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RESEARCH ARTICLE

Stereotactic body radiation therapy (SBRT) for spinal metastases: 12 years of a single center experience

Raquel Ciérvide[1] · Ovidio Hernando[1] · Mercedes López[1] · Ángel Montero[1] · Daniel Zucca[1] · Emilio Sánchez[1] · Beatriz Álvarez[1] · Mariola García-Aranda[1] · Xin Chen Zhao[1] · Jeannette Valero[1] · Rosa Alonso[1] · Jaime Martí[1] · Miguel Ángel de la Casa[1] · Leire Alonso[1] · Juan García[1] · Paz Garcia de Acilu[1] · Alejandro Prado[1] · Pedro Fernandez Leton[1] · Carmen Rubio[1]

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Abstract

Objective To assess the clinical outcomes of patients with spine metastases treated with SBRT at our institution.

Materials and methods Patients with spine metastases treated with SBRT (1 fraction/18 Gy or 5 fractions/7 Gy) during the last 12 years have been analyzed. All patients were simulated supine in a vacuum cushion or with a shoulder mask. CT scans and MRI image registration were performed. Contouring was based on International Spine-Radiosurgery-Consortium-Consensus-Guidelines. Highly conformal-techniques (IMRT/VMAT) were used for treatment planning. Intra and interfraction (CBCT or X-Ray-ExacTrac) verification were mandatory.

Results From February 2010 to January 2022, 129 patients with spinal metastases were treated with SBRT [1 fraction/18 Gy (75%) or 5 fractions/7 Gy] (25%). For patients with painful metastases (74/129:57%), 100% experienced an improvement in pain after SBRT. With a median follow-up of 14.2 months (average 22.9; range 0.5–140) 6 patients (4.6%) experienced local relapse. Local progression-free survival was different, considering metastases's location ($p < 0.04$). The 1, 2 and 3 years overall survival (OS) were 91.2%, 85.1% and 83.2%, respectively. Overall survival was significantly better for patients with spine metastases of breast and prostate cancers compared to other tumors ($p < 0.05$) and significantly worse when visceral metastases were present ($p < 0.05$), when patients were metastatic de novo ($p < 0.05$), and in those patients receiving single fraction SBRT (p: 0.01).

Conclusions According to our experience, SBRT for patients with spinal metastases was effective in terms of local control and useful to reach pain relief. Regarding the intent of the treatment, an adequate selection of patients is essential to propose this ablative approach.

Keywords SBRT · Spine metastases · Ablative · Oligometastases

Introduction

The spine is a common location for metastases and confers high morbidity as pain, spinal cord compression, hypercalcemia, and pathologic fractures [1]. Conventional external beam radiotherapy (EBRT) traditionally using schedules of 8 Gy in 1 fraction, 20 Gy in 5 fractions, or 30 Gy in 10 fractions has been a standard-of-care and a palliative approach for patients with symptomatic spine metastases [2], although long-term efficacy has been rather disappointing. Advances in systemic treatments are increasing life expectancy for metastatic patients reinforcing the need for more effective local treatment of spinal metastases.

In 1995, Hellman and Weichselbaum hypothesized that the oligometastatic state (≤5 extracranial metastases) represents an intermediary state of cancer between widely metastatic and incurable disease and curable disease [3]. For patients with oligometastatic disease, Stereotactic body radiation therapy (SBRT) allows the highly accurate delivery of dose escalated radiation treatment between one to five fractions leading to excellent local control rates (1 year: 90%) with higher pain relief as compared to conventional external spine radiation therapy (complete pain response

✉ Raquel Ciérvide
raquel.ciervide@gmail.com

[1] Department of Radiation Oncology, Hospital Universitario HM Sanchinarro, HM Hospitales, Madrid, Spain

range 46–92% vs 24%)[4–6] and a low toxicity profile (0.2% rate of neurologic injury) [7–13]) based upon a sharpness characterized by a rapid dose fall-off between target and the surrounding normal tissues.

As opposed to surgery, SBRT does not require post-surgical recovery, it can safely treat different locations at the same time and it might induce an abscopal effect particularly in hot tumors associated to a powerful immune response [14].

Although SBRT to oligometastases is associated to a better progression-free survival in some primary tumors [15], a proper patients' selection appears mandatory to maximize its effect. Here, we present the results we observed with the use of SBRT in patients with spinal metastases at our institution during the last 12 years.

Materials and methods

Patients and data acquisition

We retrospectively reviewed clinical charts from patients with diagnoses of spinal metastases attended at HM Hospitales (Madrid, Spain) between February 2010 and January 2022. Primary objective of the analysis was to evaluate local control and survival rates. Secondary objectives included pain control rate according to visual analogic scale (VAS) and incidence of vertebral fractures.

Inclusion criterial encompass patients with spine metastases, from the C1 to L5 levels, being allowed a solitary spine metastases; two separate spine levels; or up to 3 separate sites. Each of the separate sites were allowed to have a maximal involvement of 2 contiguous vertebral bodies. Patients with spinal instability, who underwent decompression and fixation surgery before spine SBRT, or patients with a history of radiotherapy in the same spinal level were excluded of this analysis. Patient´s characteristics are shown in Table 1.

Table 1 Patient's characteristics

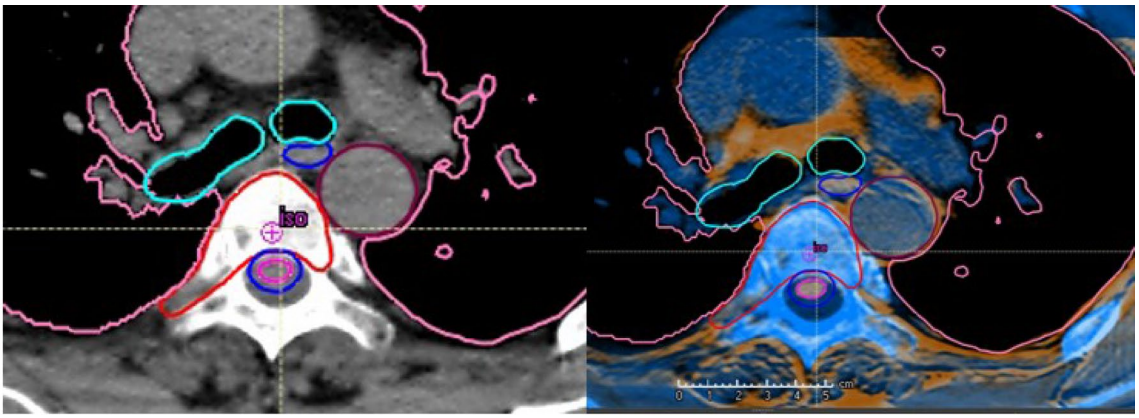
Patient's characteristics		
	N	(%)
Total patients	129	100
Fractionation		
7 Gy/5 fractions	32	25
18 Gy/single fraction	97	75
Sex		
Female	73	57
Male	56	43
Primary tumor location		
Breast	35	27
Lung	31	24
Prostate	20	15
Gastrointestinal	23	19
Others	20	15
Other bone metastases		
No	47	36
Yes	82	64
Visceral metastases		
No	78	60
Yes	51	40
Metastases		
De novo	40	31
Oligoprogression	89	69
Fracture after SRS treatment		
No	123	95
Yes	6	5
Spinal location		
Cervical	18	14
Dorsal	69	53
Lumbar	42	33
Spinal pain (VAS)		
0–3	62	48
4–7	47	36
8–10	20	16

Simulation and contouring

All patients were simulated in a stable supine position on a vacuum cushion (from D2-3 to L5) or with a shoulder mask (from cervical level to D2-3) depending on the spine level. CT planning was acquired with a slice thickness of 3 mm using a Somaton Sensation Open (Siemens Medical Solutions, Erlangen, Germany), until July 2018, since it was replaced by a Toshiba Aquilion LB (Canon Medical Systems, Otawara, Japan), using a slice thickness of 2 mm. All patients underwent MRI acquisition and a CT-MRI image registration was performed for delineation. Volumes of interest were defined using iPlan (Brainlab AG, Munich, Germany) or RayStation (RaySearch Laboratories, Stockholm, Sweden). Clinical target volume (CTV) included the gross tumor and immediately adjacent bony anatomic compartments at risk of microscopic disease extension, as described on International Spine Radiosurgery Consortium Consensus Guidelines [16] for spine SBRT. A 1–3 mm margin was added to the CTV to create the planning target volume (PTV) that could be modified at the dural margin and adjacent critical structures to allow spacing at the discretion of the treating physician, never overlapping the PTV with the spinal cord or cauda equina, and encompassing the entire GTV and CTV [15] (Fig. 1a, b). A security margin of 3 mm respect to the spinal cord, for its exclusion, was accounted for the PTV delineation during the treatment planning.

The spinal cord and cauda equina were delineated based on T1- or T2-weighted MRI images. The spinal cord was

a) CT-MRI image registration



b) CT-MRI image registration

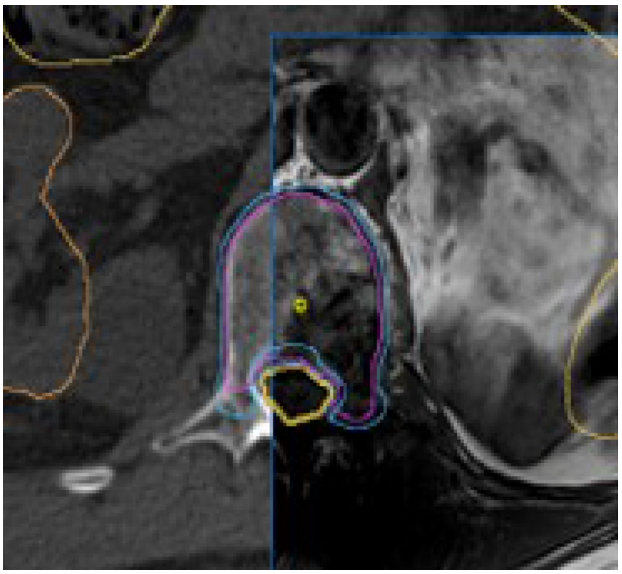


Fig. 1 Image registration

outlined starting at least 10 cm above the superior extent of the target volume, continuing on every CT slice to at least 10 cm below the inferior extent of the target volume. A 1.5 mm margin was added to the spinal cord (PRV cord). The remaining organs at risk (OARs) were outlined based on simulation CT images. Prescription dose were 18 Gy in single fraction or 5 fractions of 7 Gy on consecutive days. Both schemes were part of the intradepartmental protocol and the election of any of the schemes was at physician discretion.

Radiation treatment

From February 2010 to mid of 2015, treatment planning was performed in iPlan, with nine equally spaced intensity-modulated radiation therapy (IMRT) fields, using a dynamic multileaf collimator (MLC) rotated to follow the spinal cord shape, as seen in the Beam's Eye View (BEV), with the leaves motion. Dose calculation was based on Monte Carlo algorithm (XVMC), using dose-to-medium [17], mean variance 1% and 3 mm grid size. From mid of 2015 to nowadays, RayStation is used instead, which is based on collapsed cone algorithm. In this case, treatment plans were generated with volumetric modulated arc therapy (VMAT), with 2 or 4 full coplanar arcs, and the collimator rotated to 20° and 340°, (besides 250° and 290°, if four arcs are used), for achieving highly conformal dose, as shown in Fig. 2. Dose grid was stablished to 2 mm.

Plan was acceptable as long as $\geq 90\%$ of the target volume received the prescribed radiosurgery dose. Dose inhomogeneity was allowed within the target volume. Complete characteristics of radiation treatment and

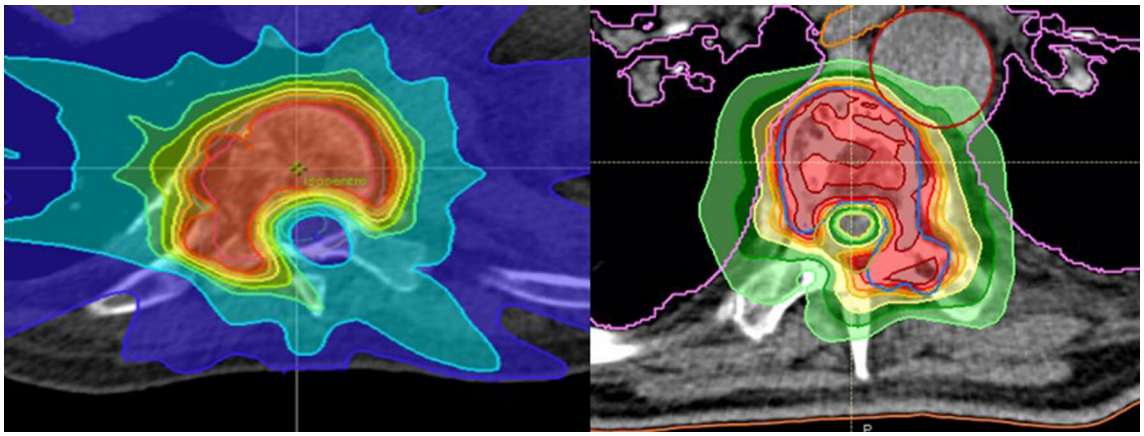


Fig. 2 Highly conformal dosimetry technique, IMRT (left) or VMAT (right)

Table 2 Treatment planning characteristics

Treatment planning characteristics			
	Average	Median	Range
1 fraction of 18 Gy			
PTV volume	41.9 cc	36.2 cc	6.6–109 cc
PTV D_{max}	19.9 Gy	19.8 Gy	18.7–21.9 Gy
PTV $D_{average}$	18.6 Gy	18.6 Gy	18–19.4 Gy
Spinal cord D_{max}	11.8 Gy	11.6 Gy	7.6–17.1 Gy
5 fractions of 7 Gy			
PTV volume	78.1 cc	58.2 cc	18.6–132 cc
PTV D_{max}	38.3 Gy	38.1 Gy	36.2–43.5 Gy
PTV $D_{average}$	35.7 Gy	36.1 Gy	33.1–38.6 Gy
Spinal cord D_{max}	21.85 Gy	23.29 Gy	11.23–32.9 Gy

recommended organ-specific dose constraints are detailed in Tables 2 and 3, respectively [18–20].

Radiation treatment was delivered in either a Novalis (Brainlab AG, Munich, Germany), with micro-MLC (3 mm leaf width) and nominal energy of 6 MV WFF, and a VERSA HD (Elekta AG, Stockholm, Sweden), with Agility MLC (5 mm leaf width) and 6 MV FFF beam energy. Patients were treated five days per week with inter and intrafraction IGRT (image-guided radiation therapy) verification using stereoscopic X-Rays images from ExacTrac System® (Brainlab AG, Munich, Germany) for Novalis unit or kV-cone-beam CT (kV-CBCT) for VERSA HD. Since the implementation of SGRT (surface guided radiation therapy) based on Catalyst HD™ (C-RAD, Uppsala, Sweden) at our department, we also incorporated not only to guide patient's set up but also to assess intrafraction surface movement.

Follow-up and evaluation

All patients were evaluated at the end of irradiation and every 3 months thereafter until death or lost follow-up. Pain intensity was documented according to the 10-point visual analog scale (VAS) (0, no pain; 10, worst pain). Pain failure was defined as an increase in the VAS rate by 2 or more from the scale at the preceding examination or an increase in analgesic requirements > 25% from baseline. Tumor response was classified by CT, PET-CT and/or MRI as complete or partial response/stable disease or tumor progression. In some unclear or controversial cases, a bone biopsy was performed to confirm tumor relapse.

Any toxicity attributable to the treatment was recorded according to the CTCAE 5.0 grading scale.

Follow-up time was considered from the end of treatment to the date of the last evaluation. Local progression-free survival (LPFS) was estimated from the last day of SBRT until local progression. Patients dying from intercurrent disease without evidence of tumor were censored at the date of death. Overall survival (OS) was defined as the time interval between treatment and the date of death, whatever the cause, or to the date of last follow-up. Statistical analysis was performed using SYSTAT, version 24.0 [IBM SPPS Statistics for Windows, Version 24.0 (Armonk, NY; IBM Corp)]. Actuarial LFS, DMFS, DFS and OS were calculated using the Kaplan–Meier method. Log-rank test was used for comparison between survival curves and the chi-square test was used for comparisons between groups. A level of $p < 0.05$ was considered statistically significant.

Table 3 Dose limitations for organs at risk

Dose limitations for organs at risk			
1 fraction of 18 Gy		5 fractions of 7 Gy	
Spinal cord	V14 < 0.035 cc	Spinal cord	Dmax < 27 Gy
	V10 < 0.35 cc		D 0.01 cc < 22.5 Gy
	V7 < 1.2 cc		
Cauda	V16 < 0.035 cc	Cauda	D max 30 Gy
	V14 < 5 cc		D 5 cc < 27.3 Gy
Esophagus	V16 < 0.035 cc	Esophagus	Dmax < 52 Gy
	V11.9 < 5 cc		D 5 cc < 27.5 Gy
Brachial plexus	V17.5 < 0.035 cc	Brachial plexus	Dmax < 32 Gy
	V14 < 3 cc		D 3 cc < 30 Gy
Heart	V22 < 0.035 cc	Heart	Dmax 52.5 Gy
	V16 < 15 cc		D 15 cc < 32 Gy
Great vessels	V37 < 0.035 cc	Great vessels	Dmax < 53 Gy
	V31 < 10 cc		D 10 cc < 47 Gy
Trachea/Larynx	V20. 2 < 0.035 cc	Trachea/Larynx	Dmax < 52.5 Gy
	V10.5 < 4 cc		D 4 cc < 18 Gy
Skin	V26 < 0.035 cc	Skin	Dmax < 39.5 Gy
	V23 < 10 cc		V36.5 < 10 cc
Stomach- Intestine	V16 < 0.035 cc	Stomach–Intestine	V35 < 0.03 cc
	V 11.2 < 5 cc		V30 < 5 cc
Kidney	Renal cortex V8.4 < 200 cc	Kidney	Ipsilateral kidney V15 < 66%
	Renal hilum V10.6 < 66%		Contralateral kidney V15 < 33%
Lung	V 7.4 < 1000 cc	Lung	V 12.5 < 10%, minor criteria 15%

Results

From February 2010 to January 2022, a total of 129 patients with 129 spinal metastases were treated with SBRT. All patients had 5 or less metastasis, so the whole sample were oligometastatic patients Patient's median age was 66 years old (range 28–84).

The 75% of patients were treated with a single fraction of 18 Gy while the remaining patients received 5 fractions of 7 Gy. Metastases from breast and lung cancer were predominants and according to spinal level, dorsal location was the most frequent (54%), followed by lumbar (33%) and cervical spine (14%). Nearly two thirds of patients (64%) had more than one bone metastases and 60% of them did not associate visceral metastases.

Only 6 patients (5%) of the cohort presented with vertebral fracture. All of them received single dose of 18 Gy. Two of them did not required more procedures and four underwent a vertebroplasty months after.

With a mean and median follow up of 22.9 and 14.2 months (range 0.5–140), respectively, six patients (5%) developed local relapse. Primary tumor of the locally relapsing metastases included: prostate cancer (1), breast cancer (1), lung cancer (1), sarcoma (1) and kidney cancer (2). Four out of six relapses received single dose and the remaining two received 5 fractions of 7 Gy.

For patients with painful metastases at attendance (74/129: 57%), all of them experienced an improvement in pain after SBRT, with a median reduction of 4 points (range 1–8) in VAS 3 months after SBRT. On univariate analysis, we did not find any relation between the pain reduction and sex, gender, age, spine location or number of fractions.

On log rank (Mantel Cox) test, the median of local progression-free survival was significantly lower for patients with dorsal compared to lumbar spine metastases (13.8 vs 32.2 months; p 0.049). However, we did not observe differences according to age, sex, primary tumor, fractionation and histology. Nor any difference were reported regarding radiation treatment schedule, and albeit two groups were not equally balanced 4/97 (4%) and 2/32 (10%) progressed locally after 18 Gy and 35 Gy respectively, although this difference was not statistically significant ($p = 0.46$). Local relapse free survival predictors are shown in Table 4.

Actuarial rates of overall survival at 12, 24 and 36 months were 91.2%, 85.1% and 83.2% respectively. On univariate analysis, overall survival was significantly better for patients with spine metastases of breast and prostate cancers compared to other tumors (1y OS: prostate 95%, breast 96.8%, lung 83.1%, gastrointestinal 83.1%, others 71%; $p < 0.05$) and significantly worse when visceral metastases were present (1y OS: visceral metastases 85.9% vs no visceral metastases 94.8%; $p < 0.05$), when patients were metastatic

Table 4 Local progression-free survival predictors

Local progression-free survival						
	1 year	*N* total	(%)	*N* relapse	(%)	*p* (Log rank test)
Global	83.3	129	100	6	100	
Age	≥66	67	52	3	50	0.27
	<66	62	48	3	50	
Sex	Female	73	56.6	3	50	0.69
	Male	56	43.4	3	50	
Primary tumor	Prostate	20	15.5	1	16.6	0.58
	Breast	35	27.2	1	16.6	
	Lung	31	24	1	16.6	
	Gastrointestinal	23	17.8	0	0	
	Others	20	15.5	3	50	
Spine location	Cervical	18	14	0	0	<0.05
	Dorsal	69	53.5	4	66.4	
	Lumbar	42	32.5	2	33.6	
Fractionation	1fx * 18 Gy	97	75	4	66.4	0.46
	5fx * 7 Gy	32	25	2	33.6	
Histology	Sarcoma-renal	16	12.4	2	33.6	0.6
	Other histologies	113	87.6	4	66.4	

de novo (1y OS: de novo 71.4% vs oligoprogression 98.9%; $p < 0.05$) and in those patients receiving single fraction SBRT (1y OS: single fraction 89.4% vs multifraction 96.8%; *p*: 0.01) as shown in Table 5 and Fig. 3. We didn't find any differences regarding histology, age, sex or if more bone metastases were present in the univariant analysis. In Table 5, we show overall survival predictors.

Regarding tolerance, only patients who underwent SBRT for cervical or high dorsal spine metastases, required AINES or dexamethasone during the week after to treat the acute esophagitis. No cases of complications attributable to SBRT were reported during treatment or follow-up period.

Discussion

High dose SBRT is considered a highly effective local approach for patients with spinal metastases. Numerous publications about management of spinal metastases are emerging since patients with metastatic spinal lesions have longer life expectancies and unmet pain management needs arise that require effective, fast and safe treatments.

In the current study, we reported our long-term experience with spinal SBRT for the last 12 years. The treatment was well tolerated by all patients with no related toxicity observed either during SBRT or at subsequent follow-up.

Main endpoint was local control. With a median follow up of 14.2 months (average 22.9; range 0.5–140 months) a local control rate of 94.6% fairly compares with other published series. Secondary endpoint was spinal pain control and all treated patients experienced a subjective

Table 5 Overall survival predictors

Overall survival				
	1 year	2 year	3 year	*p* (Log rank test)
Global	91.2	85.1	83.2	
Age				
≥66	90.5	83	78.8	0.14
<66	92	87	87	
Sex				
Female	93.1	88.7	88.7	0.18
Male	88.8	80.1	75.6	
Primary tumor				
Prostate	100	95	95	<0.05
Breast	100	100	100	
Lung	83.1	71.1	59.3	
Gastrointestinal	71	51.6	51.6	
Others	100	100	100	
Other bone metastases				
No	93.6	88.8	86.4	0.19
Yes	89.8	82.8	81.2	
Visceral metastases				
No	94.8	91.9	91.9	<0.001
Yes	85.9	75.6	69.4	
Fractionation				
1fx * 18 Gy	89.4	81.5	79.1	<0.05
5fx * 7 Gy	96.8	96.8	96.8	
Type of metastases				
De novo	71.4	53.4	53.4	<0.001
Oligoprogression	98.9	95.5	93.1	

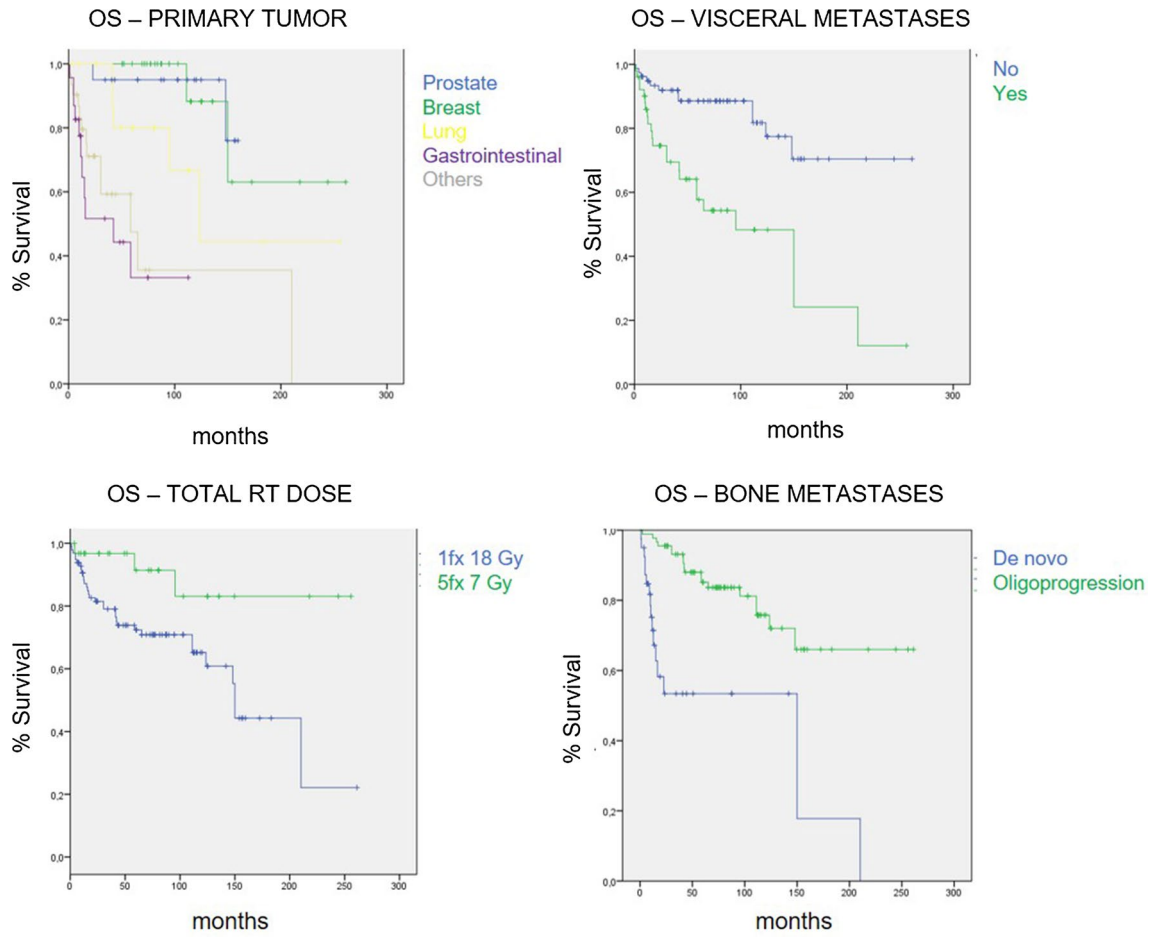


Fig. 3 Kaplan–Meier curves of overall survival after spine stereotactic body radiotherapy comparison according to primary tumor, total radiation dose and presence or absence of more bone metastases and visceral metastases

improvement in pain measured according to the VAS score with a median reduction in pain intensity of 4 points (range 1–8) at 3 months after completion of SBRT.

Regarding the association between the use of SBRT in spinal metastases and a faster and improved pain response compared to conventional fractionated palliative radiotherapy, Table 6 resumes published results of randomized studies comparing SBRT for spine metastases against radiotherapy with conventional fractionation [10, 11, 21–23]. Outcomes evidence that SBRT is not only effective in terms of local control but also in pain control relief.

We also analyzed the rate of vertebral fractures. It is established that dose per fraction is an important predictive factor for both tumor control and risk of vertebral fracture. Some studies specifically identified dose as a risk factor [24–26]. Sahgal et al. specifically cautioned physicians of vertebral fracture risk when treating with single-fraction doses of 20 Gy [26]. Previous reviews suggest that the time to fracture most commonly occurs at approximately 3 months post-SBRT [27].

However, we are aware of some limitations of our analysis. First, due to the retrospective nature of this series selection and other bias could not be excluded. Second, the low rate of local relapses did not allow to find differences between local relapse and histology, dose fractionation or the primary tumor location. Thus, metastases from generally considered radioresistant tumors [28] as renal cancer have better local control with high single doses (24 Gy) compared to low single dose (< 24 Gy) or hypofractionated schemes. Ghia et al. [28] also showed in a phase I/II trial that high single-fraction was associated with improved local control over multifractionated SBRT for renal cancer spine metastases. And similar results have been reported in patients with sarcoma [29] and melanoma [29]. Hence, it is hypothesized that the biologically effective dose (BED) escalation might be advantageous in radioresistant histologies. Unluckily, and due to the short number of patients and the low incidence of events observed, we have not been able to establish a relationship between total dose and tumor histology and magnitude of pain relief obtained.

Table 6 Randomized trials of SBRT and conventional radiotherapy for the treatment of spinal metastases

Randomized trials comparing SBRT and conventional external beam cEBRT for spinal metastases								
Year	References	Number of lesions	Dose	Number of fractions	Follow-up (months, median)	Complete pain relief (at 3 months) (%)	Local control	Overall survival
2018	Sprave et al. [10]	27	SBRT 24 Gy	1	8.1	43	NR	7.9 months (median OS)
		28	cEBRT 30 Gy	10		17.4		
2019	Nguyen et al. [18]	81	SBRT 12 Gy(> 4 cm) SBRT 16 Gy (< 4 cm)	1	NR	39	100% at 2 years	6.7 months (median OS)
		79	cEBRT 30 Gy	10		21	90.3% at 2 years	
2019	Ryu et al. [19] (RTOG 0631)	209	SBRT 16-18 Gy	1	NR	40.3	NR	NR
		130	cEBRT 8 Gy	1		57.9		
2021	Pielkenrood et al. [20] (VERTICAL study)	45	SBRT 18, 30, 35 Gy	1, 3, 5	NR	40	NR	NR
		44	cEBRT 8, 20, 30 Gy	1, 5, 10		32		
2021	Sahgal et al. [11] (CCTG study)	114	SBRT 24 Gy	2	6–7 months	35	NR	NR
		115	cEBRT 20 Gy	5		14		

Not reported

And third, overall survival is multifactorial and it depends on many other factors besides this local approach which reflect the natural progression of metastatic disease. We have included patients with metastases from several types of primary cancer and, what is utter most importance, in different metastatic stages, with or without simultaneous visceral metastases. As expected, overall survival was significantly better in patients with breast cancer compared to other primary tumors and worse when bone metastases were diagnosed de novo as compared to recurrences and when visceral metastases were also present. These data are in concordance with which is described in the literature [30]. However, we found that patients who received 5 fractions of 7 Gy live longer than those who received a single fraction of 18 Gy. This result should be considered with high caution since there could be a selection bias in the prescription dose, resulting in unbalanced distribution of prescriptions.

Conclusions

According to our experience, Stereotactic Body Radiotherapy (SBRT) for patients with spinal metastases was effective in terms of local control and useful to reach pain relief. Regarding the intent of the treatment, an adequate selection of patients is essential to propose this ablative approach.

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Data Availability Data generated or analyzed during the study are available from the corresponding author (raquel.ciervide@gmail.com) by request.

Declarations

Conflict of interest The authors declare no conflict of interest.

Institutional Review Board The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (CEIm) of FUNDACION DE INVESTIGACIÓN HM HOSPITALES (Código CEIm HM Hospitales: 23.02.2163-GHM) which certifies that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Informed Consent Informed consent was obtained from all subjects involved in the study.

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