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The INTER-ROMA Project - A survey among Italian radiation oncologists on their approach to the treatment of bone metastases

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ABSTRACT

Aims and background. Radiotherapy has an established palliative role for bone metastases but despite the large number of patients treated there is still controversy surrounding the optimal radiotherapy schedule to prescribe. The aim of this survey was to determine the decision patterns of Italian radiation oncologists in four different clinical cases of patients with bone metastases.

Methods and study design. During the latest national meeting of the Italian Association of Radiation Oncology (AIRO), four clinical cases were presented to attending radiation oncologists. The cases were different with respect to the histology of the primary tumor, performance status, pain before and after analgesics, tumor site, and radiological characteristics of the metastatic lesions. For each clinical case the respondents were asked to give an indication for treatment; prescribe doses, volumes and treatment field arrangements; decide whether to prescribe prophylactic supportive therapy or not; and provide information about factors that particularly influenced prescription. Finally, a descriptive statistical analysis was performed.

Results. Three hundred questionnaires were distributed to radiation oncologists attending the congress. One hundred twenty-five questionnaires were returned but only 122 (40.6%) were adequately completed and considered for the analysis. Considerable differences were observed among radiation oncologists in prescribing and delivering radiotherapy for bone metastases. There was also a notable divergence from international guidelines, which will be discussed in this report.

Conclusions. Despite the results of clinical trials, Italian radiation oncologists differ considerably in their decisions on treatment doses and volumes. National guidelines are needed in order that patients can be treated uniformly and better data will become available for evidence-based palliative radiotherapy.

Key words: INTER-ROMA, survey, palliative radiotherapy, bone metastases, patterns of care.

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Introduction

Bone metastases are frequent in advanced-stage cancer and constitute a common cause of morbidity, causing pain, reduced mobility, and impaired quality of life. Primary tumor sites with a high propensity for bone metastases include the lung, kidney, and thyroid (with bone metastases in 30-40% of cases at autopsy) and the prostate and breast (with bone metastases in 70% at autopsy)[1].

Palliative radiotherapy (RT) has an established role in treating cancer pain due to bone metastases[2]. Even if it is difficult to compare response rates in the published

studies due to a lack of common endpoints and criteria, overall pain relief has been found to vary from 59% to 90%[3]. Moreover, palliative RT for bone metastases accounts for a considerable proportion of the workload of RT departments[4].

Despite the large number of patients treated for bone metastases, there is still controversy surrounding the optimal fractionation schedule, total RT dose to deliver, and use of supportive care during RT. Also the criteria to take into account for evidence-based decision-making are not well defined.

Different doses and fractionation schedules have been tested in randomized trials, and the results from most of these trials demonstrated that a large single dose (e.g., 8 Gy) and more fractionated radiation (e.g., 30 Gy in 10 fractions) provided similar symptom control[5-9]. However, even if many randomized trials and overviews have addressed this issue, it has been reported that the quality of the published evidence comparing different schedules of treatment for palliative RT of bone metastases was suboptimal and that the studies presented potential bias and therefore cannot be reliably evaluated[10].

Despite these limitations, most of the studies found that 8-Gy single-fraction treatments are equivalent to higher doses (20 Gy in 4 fractions or 30 Gy in 10 fractions) for the endpoint of pain response rates[5-9,11-14]. At the same time, in several studies the re-treatment and fracture rates were higher in the arms where single-fraction schedules were used[8,9,13,14]. Two meta-analyses confirmed these conclusions[15,16].

It has been reported that the management of bone metastases must take into account the predicted duration of a patient's survival. Prognostic factors predicting a survival duration of <6 months include low performance status (ECOG ≤3 or Karnofsky ≤50), visceral organ involvement, rapid and extensive development of bone metastases, and cachexia[3].

The choice of fractionation for palliative RT is likely to have also personal, logistic and financial implications, particularly for busy centers with long waiting times. In real life, all the clinical data mentioned above have to be considered and evaluated, taking account also of local constraints. This makes the optimal treatment choice for painful bone metastases difficult and not uniform among centers[17-25]. Some studies analyzed also the impact of the patient's preference on the choice of treatment[26,27].

The INTER-ROMA Project is a national survey conducted by Young AIRO (Italian Association of Radiation Oncology) on behalf of the AIRO Palliative Care Group to assess the patterns of care in palliative RT for bone metastases among Italian radiation oncologists as well as the criteria that influence the choices. In this article we report the final results of this study.

Material and methods

Population and setting

During the latest AIRO National Congress, 300 anonymous questionnaires were presented to radiation oncologists attending the congress. The questionnaire was composed of 2 parts. In the first part details were collected about the radiation oncologist filling in the questionnaire (working region in Italy, public or private hospital, academic or non-academic title, presence or absence of trials in palliative RT in his/her center). The second part described 4 clinical cases of patients having bone metastases (Table 1). The cases differed in tumor histology, site and radiological characteristics of the lesion, and pain level before and after analgesics as defined by visual analog scale (VAS). The authors of the questionnaire had sought to create 4 everyday cases in order to assess the real-life choices in prescribing RT for bone metastases. Every clinical case was presented according to the same scheme. The questions are summarized in Table 2.

Inclusion and data collection

Three-hundred questionnaires were given to radiation oncologists before the start of the congress at the time of registration at the desk. Completed questionnaires were returned at the end of the congress. Only questionnaires containing all the answers regarding at least 3 clinical cases were considered for the final analysis. A descriptive analysis of every item of the 2 parts of the questionnaire was performed. The SPSS statistical software (SPSS for Windows, v. 14.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

One hundred twenty-five of the 300 questionnaires were returned, but 3/125 questionnaires presented only 2 correctly filled in clinical cases and were therefore excluded. The final statistics were calculated on 122 questionnaires (40.6% of the total distributed).

Radiation oncologist details

Information about the radiation oncologist filling in the questionnaire was available for 113/122 questionnaires (91.8%). Most radiation oncologists answering this part of the survey were based in Lombardy (13.1%) or Lazio (11.5%). The majority worked in public hospitals (58.2%), while 25.8% worked in academic hospitals. We found that 66.4% of the radiation oncologists did not have an academic function (*vs* 14.8% who did) and 9.8% were residents. Only 4/122 radiation oncologists declared having a clinical trial on palliative RT running at their department.

Table 1 - Description of the clinical cases

Clinical case #1	– 64-year-old woman, PS: 0 (ECOG) – Breast cancer in 1999, pT2N0M0 ER+/PR-. She underwent lumpectomy + adjuvant radiotherapy (tangential fields 50 Gy + boost to tumor bed 10 Gy) + hormonal therapy with aromatase inhibitors for 5 years – Negative follow-up until today – Dorsal pain (D9-D10) + mild elevation of CA 15-3: bone scintigraphy and MRI of spine. Total-body CT scan: negative – Bone scintigraphy: multiple sites of pathological uptake particularly at the dorsal level (D3-D5-D9-D12). MRI: multiple spinal secondary mixed lesions (osteoblastic and osteolytic metastases). Symptomatic sites present secondary lesions. No radiological or clinical signs of spinal compression. No risk of immediate bone fracture – VAS: 7 without analgesics, 5 after regular non-opioid analgesics (first step of WHO pain scale)
Clinical case #2	– 68-year-old woman, PS: 1 (ECOG) – Right lung cancer in 2005, pT2N1M0. She underwent lobectomy + adjuvant chemotherapy. Radiotherapy has never been performed in the clinical history of the patient – Negative follow-up until today – Because of lumbar pain (L2-L3), she underwent bone scintigraphy and spine MRI. Total-body CT scan + brain CT scan: 3 hepatic lesions – Bone scintigraphy: multiple sites of pathological uptake. Spine MRI: multiple spinal secondary osteolytic lesions. Symptomatic sites present secondary lesions. No radiological or clinical signs of spinal compression. No risk of immediate bone fracture – VAS: 8 without analgesics, 3 after regular weaker opioid analgesics (second step of WHO pain scale)
Clinical case #3	– 73-year-old man, PS: 0 (ECOG) – Prostate cancer in 1998, cT2N1M0, Gleason score 4+4, initial PSA: 15 ng/mL, treated with radiotherapy (pelvic nodes: 46 Gy; prostate: 74 Gy) + concomitant and adjuvant (3 years) hormonal therapy with LH-RH inhibitor – Negative follow-up until today – Because of rising PSA, the patient underwent pelvic MRI + bone scintigraphy – Pelvic MRI: negative. Bone scintigraphy: solitary bone metastasis of right femoral diaphysis. CT scan of femurs: osteoblastic lesion of 3 cm diameter at diaphysis of right femur. No signs of fracture – VAS: 0 (asymptomatic patient)
Clinical case #4	– 78-year-old man, PS: 2 (ECOG) – Left lung cancer in 2007, pT3N0M0, treated with left pneumonectomy + adjuvant chemotherapy (6 cycles) – Negative follow-up until today – Sudden dorsal (D5-D6 e D10) and lumbar (L4) pain. No clinical signs of spinal compression. The patient does not report any other symptomatic site – MRI of the spine: multiple spinal secondary osteolytic lesions. Radiological signs of dorsal spinal compression (D10). Risk of pathological fracture at cervical level (C3). Total-body CT scan: multiple liver and lung metastases – VAS: 9 without analgesics, 3 after regular opioid analgesics (transdermal fentanyl 50 μg + NSAIDs if necessary, third step of WHO pain scale)

PS, performance status; VAS, visual analog scale; NSAIDs, non-steroidal anti-inflammatory drugs.

Descriptive analysis of clinical cases

Table 3 summarizes the main results of all questionnaires, showing salient differences between the 4 clinical cases. An analytical analysis is shown in Table 4. All percentages reported in the tables concern only data of physicians who declared they would treat the patient. For example, in Table 3, 65.5% of the physicians who said they would treat the patient would deliver 30 Gy in 10 fractions. As Table 4 illustrates, there were remarkable differences in the 4 clinical cases.

With regard to doses and volumes, 30 Gy in 10 fractions was the generally preferred schedule, although only for cases 1 and 3 more than 50% of radiation oncologists agreed on this fractionation.

A single posterior field was the preferred beam arrangement for the treatment of spinal metastases (41.3% and 50.4% for clinical case 1 and 2, respectively). There was major consensus about treating the femur with anteroposterior fields (95.7%) and delivering the dose only to the gross tumor volume (GTV) (74.3%) rather than the entire femur (23.1%). Most radiation oncologists (56.4%) would deliver 30 Gy.

Performance status and prognosis were the main criteria guiding treatment prescription and modality. Responsiveness to analgesics was an important criterion, but not the most important overall.

The comfort of the patient turned out to be a minor criterion (chosen by 7.7-13.2% of radiation oncologists) and this is surprising for a treatment where quality of life should be one of the reasons to treat the patient but also to choose one treatment rather than another.

None of the radiation oncologists considered financial aspects an important criterion to take into account when deciding if and how to treat a patient.

Discussion

This is the first survey on the pattern of care of Italian radiation oncologists. The main reason to conduct this survey was that, even if bone metastases are a frequent occurrence in advanced malignant diseases and RT is widely used in treating symptomatic secondary bone lesions, the patterns of care of radiation oncologists are

Table 2 - Questions proposed to radiation oncologists for every clinical case

Question	Proposed answers
Do you treat this patient?	○ Yes ○ No, I prefer to optimize the medical therapy before treating the patient
Radiotherapy doses	○ 300 cGy × 10 ○ 400 cGy × 5 ○ 800 cGy × 1 ○ Other dose – specify: _____
Radiotherapy volumes*	○ Involved vertebra + 2 contiguous vertebrae above and below ○ Involved vertebra + 1 contiguous vertebra above and below ○ Only symptomatic vertebra ○ Other volumes – specify: _____
Field position	○ 1 posterior field ○ 2 AP-PA fields ○ 3 fields (1 post + 2 lateral fields) ○ 4 fields (1 ant + 1 post + 2 lateral fields) ○ Other – specify: _____
Prophylactic supportive therapy (multiple answers allowed)	○ Topical therapy for skin reactions ○ Treatment for nausea/vomiting ○ Proton pump inhibitors ○ Corticosteroids ○ Other prophylactic supportive therapy Specify: _____ ○ No prophylactic supportive therapy
Please indicate factors that influenced your choices (multiple answers allowed)	○ PS ○ Disease extent ○ Initial VAS ○ Response of VAS to analgesics ○ Site of metastasis ○ Patient age ○ Patient prognosis ○ Radiological aspect of the lesions ○ Expected RT toxicity ○ Personal habits ○ Patient comfort ○ Waiting list of your center ○ Financial aspects (reimbursement of radiotherapy treatment)

AP-PA, anteroposterior-posteroanterior; PS, performance status; VAS, visual analog scale.
*In case 3 the proposed volumes were: GTV + margins, the entire right femur, other volume (specify).

not uniform and treatment may vary widely between countries and, in the same country, between physicians[28-33]. In 2000, Chow *et al.*[28] stated that even if "local field external radiotherapy remains the mainstay of therapy … for bone metastases … the reasons why the results of randomized studies on bone metastases have no impact on the patterns of practice are worth exploring." Pergolizzi *et al.*[30] and Fairchild *et al.*[20] reached the same conclusion 4 and 9 years later.

As we described in the introduction, different clinical, technical and local issues may have an impact on the decision to prescribe RT but also on the indication for RT treatment[3,8-15,22-25]. There are different reasons for this situation.

First of all, the issue of defining the indication for RT treatment is rather complex. The role and place of RT in treating cancer pain are not clearly defined, even if its efficacy has been demonstrated[15,16,25].

The guidelines of the World Health Organization are probably the most important reference in cancer pain management[34]. They describe a 3-step ladder that specifies treatments according to pain intensity. The treatment of choice is analgesics (non-opioid or opioid), which may be delivered with adjuvant treatment according to the clinical condition of the patient. A radiotherapy step is not clearly defined in this ladder but is probably included among the adjuvant treatments. When to prescribe RT remains an unsolved issue. Referring to the WHO ladder, the guidelines of the National Cancer Institute[35] state that "at each step, the doctor may prescribe additional drugs or treatments (for example, radiation therapy)." The National Comprehensive Cancer Network (NCCN) guidelines for adult cancer pain[36] describe different "non-pharmacologic options" (positioning instruction, physical therapies, acupuncture, ultrasonic or transcutaneous electrical nerve stimulation, heat and/or ice) but do not list RT among these options. The radiation oncologist is not included among the "speciality consultations for improved pain management." RT is mentioned only as a possible modality to treat local

Table 3 - Principal answers given by radiation oncologists for every clinical case

Clinical case	Do you treat patient? (yes, %)	Main criterion for treating patient (%)	Preferred dose schedule (total dose Gy/fractions, %)	Preferred volume schedule (volume, %)	Supportive therapy (at least 1/ at least 2, %)
#1: breast, PS 0, VASi 7 and VASa 5, D9-D10, osteolytic and ostoblastic lesions	88.7	Prognosis (55.7)	30/10 (65.5)	D8-D11 (34.4)	28.7/39.3
#2: lung, PS 1, VASi 8 and VASa 3, L2-L3, osteolytic lesions	87.6	Prognosis (59.5)	20/5 (50.1)	L1-L4 (56.5)	26.4/20.7
#3: prostate, PS 0, VASi and VASa 0, osteoblastic right femoral lesion	31.9*	PS (33.3)	30/10 (56.4)	GTV + margins (74.3)	15.4/0
#4: lung, PS 2, VASi 9 and VASa 4, critical osteolytic lesion of C3 + D5-D6 osteolytic lesions + D10 osteolytic lesion with spinal compression	92.7	Radiological aspect of lesions (67.5)	8/1 (30.6)**	Critical lesion + spinal compression + symptomatic lesion (39.5)	35/46.7***

*Only 31.9% of radiation oncologists declared to treat the patient because of VASi and VASa = 0.
**10/122 physicians chose to treat critical lesions and spinal compression with 5 fractions of 4 Gy and symptomatic lesions with a single 8-Gy dose.
***62.9% prescribed corticosteroids.

bone pain[37]. It is also because of this lack of strong indications that radiation oncologists do not always agree on the indication of RT for a symptomatic patient. Our study confirms this. It should be noted that the response to analgesic drugs was no major determinant of the indication for RT among our respondents (49.2%, 36.4%, 0% and 30.6% for case 1, 2, 3 and 4, respectively). Other criteria have been mentioned by physicians, and it is rather surprising that the decision to deliver palliative RT is linked to issues other than the efficacy of the prescribed analgesics. It seems that for radiation oncologists RT was not a complementary or parallel step in managing cancer pain.

The doses and volumes of RT are also a topic of discussion for radiation oncologists. As described above, clinical trials and meta-analyses have shown that 8-Gy single-fraction treatments are equivalent to higher doses (20 Gy in 4 fractions or 30 Gy in 10 fractions) for the endpoint of pain response rates[5-16,38,39]. So, efficacy could not be a criterion for the choice of the optimal fractionation. At the same time, re-treatment and fracture rates were higher in arms treated with single-fraction schedules in several studies[8,9,13-15]. In our opinion, this should not be the only reason for choosing single fraction or not. Schedule choice should also take into account chronic RT-related toxicities, which are particularly linked to daily doses of RT[40]. Single-fraction treatment could be reserved to patients with a poorer prognosis, where the risk of developing chronic toxicities is less important. The knowledge of critical doses to organs at risk and of the interval between RT and the appearance of side effects (acute and chronic) are important issues in this context and might be one of the criteria to use in the choice of doses and volumes, just like in curative treatments. An important review on this subject was recently carried out by the French Society of Oncology Radiotherapy (SFRO)[41-51].

Studies on treatment volumes for bone metastases are lacking. To our knowledge, no relevant article and/or guideline on treatment volume definition for bone metastases has been published. Because of the differences between the proposed clinical cases, the design of our study was not addressed to identifying statistical differences in the choice of treatment volumes.

Field arrangement has not been extensively studied but some reports exist in the literature. Recently, Andic *et al.*[40] reported the results of a dosimetric comparison of different treatment plans for spinal bone metastases. The most important conclusion was that, when possible, 2 opposed fields should be used. Indeed, the study demonstrated that better coverage of the planning treatment volume (PTV) could be achieved with 2 parallel opposed fields than with a single posterior field[40]. With regard to single posterior fields, particular attention should be paid to the depth of the prescription point. Barton *et al.*[52] reported important variation (up to 50%) in the received dose with changes in the prescription depth. The radiation oncologists taking part in the present survey preferred a single posterior field for dorsal and lumbar spine metastases (41.3% and 50.4% for cases 1 and 2, respectively), and 2 opposed fields for femoral and cervical spine metastases (AP-PA, 95.7% and 2 lateral fields, 100% for cases 3 and 4, respectively). The results of the survey concerning treatment field arrangements therefore do not seem to follow the evidence of published dosimetric studies.

There are many reports and guidelines on the use of prophylactic supportive therapies during RT to reduce

Table 4 - Analytical comparison of answers given by radiation oncologists for every clinical case

Question	Proposed options	Clinical case 1 (%)	Clinical case 2 (%)	Clinical case 3 (%)	Clinical case 4 (%)
Do you treat this patient?	Yes	88.7	87.6	31.9	92.7
	No, I prefer to optimize medical therapy first	11.3	12.4	68.1	7.3
Radiotherapy doses	300 cGy / 10 fractions	65.5	26.8	56.4	28.2
	400 cGy / 5 fractions	21.8	50.1	25.6	25.8
	800 cGy / 1 fraction	9.1	22.2	10.3	30.6
	Other doses	3.6	0.9	7.7	6.5
Radiotherapy volumes	Involved vertebra + 2 contiguous vertebrae above and below	17.9	56.5	74.3 (GTV + margins)	39.5 (symptomatic lesions + critical lesions)
	Involved vertebra + 1 contiguous vertebra above and below	34.4	10.2	23.1 (right femur)	0.8 Only symptomatic lesions (pain)
	Only symptomatic vertebra	23.4	25.0	-	Spinal compression + lytic lesion (simultaneously) 30.1 Symptomatic lesions + spinal compression 16.4
	Other volumes	23.3	8.3	2.6	4
Field arrangement	One posterior field	41.3	50.4	4.3	-
	Two AP-PA fields	26	28.6	95.7	-
	Three fields (1 posterior and 2 lateral fields)	22.1	9.5	0	-
	Four fields (1 anterior + 1 posterior + 2 lateral fields)	2.9	3.9	-	-
	Other	7.7	7.6	0	-
Timing (only for clinicians who declared they would treat at least 2 volumes)	-	-	-	-	– At the same time 43.5% – Sequential treatment 23.4% – Not declared 33.1%
Prophylactic supportive therapy (multiple answers allowed)	Topical therapy for skin reactions	17.2	13.2	12.8	12.9
	Treatment for nausea/vomiting	40.2	23.1	2.6	32.3
	PPI	31.1	11.6	0	29.8
	Corticosteroids	23.8	18.2	17.9	62.9
	Other prophylactic supportive therapy	5.7	7.4	2.6	4.8
	No prophylactic supportive therapy	23	38	48.7	6.5
Please indicate factors that influenced your choices* (multiple answers allowed)	PS	54.9	51.2	33.3	44.4
	Disease extent	32.8	38.8	30.8	46.8
	Initial VAS	34.4	40.5	12.8	35.5
	Response of VAS to analgesics	49.2	36.4	-	30.6
	Site of metastasis	39.3	31.4	28.2	58.1
	Patient age	36.9	19.8	7.7	16.9
	Patient prognosis	55.7	59.5	30.8	50.8
	Radiological aspect of the lesions	39.3	42.1	15.4	65.3
	Expected RT toxicity	7.4	9.9	2.6	6.5
	Personal habits	0.8	2.5	0	1.6
	Patient comfort	12.3	13.2	7.7	10.5
	Waiting list of your center	5.7	6.6	2.6	1.6
	Financial aspects (reimbursement of RT treatment)	0	0	0	0

Boxes with a "-" comprise questions that were not pertinent to the considered clinical case.
*Only for physicians who declared they would treat the patient.

the incidence and grade of radiation-related toxicities[53-55]. Our results show that 23%, 38%, 48.7% and 6.5% (from case 1 to case 4, respectively) of the radiation oncologists in our study declared not to prescribe supportive care. Among the "prescribing clinicians" there was considerable variance in the supportive care prescribed. Most agreement was observed regarding the prescription of corticosteroids in clinical case 4 (62.9%), while other proposed supportive treatments would be prescribed by 2.6-40.2% of clinicians.

In our study, prognosis was the major factor determining RT decision-making in cases 1 and 2, while patient performance status and the radiological characteristics of the lesions were the main decision criteria in cases 3 and 4, respectively. Financial, logistic and personal issues were not particularly considered by the physicians in our study. This is clearly not in line with the published indications regarding this issue[21-24]. Indeed, single-fraction RT provides equal palliation and quality of life and has lower medical and societal costs than fractionated therapy, and should therefore be the standard palliative treatment for cancer patients with painful bone metastases. In our experience, the cost-effectiveness of single-fraction treatment has not been taken into account by the physicians taking part in this study.

Conclusion

Unlike other clinical situations, the indication for and prescription of RT for bone metastases is still not an evidence-based process. Our study confirms that palliative RT often has an empirical basis where the radiation oncologist takes into account clinical and nonclinical elements. A multidisciplinary effort is necessary to create Italian national guidelines that take account of the comprehensive evidence of the literature regarding all aspects of palliative radiation therapy for bone metastases.

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