documented diagnosis of painful bone metastases: 72.3% were females and 27.7% were males, aged 62.49±12.21 years. The majority of patients reported breast cancer (Table I). Multiple metastases were found in 98.6% of patients, with the most common site being the spine (47.8%) as reported in Table I.

All patients received an appropriate treatment delivered by 6 MV photon linear accelerator, except 24, whom were treated with helical tomotherapy (HT). Decisions regarding RT, including fractioned dose and technique, were individualized according to clinical conditions, primary tumor site, tumor natural history, and life expectancy in collaboration with the oncological team.

Patients with longer life expectancy, better performance status and increased bone stability, were preferentially subjected to a total RT dose of 20 Gy (4 or 5 fractions) or 30 Gy (10 fractions), while

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those with shorter life expectancy, lower performance status, or bone instability, were treated with 8 Gy (single-fraction). Osteolytic lesions, after a clinical evaluation by oncologists, could be concomitantly treated with bisphosphonates; this therapy could also be prolonged after the end of RT procedures for a maximum of twelve months. According to Italian law 38/2010, during RT, patients were treated with short-acting opioids (SAO) or rapid-onset opioids (ROOs) in order to manage predictable pain or exacerbations of pain due to positioning and set up procedures, to avoid interruption of RT.

Patients were monitored before and six months after the end of treatment. Informations regarding pain intensity and performance status were collected at these times. Pain was measured by a 11-point Numeric Rating Scale (NRS), where 0 means absence of pain and 10 means the worst tolerable pain. Performance status was evaluated by the Karnofsky Index (KI). Patients receiving analgesic therapy with opioids and who reported Breakthrough cancer pain one to four times day in the period previous to RT were treated with ROOs before starting the positioning procedures related to RT. We evaluated tolerability and efficacy by NRS for the intensity of the pain, pain intensity difference (PID) for the difference of intensity of pain with administration of the drug, and general impression (GI) for the evaluation expressed by the patients themselves using a 5-point verbal scale.

A session of RT was considered successfully concluded if there was no increase of pain (PID >1) and if the session was regularly carried out. Moreover, we defined responders as those patients who had a PID <2 at the end of RT.

Statistical analysis. During the analysis, all the variables considered in this Study were evaluated, and for each of these descriptive statistics were carried out: mean, standard deviation, range, minimum and maximum values for continuous variables, absolute and relative frequencies for categorical variables. The descriptive analyses were conducted for the total population and for the subgroups made of subjects broken down by primary tumor, dose of Gy, gender and bisphosphonates at baseline and after 180 days. In addition to analyzing the impact of dose of Gy on NRS and Karnofsky Index were launched Student's *t*-test (with Bonferroni-Holm for independent samples and paired) and one-way ANOVA (preceded by the analysis of the theoretical distribution-kurtosis-and by the between and within group variance test) for the correct inference analysis of all possible differences on primary tumor with or without presence/absence of bisphosphonates. Possible interdependence between two or more variables, and possible associations between clinical characteristics and therapeutic interventions (dose of Gy) administered and placed in the Study were evaluated, using statistical tests of parametric and non-parametric, even at multivariate level (Chi-square, Binomial Test). Data was processed using SPSS® (IBM, Armonk, New York, USA) version 10.0.

Results

A single fraction of RT (8 Gy) was used in 37.8% of cases, whereas 37.3% and 22.7% of cases were treated with 10 fractions of RT (30 Gy) or five fractions of RT (20 Gy), respectively. The mean pain intensity value at baseline was 7.31±1.89 and the mean KI was 68.82±14.43. We found differences in terms of reduction of pain in some subgroups of patients.

Table I. Number and percentages of patients with primary cancer and metastases.

	No.	%
Primary cancer site		
Breast	193	42.1
Lung	103	22.5
Prostate	31	6.8
Gastrointestinal	37	8.1
Urinary	26	5.7
Other	68	14.8
Total	458	100
Metastasis site		
Spine	219	47.8
Pelvis	103	22.5
Extremities	79	17.2
Extremities + pelvis	8	1.7
Spine + pelvis	14	3.1
Other	35	7.6
Total	458	100

In particular, in patients affected by bone metastases from breast cancer, the mean baseline NRS was 7.32±1.98 and after 180 days, it was significantly reduced to 4.36±2.64 ($p<0.001$). The baseline KI was 69.61±13.42 and after 180 days significantly increased to 79.21±12.19 ($p<0.001$). In patients affected by bone metastases from lung cancer, the NRS at baseline was 7.19±1.36 and decreased to 4.0±2.79 after 180 days ($p<0.001$), and in those with metastases from prostate cancer, the NRS at baseline was 7.92±1.89, significantly decreasing to 2.5±3.07 after 180 days ($p<0.001$).

A minority of patients were affected by bone metastases from other tumor types, since we were unable to analyze them definitively. We analyzed the breast cancer sub-group in order to understand the effect of RT because this sub-group represented the largest uniform group in our follow-up (Table II).

For the breast cancer cohort overall, the mean NRS was 4.36±2.64 and the mean KI was 79.21±12.19 at the end of the study period. However pain reduction was significantly more evident in patients treated with a single fraction of 8 Gy ($p<0.001$ ANOVA test) when compared with treatments delivered with 20 Gy and 30 Gy. Furthermore, patients with breast cancer who received bisphosphonates had achieved greater benefits in terms of reduction of pain, although not statistically significantly, and in KI ($p<0.05$ *t*-test), regardless of the received dose of radiation (Table III). All patients treated previously with ROOs in order to prevent severe pain from positioning completed the RT. Regarding the difference in pain intensity, 72% of patients were considered responders (having a PID <2 at the end of RT), while 68% of patients expressed their own satisfaction with the pharmacological treatment associated with RT, based on the GI assessment.

Table II. *Numeric Rating Scale (NRS) and Karnofsky Index (KI) for breast cancer subgroups receiving different fractionation dose of radiation.*

Dose (no. of fraction)	Baseline			After 180 days		
	No. of patients	NRS	KI	No. of patients	NRS	KI
8 Gy (1)	36	7.46±2.35	62.22±18.38	32	2.97±2.77	74.06±16.82
20 Gy (5)	35	6.75±2.13	72.65±9.63	35	4.72±2.52	79.71±10.14
30 Gy (10)	65	7.59±1.32	71.11±10.94	65	5.06±2.25	79.38±12.65

Discussion

RT provides palliation of painful bone metastases in 50-80% of patients with up to one-third of patients achieving complete pain relief (5). When pain is present, the underlying mechanism may be the stretching of periosteum by tumor, mechanical damage to bone at the tumor site, neurogenic pain resulting from nerve entrapment by the tumor (7). RT is an efficient treatment in achieving pain relief. Many randomized trials have reported equivalent pain relief among different fractionation schemes (30 Gy in 10 fractions, 20 Gy in five fractions, and a single fraction of 8 Gy), although longer treatment has the advantage of lower incidence of re-treatment of the same site (5, 8-11). Usually the decision of the fractionation scheme depends on both the conveniences to the patients and caregiver (5). Moreover, the patient's clinical condition, primary tumor site and its natural history, and life expectancy should be considered in order to treat the patient in the most clinically appropriate way.

RT can be complicated by the onset of exacerbations of pain due to positioning and maintenance of the position during RT (12). This can determine the need for interruption of the therapeutic session or even of the therapy cycle (8). Recent guidelines (13-15) recommend the use of immediate release-morphine for the treatment of predictable pain. In clinical practice, the use of immediate-release morphine before the beginning of RT allows a higher number of patients with breakthrough pain to complete the scheduled RT (12).

Our analysis confirmed the efficacy of a single-fractionation scheme (8 Gy) in providing pain reduction due to bone metastases in patients with breast cancer who had a statistically lower baseline KI (62.22±18.38). At follow-up, KI remained improved in breast cancer patients treated both with multiple sessions and a single session of RT. Few patients (n=5) scheduled for one single radiation required new treatments to achieve a better reduction in pain.

In our study, bisphosphonates, which have an analgesic efficacy in patients with painful bone metastases from solid tumors (16, 17) seemed to aid the analgesic effect of RT. Patients who were scheduled to receive RT may experience pain and the RT team must be alerted to manage this

Table III. *The table shows changes of pain by Numeric Rating Scale (NRS) and Karnofsky Index (KI) in patients with and without adjuvant therapy based on bisphosphonates. Difference between final (after 180 days) and baseline values.*

	Bisphosphonate use				p-Value
	No. of patients		Difference in NRS		
	Yes	No	Use	Non-use	
NRS	78	26	-3.11	-3.38	p=0.681
Karnofsky Index	75	23	12.0	5.6	p<0.0001

symptom to prevent pain from positioning-based therapies using opiates and adjuvants for better global management of cancer patients (8, 12). Indeed, in some cases, we administered ROOs in order to prevent or treat the exacerbation of pain. Incidental (or procedural) pain may negatively-impact RT, requiring interruption of the therapeutic session or even the entire therapy cycle and preventing correct management of the patient and an appropriate and effective use of resources (8).

Conclusion

Our study underlines that radiotherapists have to participate in the management of cancer pain, and in particular for patients with pain due to bone metastases. It also highlights the importance of new scientific knowledge and legislation in the management of these patients. The use of ROOs to prevent predictable pain in patient with cancer is a crucial step in managing RT. Moreover, an interdisciplinary approach in pain management is recommended in order to choose the best therapeutic option available. A combination of RT with pharmacological treatment should be taken on the advice of pain specialists and palliative care professionals.

Competing Interest

There are no financial competing interests to declare.

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