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RESEARCH ARTICLE

Reirradiation on spine metastases: an Italian survey on behalf of palliative care and reirradiation study groups of Italian association of radiotherapy and clinical oncology (AIRO)

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Abstract

Aim This survey derived from the collaboration between the Palliative Care and Reirradiation Study Groups of the Italian Association of Radiotherapy and Clinical Oncology (AIRO). Its aim was to obtain a real "snapshot" on the treatments of spinal metastases, focusing on reirradiation, among radiation oncologists in Italy.

Methods The survey was elaborated on SurveyMonkey's online interface and was sent via e-mail to all Radiation Oncologists of AIRO that were invited to anonymously fill in the electronic form within 60 days. The questionnaire was prepared by the AIRO "Palliative care" and "Reirradiation" Study Groups and it consisted of 36 questions, 19 single-choice questions, 10 multiple-choice questions and 6 open questions. The data were analyzed and represented with tables and graphs.

Results The survey shows that palliative radiotherapy remains a field of interest for most ROs in the Italian centers. 3D Conventional Radiation Therapy (3DCRT) alone or in combination with other techniques is the primary choice for patients with a life expectancy of less than 6 months. For patients with a life expectancy of more than six months, there is an increased use of new technologies, such as Volumetric Modulated Arc Therapy (VMAT). Factors considered for retreatment are time between first and second treatment, dose delivered to spine metastasis and spinal cord in the first treatment, vertebral stability, symptoms, and/or performance status. The most feared complication are myelopathy followed by vertebral fracture and local recurrence. This explain an increasing focus on patient selection and the use of high technology in the treatment of metastatic patients.

Conclusion Stereotactic body radiotherapy (SBRT) and image-guided radiotherapy allow the administration of ablative RT doses while sparing the constraints of healthy tissue in spinal metastases. However, there is still an unclear and heterogeneous reality in the reirradiation of spinal metastases. A national registry with the aim of clarifying the most controversial aspects of vertebral metastasis retreatments will enable better management of these patients and design more targeted study designs.

Keywords Radiotherapy · Reirradiation · Pain · SBRT · Spinal cord

Abbreviations

AIRO	Association of Radiotherapy and Clinical Oncology
cERBT	Conventional external beam radiotherapy
re-RT	Reirradiation
SBRT	Stereotactic body radiotherapy
CTV	Clinical Target Volume
PTV	Planning Target Volume
ROs	Radiation Oncologists
3DCRT	3D Conventional Radiation Therapy
Dmax	Maximal dose
BED	Biological Equivalent Dose
GTV	Gross Tumor Volume
VMAT	Volumetric Modulated Arc Therapy
EQD2	Equivalent total doses in 2-Gy fractions
OARs	Organs at Risk

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Introduction

About 40% of advanced cancer patients have spinal metastases, which cause pain and reduce quality of life. Palliative conventional external beam radiotherapy (cEBRT) is the cornerstone of spinal bone metastases management in these patients for symptom control. However, 10–20% of patients require retreatment after cEBRT [1].

Reirradiation (re-RT) of spinal metastases is generally limited by the first treatment delivered dose, requiring a lower dose to respect the cumulative risk of radiation-induced toxicity. [2] Innovations in systemic therapy improved prognosis in metastatic patients, so the need for a safe re-RT course for spine metastasis is growing.

High-tech stereotactic body radiotherapy (SBRT) techniques allow the use of a treatment that increases the dose to spinal metastases while exposing critical neural tissues to a low dose (spinal cord and thecal sac). SBRT in spinal retreatment allows for a higher dose to be delivered than in the initial cycle of cEBRT, resulting in improved pain and local control. [3]

We present the data from a survey, born from the collaboration between the Palliative Care and Re-RT Study Groups of the Italian Association of Radiotherapy and Clinical Oncology (AIRO), designed to obtain an actual "snapshot" regarding spinal metastases treatments, focusing in particular on re-irradiation, among radiation oncologists in Italy.

Materials and methods

The survey was elaborated on SurveyMonkey's online interface (http://www.SurveyMonkey.com) and was sent via e-mail on November 2021 to all Radiation Oncologists registered with AIRO. The questionnaire of survey was prepared by the AIRO "Palliative care" and "Reirradiation" Study Groups. It consisted of 36 questions, 19 single-choice questions, 10 multiple-choice questions and 6 open questions.

Items 1–9 collected general information regarding the Radiation Oncology centers characteristics, the patients treated annually, the expertise of the responders. The next four questions (items 10–12) collected information about the spinal retreatment performed annually in the centers and about the staff dedicated to them. Questions 14–21 concerned two settings of patients undergoing the first radiation treatment of spine, the one with a life expectancy greater than 6 months, and the other one with a life expectancy of less than 6 months. The questions assessed technique, treatment volume, prescribed dose, and maximum dose to the thecal sac. Questions 22–36 collected about re-RT spine metastasis. The items 22–25 assessed the choice of technique in spinal retreatment and the factors conditioning the indication for retreatment according to life expectancy; the questions 26–30 concerned contouring, Clinical Target Volume (CTV)- Planning Target Volume (PTV) expansion and the use of immobilization systems. Question 31 was about the dose and fractionation used in re-RT, 32 was about the maximum cumulative dose to thecal sac. The last 4 questions (33–36) were related to the frequency of treatment, the most feared type of complication, the factors that excluded an indication for retreatment. Finally, the availability to share data in a national registry was requested. All subjects were invited to anonymously fill in the electronic form within 60 days. Answers were automatically performed by SurveyMonkey. We analyzed and represented the data with tables, and circular sector graphs.

Results

General consideration (1st-13th items)

Radiation Oncologists (ROs) from 17 of the 20 Italian regions responded to the survey. A total of 56 Italian ROs accounting for 43 Italian centers completed the questionnaire. More information about these centers can be found in Supplementary Table s1, and a complete version of the questionnaire can be found in Supplementary Table s2.

Management of the spine metastases (14th-21st items)

The part of the survey focusing on the treatment of "naive spinal lesions" was divided into 2 parts: questions 14–16 concerning patients with a life expectancy of fewer than 6 months, questions 18–20 concerning patients with a life expectancy greater than 6 months.

Table 1 shows the data relating to the techniques and volumes in both patient settings.

If patients had a life expectancy greater than 6 months, the percentage of ROs using 3D Conventional Radiation Therapy (3DCRT) alone decreased from 24 to 9%, while the percentage of ROs using 3DCRT in combination with other techniques decreased from 47 to 13%. VMAT and SBRT, on the other hand, increased to 64 and 62%, respectively.

In the 16th and 20th items, the prescribed dose was investigated in the two proposed settings. In the first setting, 38, 43, and 11% of ROs preferred 8 Gy, 20 Gy/5fractions (fx), or 30 Gy/10fr, respectively (Fig. 1a). The prescription dose in the second setting was quite variable (Fig. 1b), with many answers indicating both conformal and SBRT treatments.

Table 1 Techniques and volume in different setting of metastases spine patients

Techniques			Volume							
			Whole vertebra		Whole vertebra + GTV or segment with lesion		GTV + segment with lesion		GTV	
	Life expectancy		Life expectancy		Life expectancy		Life expectancy		Life expectancy	
	< 6 mo	> 6 mo	< 6 mo	> 6 mo	< 6 mo	> 6 mo	< 6 mo	> 6 mo	< 6 mo	> 6 mo
One option	**25**	**20**	**16**	**8**	**0**	**11**	**7**	**0**	**0**	**1**
3DCRT	13	5	11	4	0	0	0	0	0	0
IMRT	0	2	5	4	0	2	4	0	0	0
VMAT	9	6	0	0	0	2	3	0	0	0
SBRT	3	7	0	0	0	7	0	0	0	1
Two options	**16**	**21**	**11**	**5**	**0**	**14**	**3**	**0**	**0**	**0**
3DCRT + VMAT	10	1	6	1	0	0	2	0	0	0
3DCRT + IMRT	4	1	4	1	0	0	0	0	0	0
3DCRT + SBRT	1	1	1	0	0	1	0	0	0	0
IMRT + VMAT	0	3	0	1	0	2	0	0	0	0
IMRT + SBRT	0 1	2	0	0	0	1	0	0	0	0
VMAT + SBRT		13	0	2	0	10	1	0	0	0
Three or more options	**12**	**12**	**1**	**2**	**6**	**8**	**4**	**0**	**0**	**1**
3DCRT + VMAT + SBRT	2	2	0	0	1	1	0	0	0	0
3DCRT + IMRT + VMAT	3	0	1	0	1	1	0	0	0	0
IMRT + VMAT + SBRT	2	7	0	1	0	4	2	0	0	1
IMRT + VMAT-PT	0	1	0	0	0	1	0	0	0	0
3DCRT + IMRT + VMAT + SBRT	5	2	0	1	4	1	2	0	0	0

3DCRT 3D conformal Radiation Therapy, *IMRT* intensity-modulated Radiation Therapy, *VMAT* Volumetric Modulated Arc Therapy, *SBRT* Stereotactic Body Radiation Therapy, *PT* Proton Therapy

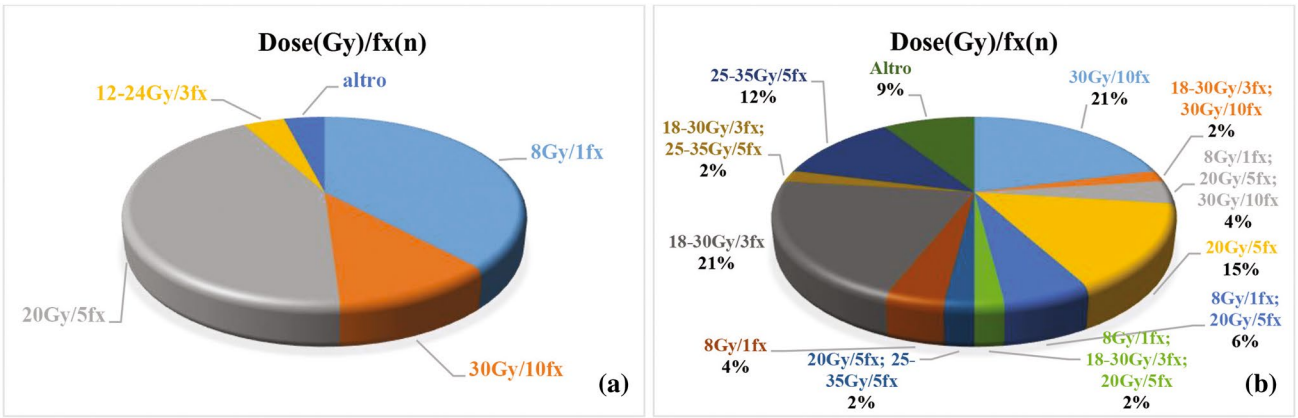

Fig. 1 **a** Prescription dose in the first setting of patients; **b** prescription dose in the second setting of patients

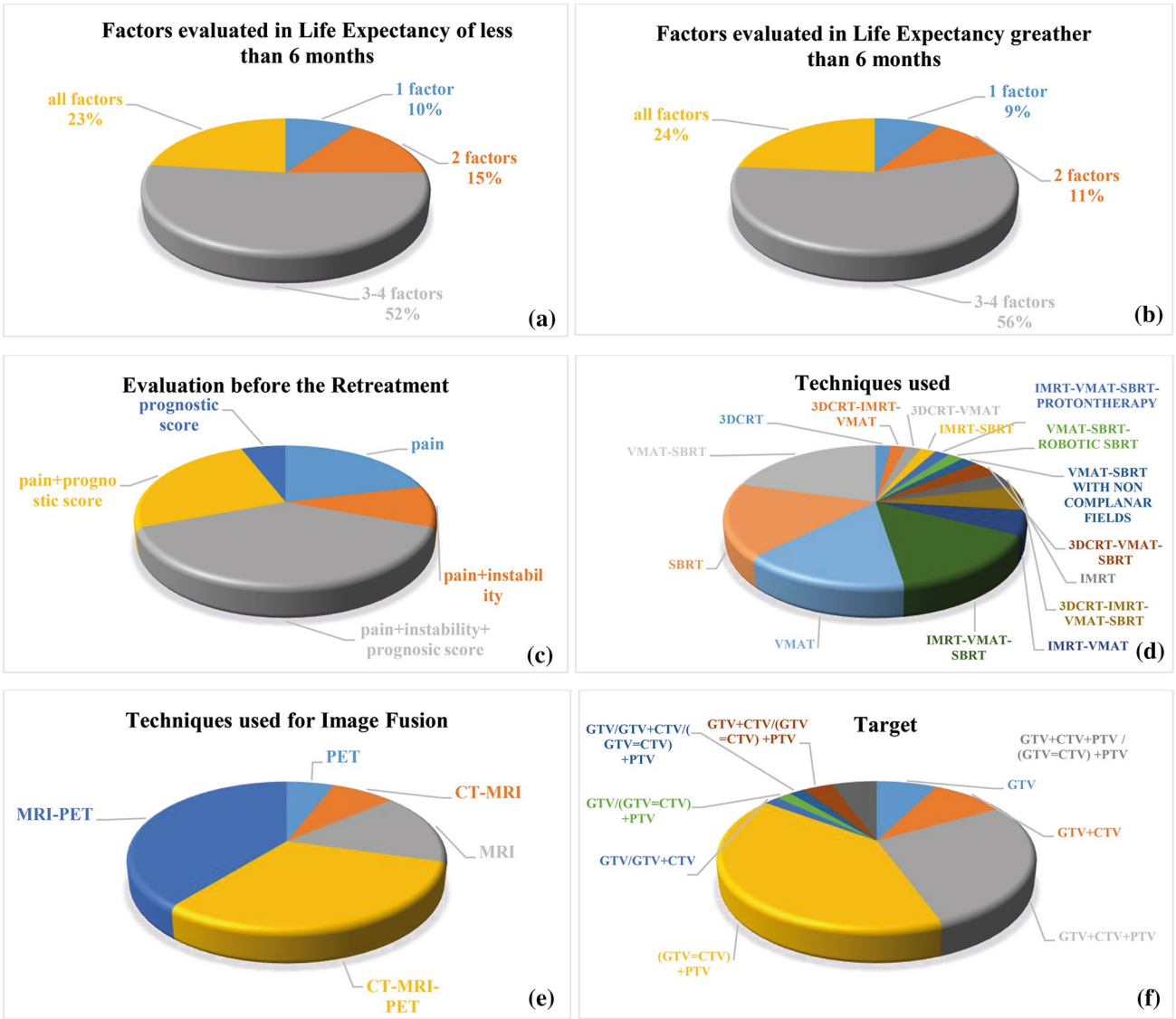

Fig. 2 **a** Number of factors evaluated in the first setting; **b** number of factors evaluated in the second setting; **c** combination of factors evaluated; **d** techniques used for retreatment; **e** image-fusion used for contouring; **f** target in retreatment

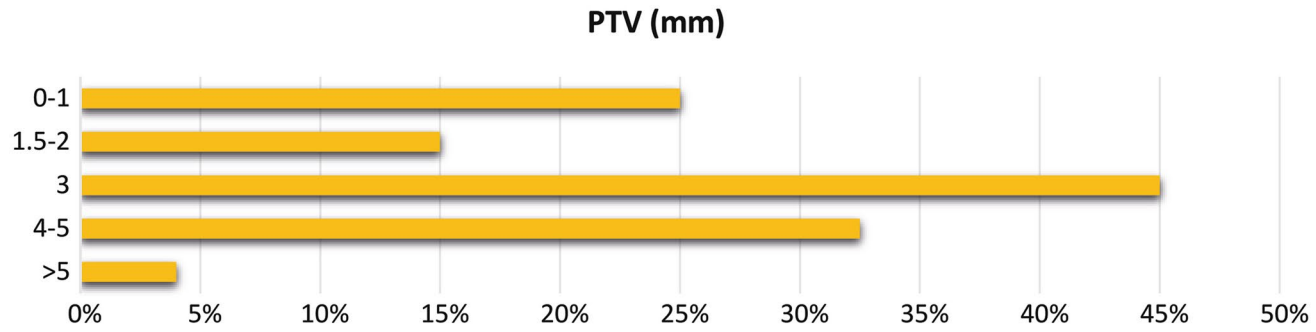

Fig. 3 Expansion for PTV in retreatment of spine metastases

Table 2 Dose/fraction used in vertebral metastases retreatment

Dose/fx	Exclusive choice	%	First choice	%	Second choice	%	Third choice	%
6-8 Gy/1fx	5	10.6	10	21	5	10.6	5	10.6
20 Gy/5fx	0	0	4	8.5	5	10.6	1	2.1
30 Gy/10fx	1	2.1	2	4.5	2	4.5	2	4.5
18–21-24-30 Gy/3fx	1	2.1	2	4.5	4	8.5	2	4.5
25–30-40 Gy/5fx	1	2.1	1	2.1	5	10.6	4	8.5
25 Gy/10fx	1	2.1	1	2.1	0	0	1	2.1
10–12-16-18 Gy/1fx	0	0	1	2.1	1	2.1	2	4.5
Total Bed < 110 Gy	1	2.1	0	0	0	0	0	0
BED2 > 130 Gy	1	2.1	0	0	0	0	0	0
35 Gy/7fx	0	0	1	2.1	0	0	0	0
30-40 Gy/20fx	0	0	1	2.1	1	2.1	0	0
12 Gy/4fxBID	0	0	0	0	1	2.1	0	0
24 Gy/4fx	0	0	0	0	0	0	1	2.1
16 Gy/2fx	0	0	0	0	1	2.1	0	0
30 Gy/6fx	0	0	0	0	1	2.1	0	0
125 Gy/20fx BID	0	0	0	0	0	0	1	2.1

Gy Gray, *BED* Biologically Effective Dose, *fx* fraction, *BID* bis in die

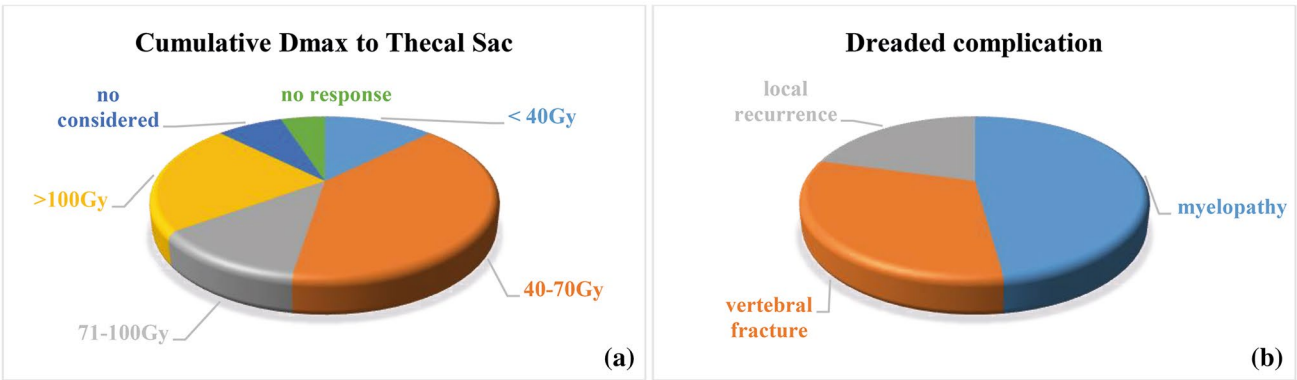

Fig. 4 **a** Cumulative maximun dose to thecal sac; **b** complication that ROs feared in retreatment

Regarding the questions on the maximal dose (Dmax) at thecal sac (17th and 21st item), while in the first setting, a maximum dose of less than 50 Gy was used in EQD2 for all types of fractionations, in the second setting the answers were very heterogeneous, with values of Dmax between 20 and 50 Gy depending on the used fractionation. More details are shown in the supplementary data (Table s3, s4).

Strategy of spine reirradiation (22th-36th items)

This section of the survey focused on re-RT of prime lesions and also in this case two clinical settings were analyzed: patients with a life expectancy inferior or superior to 6 months. ROs appear to consider different aspects of life expectancy (22nd and 25th items) in both clinical settings: time between first and second treatment, delivered dose to the spine and spinal cord in the first treatment, spinal stability, symptoms, and/or performance status (Fig. 2a, e and b). The supplementary data contain additional information (Table s5).

Figure 2c and d illustrate patient-related factors considered for retreatment (item 23), as well as the technique employed (item 24). Figure 2e depicts an image-fusion technique (items 26–27) and the target used in retreatment (item 28).

Question 29 considered the CTV-PTV expansion in the contouring of a spinal lesion retreatment, the Fig. 3 shows answers with percentage of choice.

The 30th item evaluated the use of immobilization systems and 77% of ROs use them for patients candidates to retreatment for spinal metastases. Regarding the type of system (please note that ROs could list more than one system), the most used type was vacuum bag (58%) and thermoplastic mask (46%).

Table 2 shows the data from the 31th item on doses/fractions used in spine metastases retreatment. The exclusive choice was distinguished from a first, second, or third choice.

The 32th item, whose results are shown in Fig. 4a, investigated the cumulative maximum Biological Equivalent Dose to thecal sac (total BED $\alpha/\beta 2$) for spinal metastases retreatment: a total of 40 options was registered and the most frequent constraint was 40-70 Gy (40%). The 34th item (Fig. 4b) assessed the complication that ROs feared most in retreatments.

The 33th item focused on the frequency of treatment and daily frequency was the preferred system by the 70% of ROs, while the remaining 30% choose alternate days.

The 35th item (Supplementary Table s4) evaluated which factors could cause possible exclusion from a SBRT retreatment: age, vertebral deformation, vertebral fracture, presence of a lytic lesion, and vertebral body involvement greater than 40%. (More than one choice was allowed).

When only one factor was considered, 74% of ROs indicated vertebral fracture; when two factors were considered, 56% indicated vertebral fracture and more than 40% vertebral body involvement. Those who considered four or more factors had a vertebral fracture in 100% of the cases, and a vertebral body involvement of more than 40% in 91% of the cases. The other three factors were not very representative (Table s5–6 in Supplementary data).

The last question (36th item) investigated the availability of data sharing in a national register among the ROs and the adhesion to the proposal was 98%.

Discussion

In the management of patients with bone metastases, those involving the spine represent a major problem for associated symptoms and complications. [4, 5] Radiotherapy plays an important role in the management of spinal metastases, such as pain or neurological compromise. [6, 7]

Radiation treatment records a complete response rate of 0–20% and a partial response rate of 60%. These data combined with the increased survival of patients thanks to integrated therapy, explain the increasing need for spinal Re-RT. (6) Reirradiation may be necessary in case of no pain relief after the first radiotherapy, in case of partial response, or in case of total or partial pain relapse. [8, 9] Spinal re-RT is an important issue due to the proximity of several critical structures, in particular the spinal cord. Respect for cumulative spinal cord tolerance has resulted in a conservative practice with the use of biologically effective doses lower than those initially administered. [9, 10]

The first observation we can draw from the results of this survey is that palliative radiotherapy remains a field of interest for the majority of ROs in Italian centers.

In the first treatment setting, the questions about technique selection and target delineation were particularly intriguing.

According to the interviewees' responses, 3DCRT alone or in combination with other techniques was the preferred treatment for patients with a life expectancy of less than 6 months, which is consistent with the current literature. [11–21] The entire vertebra was the target in most cases in this same setting, with 26% of interviewees indicating the Gross Tumor Volume (GTV) plus the bone segment containing the lesion as target.

In patients with a life expectancy of more than six months, however, the results showed a decrease in the use of 3DCRT, either alone or in combination with other techniques, and an increase in the availability of new technologies such as

Volumetric Modulated Arc Therapy (VMAT). This result could be interpreted as a need to save OARs, particularly for a possible future new treatment at the same or a nearby site. In fact, data analysis on the volume of treatment revealed that the entire vertebra was indicated in only 28% of cases, while GTV alone or GTV plus the segment containing the lesion was chosen in 66% of cases, partially in accordance with the indications expressed by Cox et al. [22].

This differentiation was also found in the doses and fractionation indicated in the two settings, with a preference for higher doses and SBRT in patients with higher life expectancy.

About the retreatment setting, the survey showed interesting data on patient-related factors considered for retreatment (time between first and second treatment, dose delivered to spine metastasis and spinal cord in the first treatment, vertebral stability, symptoms, and/or performance status).

These patient-related factors were taken in the account both in patients with a life expectancy inferior or superior to 6 months (75 and 80% of cases, respectively). In particular, the more considered factors were pain, vertebral instability, and the used prognostic score.

Regarding the possible technique, a great relevance of high technologies use was found, in particular, VMAT; moreover, most ROs reported prescribing the dose at PTV and the most used CTV-PTV expansion of 3 mm.

Other interesting results were the one on doses and fractionations for retreatments: it was possible to give more than one answer, so more combinations were possible. Among the ROs giving only one answer, the most used dose was 8 Gy/1fx, while among the ROs giving more than one answer, the first choice was always the dose of 8 Gy in 1 fx, followed by 20 Gy/5fx, 30 Gy/10fx, and with the same percentage SBRT with doses 18-21-24-30 Gy/3fx.

Comparing these data with the ones from question 14 relating to the techniques used, among the ROs selecting an exclusive choice of 8 Gy/1fx, only one case declared that he used SBRT. It is possible that the fractionation choice may have been influenced by the type of technology available.

Among ROs giving only one answer, the second most selected choice was mostly a treatment in 8 Gy/1fx, 5 fractions (20-25-30-40 Gy/ 5fx), followed by SBRT with 18-21-24-30 Gy/3fx or 10-12-16-18 Gy/1fx.

In the case ROs giving multiple options, 8 Gy/1fx given with 3DCRT technique was preferred in all patient except one where the VMAT technique was used.

Among who selected 20 Gy/5fx, VMAT was indicated as the main used technique; for SBRT doses the selected techniques were VMAT and robotic-SBRT. This trend was confirmed in the analysis of second choices.

The third choice for ROs giving only one answer was 8 Gy/1fx, followed by SBRT 18-21-24-30 Gy/3fx, or 10-12-16-18 Gy/1fx, and then by 25-30-40 Gy/5fx.

Finally, in the third choices, the 8 Gy/1fx dose was predominant, because VMAT and robotic-SBRT were indicated in the first and second choices. Concerning the retreatment exclusion criteria, the most indicated was vertebral instability.

Regarding the complication that ROs feared most in retreatments, the most feared resulted myelopathy followed by vertebral fracture and local recurrence.

This may explain why there has been an increasing focus on patient selection and the use of high technology in the treatment of metastatic patients.

Advances in radiotherapy such as SBRT and image-guided radiotherapy have enabled the delivery of ablative RT doses while sparing healthy tissue constraints in spine metastases.

Hamilton et al. [23] reported the first spine SBRT series (5 patients) based on a rigid spinal immobilization device and delivery of 10 Gy in a single fraction. Milker Zabel et al. [24] further reported on the use of a noninvasive near-rigid external body immobilization and conformal treatment delivery.

The increase in dose to the tumor can improve local control, as was observed in a retrospective study from Damast and colleagues who reported a significant decrease in the local failure after Image Guided-IMRT with five 6-Gy fractions (BED 48 Gy10 and 120 Gy2) compared to five 4-Gy fractions (BED 28 Gy10 and 60 Gy2) [19]. In this case, SBRT allows to increase the dose in retreatment by optimizing tumor coverage and sparing Organs At Risk (OARs).

Sahgal et al. recommend for re-RT SBRT delivered in 1–5 fractions a cumulative dose equivalent to the thecal sac in equivalent total doses in 2-Gy fractions (EQD2) not exceeding 70 Gy (BED < 140 Gy2), a re-RT SBRT EQD2 thecal sac not exceeding 25 Gy (BED 50 Gy2). Furthermore, the relationship between the latter and the former should not exceed the value of 0.5 and recommend a minimum time interval between first and second irradiation of at least 5 months [25].

The Dmax to the thecal sac was the most contentious topic in this survey: while the results were consistent with the literature in the treatment of "naïve" patients, there was significant heterogeneity in responses in the case of retreatments, which were difficult to group (see supplementary materials). This result could be explained in part by a lack of data in the current literature: as Myrehaug et al. (9 describe, this could lead to more conservative practices among ROs, using lower biologically effective doses than were initially delivered). This could explain the 58% overall response rate and CR rates ranging from 16 to 28% reported in a recent metanalysis by Huisman et al. [26].

On the other hand, it could be explained by some centers' inability to access advanced techniques (e.g., SBRT).

Conclusions

Even when the method of data collection and the number of participants are considered, the results show a still unclear and heterogeneous reality in spinal metastases reirradiation, a setting in which single center experience is likely to play a significant role in this type of treatment.

These various approaches are most likely related to a lack of appropriate studies. As a result, new clinical studies on this topic are required. As far as we are concerned, a first step could be the collection of data from various Italian centers in a national register with the goal of clarifying the more contentious aspects of vertebral metastasis retreatments to allow better management of these patients and the design of more focalized trial designs.

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Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent for publication All authors gave their consent for publication of the paper.

Informed consent Not applicable.

Research involving Human Participants and/or Animals Not applicable.

Ethical approval Not applicable.

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