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Original research article

Radiation therapy for bone-only metastases in breast cancer patients: A GOCO survey of current clinical practice

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ABSTRACT

Introduction: The role of radiation therapy (RT) for patients with bone-only metastatic (BOM) breast cancer has not been investigated sufficiently. The aim of this survey was to evaluate current clinical practice in treating breast cancer patients with BOM in Radiation Therapy Departments in Catalonia and Occitania within the scope of the GOCO group.
Materials and methods: An electronic questionnaire was completed by experienced radiation oncologists from fourteen RT centers. The items surveyed the professional experience, therapeutic approach, technique, dose stereotactic body RT (SBRT) availability.
Results: All Radiation Oncology Departments (ROD) in Catalonia (12) and Occitania (2) responded to the survey. Eleven (78.5%) of the RODs advise RT for BOM as initial treatment in the oligometastatic setting. RT to asymptomatic bone oligometastases is more often restricted for "risky lesions". The most inconsistent approaches were the treatment for asymptomatic lesions, when to treat bone metastases with respect to systemic treatment (ST) and the indication for RT after a complete response to ST.
Conclusion: While BOM breast cancer patients have a relatively good prognosis, there is a lack of consistency in their approach with RT. This can be explained by the absence of evidence-based guidelines and an incomplete availability of SBRT.

1. Introduction

Bone-only metastasis (BOM) is a term that means the presence of bone metastasis without evidence of any other organ involvement.[1–4] However, there is limited information about the optimal management and clinical outcome of BOM in breast cancer patients.

Bone is the most common site of breast cancer metastases and of first distant relapse particularly for patients with Luminal A and B/Her2 negative disease,[5,6] and in a 75% bone metastases are associated with skeletal-related events.[7] In addition, BOM occurs in 17–37% of patients with distant relapses,[8] and is known to be a factor associated with improved survival compared to visceral metastases.[9–11]

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Questionnaire (clinical questions):

- Years of experience: <5/5-10/10-15/15-20/>20
- Number of patients treated per year: <100/100-200/200-300/300-400/>400
- Do you usually treat oligometastatic patients? Yes/no
- Do you treat asymptomatic bone-metastases in the oligometastatic setting? Yes/no/only if risky lesions
- In your opinion, what is the best time to treat bone-metastases in the oligometastatic setting? After systemic treatment and reevaluation/ before systemic treatment/ before systemic treatment only in case of symptomatic lesions
- In case of the patient has started with systemic treatment and presents a clinical complete response, what do you do? We won't treat now/ We will treat anyway
- You have decided to treat the aforementioned patient. What kind of radiotherapy will you perform? We will perform a SBRT/ we indicate SBRT but is not available at my institution/we will perform a hypofractionated standard RT/ we will perform a normofractionated standard RT

Fig. 1. Clinical questions of the survey.

Radiotherapy (RT) is an effective palliative treatment of bone metastases with the most common dose schedules being 30 Gy in 10 fractions, 20 Gy in 5 fractions or a single dose of 8 Gy. However, since the concept of oligometastases was proposed, various studies over the last decade have reported on the benefits of local modalities in terms of local control of metastatic lesions, progression-free survival and overall survival.[12–14] So, in selected cases with small-volume and limited metastasis, it is possible to perform stereotactic body RT (SBRT) that delivers an ablative single fraction or a small number of high-dose fractions that, in the case of bone metastases, has usually been reserved for lesions located in the spine.[15] Nevertheless, the role of RT (either conventional or SBRT) for patients with BOM breast cancer has not been investigated sufficiently and recent cancer treatment guidelines on diagnosis and treatment of bone metastasis do not consider this distinctive situation.[16,17]

So, the aim of our survey was to evaluate clinical practice in treating breast cancer patients with BOM – particularly in the oligometastatic setting – among RT centers from Catalonia and Occitania (Languedoc-Roussillon and Midi-Pirinées) forming part of the *Grup Oncològic Català-Occità* (GOCO Group).

2. Materials and methods

A brief electronic questionnaire was sent to fourteen Radiation Oncology Departments (ROD) within the scope of the GOCO group (Hospital Univesitari Arnau de Vilanova, Lleida, Spain; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Parc de Salut Mar, Barcelona, Spain; Hospital Clínic, Barcelona, Spain; Hospital Quirón, Barcelona, Spain; Hospital de la Vall d'Hebron, Barcelona, Spain; Institut Català d'Oncologia - Hospital Duran i Reynals, Barcelona, Spain; Institut Català d'Oncologia - Hospital Germans Trias i Pujol, Badalona, Spain; Hospital General de Catalunya, Institut Oncològic del Vallès, Sant Cugat, Spain ; Hospital Plató, Barcelona, Spain; Institut Català d'Oncologia - Hospital Josep Trueta, Girona, Spain; Institut de Cancérologie de Montpellier - Val d'Aurelle, University of Montpellier, France; Institut Universitaire du Cancer de Toulouse, Toulouse, France; Hospital Universitari Sant Joan de Reus, Tarragona, Spain) between January 2017 and May 2018.

The questionnaires were completed by 15 Radiation Oncologists experienced in breast cancer.

The following items were surveyed: professional experience (2 questions), therapeutic approach (4 questions), technique and dose (2 questions) and SBRT availability (2 questions) (Fig. 1).

Responses were tabulated and descriptive statistics are provided.

Table 1
More relevant responses to the survey. RT: radiation therapy. SBRT: stereotactic body RT.

Question:		n	%
Do you consider RT for oligometastases?			
	Yes, and we treat ourselves	11	78,57%
	Yes, but we refer to another centre	2	14,29%
	No	1	7,14%
Do you consider for RT assymptomatic bone lesions?			
	Only for "risky lesions"	7	50,00%
	Always	2	14,29%
	In a clinical trial	2	14,29%
	None of the above	2	14,29%
Availability for SBRT			
	Yes	10	71,43%
	No	4	28,57%
If SBRT available, which locations can you treat?			
	Lung, brain, liver	4	57,14%
	Lung, brain, liver, bone (includes spinal)	5	71,43%
	Only lung	1	14,29%

3. Results

All RODs in Catalonia (12) and Occitania (2) responded to the survey. The majority of the surveyed Radiation Oncologists had more than 20 years' experience. Half of the RODs see at least 300 breast cancer patients per year. Eleven (78.5%) RODs advised RT for oligometastases and are able to treat those patients at their institution (without referral to another institution). In only one ROD, RT for oligometastases is not yet considered as the first approach. RT to asymptomatic bone oligometastases is mainly restricted for "risky lesions", such as the risk of fractures or the risk of cord compression (Table 1). The availability for SBRT was only 50%, although the technique is being implemented in some centers at the time of this writing.

The most inconsistent approaches were: the RT indication for asymptomatic bone metastases, the best time to treat those lesions (before or after systemic treatment), and the indication for RT to patients that are in a CR after systemic treatment (ST) in a consolidative approach. Controversy in clinical practice is summarized in Figs. 2 and 3.

4. Discussion

The treatment of BOM among experienced Radiation Oncologists varied greatly in our survey. While it is known that patients

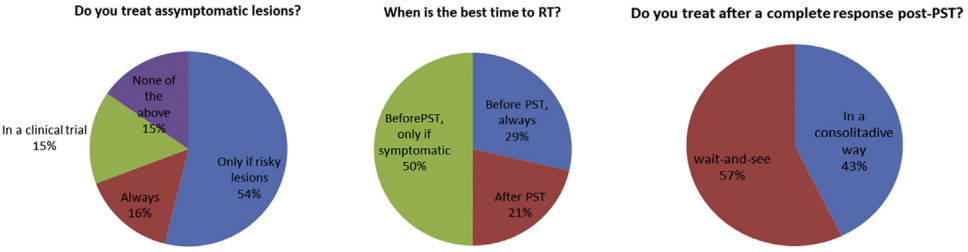

Fig. 2. More inconsistent responses between experienced Radiation Oncologists. PST: primary systemic treatment.

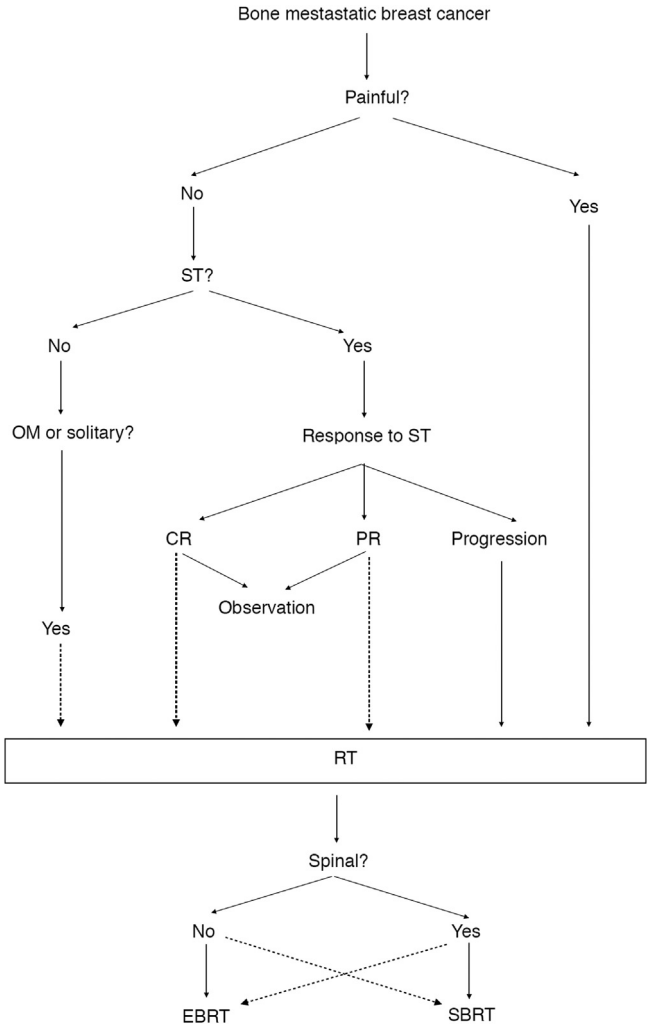

Fig. 3. Management flow for bone metastatic breast cancer patients based on the survey. The dashed line symbolizes the subjects of controversy. ST: systemic therapy. OM: oligometastases. CR: complete response. PR: partial response. RT: radiotherapy. EBRT: external beam radiotherapy. SBRT: stereotactic body radiotherapy.

with BOM have a better prognosis[1,9,10] and might be a distinct clinical entity among metastatic breast cancer patients, there is still a lack of consistency in the approach to treatment of these patients.

A complete response (CR) to ST has been shown to correlate with prolonged survival.[18] Patients with locally advanced disease that achieve a CR after neoadjuvant ST seem to benefit from post-mastectomy radiation therapy in terms of distant metastasis free survival, cancer-specific survival and overall survival.[19] However, little is known if there is a role for consolidative irradiation to the metastases after ST. In the present survey, the majority of Radiation Oncologists prefer to start with a ST and save RT for symptomatic bone lesions. Only a minority recommend RT in a consolidative approach after a CR obtained with systemic therapy. While there is no evidence to support consolidative RT after obtaining a CR, some authors have suggested a potential benefit. Milano et al.[20,21] published a series of 121 oligometastatic patients treated with SBRT. The study reported that patients with radiographic progression after systemic therapy at the time of being referred for SBRT fared significantly worse than patients with a stable or regressing disease. However, only 19 breast cancer patients showed a response or stable disease, of which only some received RT as a consolidation. Therefore, the benefit of consolidative RT after a CR to systemic therapy needs to be explored in further studies.

Palliative RT to bone metastases is well accepted as an effective treatment to ease pain and improve the quality of life of patients with metastatic disease. While the most common fractionation schedules of conventional RT are 30 Gy in 10 fractions, 20 Gy in 5 fractions and 8 Gy in 1 fraction, doses of 50 Gy or higher seem to improve local control.[22] So, the use of SBRT for bone metastases is encouraging although it is a more complex technique and is more often reserved for treatment of spinal bone metastases. Milano et al.[20] reported the outcomes of 40 selected metastatic breast cancer patients with fewer than 5 extracranial lesions, showing a 4-year overall survival of 59%, and a local lesion control of 89%. The RACOST randomized trial in the Netherlands[23] is comparing a conventional single dose of 8 Gy with a single SBRT dose of 20 Gy for pain reduction and quality of life for patients with spinal metastases. The results of that study are yet to be published.

Patients with BOM disease, which accounts for 41% of metastatic bone lesions that can be at present diagnosed with contemporary tools, deserve special consideration.[24] Either after conventional RT or SBRT, these patients have a more favorable outcome compared to patients with multiple metastases or with other metastatic sites.[21,22,24] In a series of 565 bone metastatic patients[1] with a median number of involved bones of 2 (range, 1–5), radiation therapy was delivered to a 13%. In the study, patients with single bone metastasis compared to those with multiple metastases showed a better progression free-survival (24 vs. 14 months respectively, $p = 0.002$) and a better overall survival as well (79 vs. 50 months, $p = 0.005$). Therefore, we suggest that SBRT should be considered suitable in these cases. The promising results of the study SABR-COMET, where breast cancer patients accounted for almost a quarter of the included patients and most of them having 1–3 metastatic locations,[25] has shown that patients treated with SBRT improved their median overall survival from 28 months to 41 months ($p = 0.09$) as well as progression-free survival (6.0 vs. 12.0 months, $p = 0.001$). Moreover, the CORE study[26] is a randomized controlled trial being conducted in the UK for patients with oligometastatic disease (up to 3 metastatic sites) from breast, prostate and non-small cell lung cancers. The study will evaluate whether the addition of SBRT to standard therapy improves progression-free survival outcomes in patients with a limited burden of oligometastatic disease.

Another issue of particular interest will be the introduction of emerging therapies such as immunotherapy in metastatic breast cancer patients in combination with RT. Particularly SBRT would

have the potential to stimulate a tumor-specific immune response and/or generate an abscopal effect. While the optimum sequence of RT and immunotherapy remains to be found, the combination in the oligometastatic setting should be explored.[27]

Finally, our survey has revealed that only 71% of RODs have implemented SBRT techniques. The ESTRO-HERO survey reported that in 2014 access to RT equipment varied greatly across Europe between countries[28] and, especially, in low-income countries and mostly in Southern and Central-Eastern Europe there is a limited access to modern RT equipment. This calls for more effort to improve equity and accessibility of patients to high technology equipment in order to provide the best possible services to patients.[29]

5. Conclusion

This survey shows that there is a lack of consistency and insufficient evidence for the best therapeutic approach to treatment of breast cancer patients with BOM, although SBRT appears to be the most promising and deserving of future development. While a local radical treatment might be suitable for solitary metastases, only 70% of the RODs are fully equipped to perform SBRT. This calls for further studies in the field, and more effort to make SBRT more generally available.

Conflict of interest

None declared.

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