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Robotic Stereotactic Body Radiotherapy for Spine Metastasis Pain Relief

Daniel Rivas [1], Alejandro de la Torre-Luque [2,*], Vladimir Suárez [3], Rafael García [4], Castalia Fernández [5], Daniela Gonsalves [5], Elena Moreno-Olmedo [6], María Isabel Núñez [7,8,9,*] and Escarlata López [10]

1 Department of Radiation Oncology, GenesisCare, 29018 Málaga, Spain; daniel.rivas@genesiscare.es
2 Department of Legal Medicine, Psychiatry and Pathology, Complutense University of Madrid, CIBERSAM, 28040 Madrid, Spain
3 Independent Researcher, 28043 Madrid, Spain; vladysu@yahoo.com
4 Department of Radiation Oncology, Hospital Ruber Internacional Cyberknife, Quiron, 28034 Madrid, Spain; rafael.garciag.ce@ruberinternacional.es
5 Department of Radiation Oncology Cyberknife, GenesisCare, 28043 Madrid, Spain; castalia.fernandez@genesiscare.es (C.F.); daniela.gonsalves@genesiscare.es (D.G.)
6 Department of Stereotactic and MR-Guided Radiotherapy, Genesiscare UK and Department of Oncology, Oxford University Hospitals NHS Foundation Trust, Oxford OX4 6LB, UK; elena.moreno2@genesiscare.co.uk
7 Department of Radiology and Physical Medicine, Granada University, 18016 Granada, Spain
8 Biopathology and Regenerative Medicine Institute (IBIMER), Centre for Biomedical Research, Granada University, 18100 Granada, Spain
9 Biosanitary Research Institute, ibs.Granada, 18012 Granada, Spain
10 GenesisCare Spain South Chief Medical Officer, 29018 Málaga, Spain; escarlata.lopez@genesiscare.es
* Correspondence: af.delatorre@ucm.es (A.d.l.T.-L.); isabeln@ugr.es (M.I.N.); Tel.: +34-680694682 (A.d.l.T.-L.); +34-958242077 (M.I.N)

Abstract: Spinal metastasis may occur in 40–70% of patients with cancer. Symptoms can vary from pain to spinal cord compression (SCC) and can affect their quality of life (QoL). Stereotactic body radiotherapy (SBRT) allows dose escalation of spinal tumor metastases, minimizing doses to organs at risk and improving pain control. The aim of this study is to retrospectively describe our institution's experience with robotic SBRT (CyberKnife®, Accuray Incorporated, Sunnyvale, CA, USA) for spinal metastases, in terms of feasibility, oncological results, toxicities, and pain relief observed. In total, 25 patients with 43 lesions were assessed, most of them with dorsal metastases (48.8%). The median total dose was 27 Gy (16–35 Gy), the median number of fractions administered was 3 (1–5), and the median dose per fraction was 9 Gy. Pain was evaluated using the visual analogue scale at baseline and at the end of treatment. The statistically significant reduction in pain ($p < 0.01$) was associated with the total dose of radiotherapy delivered ($p < 0.01$). Only one patient developed grade 3 dermatitis. Female gender, adenocarcinoma tumors, and lack of previous surgery were associated with better response to SBRT ($p < 0.05$). Robotic spine SBRT is feasible, well-tolerated, and improves patients' QoL through a statistically significant reduction in pain, so it should be offered to patients at an early stage in their process.

Keywords: spinal SBRT; robotic SBRT; CyberKnife; spinal metastases

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1. Introduction

Approximately 40–70% of patients with cancer will develop bone metastases [1] during the timespan of their disease [2], resulting in a significant reduction in their quality of life (QoL) as well as an increase in healthcare costs and service utilization compared to patients without bone metastases [3]. The incidence increases because of improving cancer survival rates [4]. Spinal metastasis may mainly affect the thoracic spine (70%), followed by the lumbar spine (20%) [5]. Out of these patients, 10% will develop spinal cord compression (SCC), a serious disabling condition that requires urgent treatment [6]. Spinal metastasis

can also lead to significant complications—such as pain, due to destruction of bone tissue and/or neurological complaints [7]—in up to 90% of patients [8].

The spinal metastasis incidence is more common during the evolution of these primary tumors: lung (24%), breast (24%), liver (12%), prostate (11%), and kidney (11%) [1]. Most symptomatic lesions develop due to breast, prostate, and lung cancer (56–74%), and are most common in the thoracic spine (51–67%). Pain occurs due to the destruction of bone tissue and/or nerve root and/or SCC. Both RT and surgery are effective in treating these symptoms [9].

Symptoms relief can be achieved with conventional fractionated conformal external beam radiotherapy (cEBRT) because it is convenient and cost-effective. Nevertheless, given the longer survival of patients with metastatic cancer, we should try more radical treatments due to the improvements that are evident in systemic therapies, such as targeted therapies and immunotherapies. In addition, the low radiation tolerance of the spinal cord and cauda equine requires optimal radiation dose delivery for durable tumor control [2]. However, since the treatment dose is limited by organs at risk (OARs), it is not possible to reach ablative doses within the tumor volume with cEBRT. Complete response rates of 17–34% and partial responses of 49% have been described with cEBRT, with an overall response rate of 60–66%. In addition, it has been reported that a retreatment incidence between 7.4 and 21.5% can be seen, depending on the fractionation schedule [10,11].

On the other hand, SBRT allows for greater dose fall-off, minimizing doses to the spinal cord and to other surrounding tissues. This allows dose escalation to the tumor volume, which improves the chances of overcoming it. With SBRT, tumor control rate is greater than 80% [12–15], reaching 91.6% in patients with more than 5 years of survival [16]; shows a low incidence of serious complications such as myelopathy (0.4%) [2,17]; and enables patients to preserve function [2]. So, spine SBRT obtains high local control rates (84–90%) and it is a safe treatment with low toxicity [18].

Traditionally, metastatic spinal lesions have been treated with doses and fractions of RT considered safe for the spinal cord and used for the purpose of pain relief and local control (LC) of these lesions. The doses commonly used in this regard are 10 fractions of 3 Gy, 5 fractions of 4 Gy, or 1 fraction of 8 Gy. We are now able to deliver higher, biologically effective and radical doses because we can better tailor the dose and limit the toxic dose at the level of the spinal cord. SBRT is usually administered in 1 to 5 fractions with more than 6 Gy per fraction. Disease progression at the spinal level is associated with neurological morbidity, pain, and limited adjuvant treatment options, making SBRT ideal for this location as it improves local disease control and improves symptoms [19].

The Canadian Association of Radiation Oncology defines SBRT as the precise delivery of highly conformal, image-guided, hypo-fractionated external beam radiation therapy that is delivered in one or a few fractions to an extracranial target with biologically equivalent doses to a conventional fractionated radical treatment [20]. SBRT regimens use doses of 16–18 Gy in one fraction, 24–26 Gy in 2 fractions, 24–27 Gy in 3 fractions, and 30–40 Gy in 5 fractions [19,21].

Some prospective trials have studied the role of SBRT for spinal metastases. In a phase I/II trial that enrolled 61 patients with non-cervical spine tumors, the study showed a control rate of 88% with 18 months of follow-up with a single-fraction SBRT [22]. The RTOG 0631 was a phase II trial that included 44 patients with 1–3 spinal metastases. The administration of a 16 Gy single-fraction SBRT was shown to be feasible [23].

The phase III SC.24 clinical trial demonstrated that spinal SBRT was superior to cEBRT in terms of pain relief and has therefore been established as one of the standard treatments [24,25].

Spinal SBRT is practiced today as an alternative to conventional palliative radiation in primary treatment, re-irradiation, and in the post-operative setting, albeit with no or very few randomized trials to support its practice. However, it is true that the limitations of spinal SBRT, as well as its possible complications, are known to a greater extent [20]. Possible complications include vertebral body fractures (VBF) (11–39%) and myelopathy

(0.4%) [19,24]. Another possibility is the appearance of the "Pain Flare" effect (14–68%), a transient increase in pain that can be controlled with corticosteroids as a preventive measure.

The aim of this study is to describe our institution's experience with robotic SBRT for spinal metastases in terms of feasibility, oncological results, toxicities, and pain relieve. Also, we will analyze factors associated with responses following SBRT.

2. Materials and Methods

Between July 2011 and January 2017, 25 patients with 43 lesions were treated. A retrospective study was conducted evaluating the records of patients diagnosed with vertebral spine metastases treated with Robotic SBRT CyberKnife® VSITM System version 9.0 ® (Accuray Incorporated, Sunnyvale, CA, USA) at our institution. Clinical and dosimetric characteristics of these patients were recorded, as well as the date of the first and last medical control. Pain evaluation was assessed at first consultation and one month after the last SBRT using the visual analogue scale (VAS) (we search for a faster analgesic response). Surveillance imaging was common and scheduled at the discretion of treating physicians. Disease progression and late toxicity were assessed using both the clinical exam and radiographic follow-up (RECIST criteria, version 1.1), when available. Toxicity was graded retrospectively using the Common Toxicity Criteria, version 4.0. (CTCAE). All treatment decisions were made in multidisciplinary teams (MDTs), considering patient benefit in terms of pain relief, LC, and QoL. In the MDTs, the neurosurgeons and radiation oncologists established the spinal instability neoplastic score (SINS) of each lesion, and a minimally invasive surgery was prescribed prior to SBRT if needed (Figure 1).

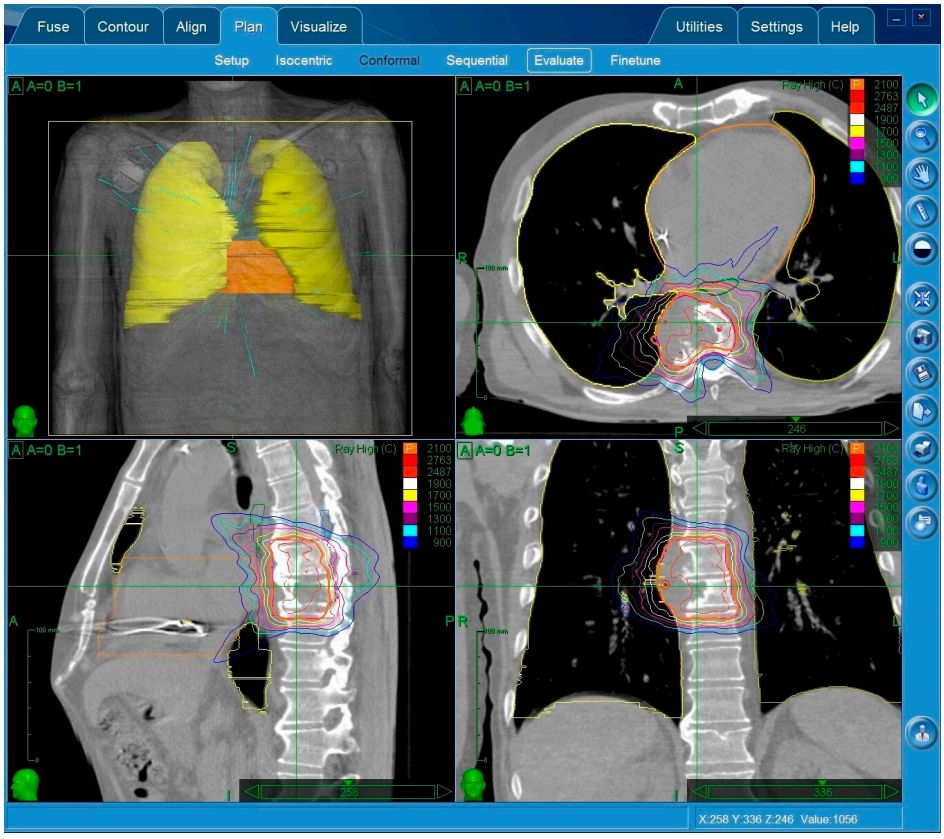

Figure 1. SBRT plan treatment dosimetry (SINS* = 7 or potentially unstable); * spinal instability neoplastic score.

All patients provided written informed consent, which was required due to the retrospective nature of this study. The GenesisCare Clinical Leader Forum (CLF) approved the analysis of patient data.

2.1. Treatment Planning

Treatment planning was based on a 1.25 mm thin slice of computed tomography (CT) scan with contrast-enhanced T1- and T2-weighted magnetic resonance imaging (MRI). If necessary, positron emission tomography (PET) was also used to assist with lesion contouring. During treatment, tumor target volume location was performed with Xsight® Spine tracking (Accuray, Sunnyvale, CA, USA). This tracking system corrects translations and rotations in real time with sub-millimeter accuracy without interfering with cementation or screws. Contouring of lesions and OARs was performed by expert radiation oncologists according to the guidelines published in 2012 [26]. The spinal cord was contoured from 6 mm above to 6 mm below the tumor volume [23]. Dose and fractionation were chosen according to tumor target volume and OAR tolerance doses. When appropriate, tolerance doses for spinal cord or cauda equina were chosen depending on the administered fractionation. The prescription isodose curve was chosen by the radiation physicist in collaboration with the radiation oncologist. The minimum coverage with a dose prescription of target volume required to treat patients was 90%. The Treatment Planning System (TPS) was the Multiplan 4.6® (Accuray, Sunnyvale, CA, USA).

2.2. Statistical Analysis

The study endpoints were clinical pain response and LC. Pain clinical response was defined as any decrease in the VAS punctuation. Pain was assessed at the first consultation, one month after finishing SBRT. Of the 43 lesions treated, 33 were also evaluated at three months, of which one lesion had no improvement, 7 lesions had a partial improvement in pain and the remainder, and 25 lesions had a complete analgesic response. The VAS ranged from 0 to 10, with 0 being no pain and 10 being severe pain. LC was defined as a radiological response according to RECIST criteria. Acute toxicity was assessed with the CTCAEv4.0 scale.

Descriptive analysis of baseline characteristics and treatment outcomes was performed. Student's t-test was used to evaluate the statistical significance of the difference in VAS before and after SBRT. The Shapiro–Wilk test was performed to evaluate the normal distribution of VAS before and after treatment. The significance level was set at p-value < 0.05. All statistics were performed in SPSS IBM Co. v.22.

2.3. Data Analysis

Data were described using median and range for continuous variables, and using proportion of cases (in percentage) for categorical and dichotomous factors.

Multilevel generalized linear modelling was used to study the relationship between pain outcomes and covariates of interest (sociodemographic, clinical, and treatment-related factors). The repeated-measure factor (i.e., the patient underwent RT more than once) was used as a multilevel variable. First, univariate models were conducted. Factors significantly associated with the outcome were included in a multivariate model (including all the significant covariates). For the multivariate model, the Akaike criterion index (AIC) was used to compare the model with covariates to the unconstrained model. The odds ratio (OR) was used as an effect size (loading coefficient) estimate.

All analyses were performed using R software x64 3.0.1 (psych, car, and glmer packages).

3. Results

A total of 25 patients with 43 spinal metastases were treated with robotic SBRT between July 2011 and January 2017. Patients had a median age of 56 years (range: 28–80), and an adequate Karnofsky performance status (KPS) (mean = 90%). The most common histologies of primary tumors were breast (32.6%), prostate (21%), lung (14%), and colorectal carcinomas (7%). Most participants (74.4%) were treated due to an adenocarcinoma. Patients were mostly naïve to systemic treatment (79% of the sample). Moreover, 58% of participants received at least a first-line chemotherapy treatment. Baseline patient characteristics are

shown in Table 1. The frequency of vertebral bodies involved is shown in Table 2, which shows that some of the treatments administered involved more than one vertebra.

Table 1. Patient characteristics.

	Number	Percentage (%)
Age		
Years old (median)	56 (28–80)	
Sex		
Male	11	44
Female	14	56
Visceral Metastases		
Yes	20	45.5
No	23	53.5
Visceral Metastases Localization		
Lung	8	18.2
Cerebral	4	9.1
Nodes	1	2.3
Multiple localizations	7	15.9
Histology		
Breast cancer	14	32.6
Prostate cancer	8	18.6
Lung cancer	6	13.9
Colorectal cancer	3	7
Other	12	27.9
Bone Metastases		
Single	8	18.6
Multiple (<5 lesions)	35	81.4
Prior to CT		
No	18	42
Yes	25	58
Initial KPS Index		
Mean	88.14 (SD 10.29)	-
Prior to RT in Other Locations		
No	36	83.7
Yes	7	16.3
Infield Prior to RT		
No	35	81.4
Yes	8	18.6
Spine Surgery Prior to RT		
No	34	79
Yes	9	21

RT: radiotherapy; CT: chemotherapy

Table 2. Frequency of vertebral bodies affected.

Location of Spine Metastasis	Nº
Cervical	8
Thoracic	21
Lumbar	13
Sacral	1
Total lesions	43

The median time from cancer diagnosis to bone metastasis was 47.76 months (range 0–154.1). The median follow-up for pain control was 15.17 months (range 0.2–85.18). Regarding RT toxicity, only one patient experienced grade III dermatitis. No other participant reported RT toxicity. Pain levels did not differ significantly between time points, as assessed by clinicians $\chi 2$ (2) = 1.06, p = 0.60. However, VAS scores significantly decreased between

assessment points, t (28) = 4.14, $p < 0.01$, Cohen's d = 0.72. SBRT treatment features are displayed in Table 3.

Table 3. Treatment features and follow-up.

	Statistic
Time from diagnosis to bone metastasis (months)	47.24 (range 0–154.1)
Time from metastasis to RT start (months)	22.4 (range 0.85–87.16)
Time from RT end and first pain control (months)	3.3 (range 0.1–13.02)
Time from RT end and last pain control (months)	15.2 (range 0.2–85.2)
Prescribed dose (Gy)	27 (range 16–35)
Treatment fraction (Gy)	3 (range 1–5)
Dose per fraction (Gy)	9 (range 5–16)
BED10 (Gy)	51.3 (range 35.7–60)
Curve prescription (% ≥80%)	55.8
RT Coverage (% ≥95%)	74.4
Mean dose CTV (Gy)	2982.1 (range 1781–3963.6)
CI	1.2 (range 1.03–1.32)
HI	1.25 (range 1.14–1.35)
Median dose in spinal cord (Gy)	657.7 (range 0.6–17)
Pain assessment (clinician assessment)	
First control (1 month)	3 (range 0–3)
Last control (3 months)	3 (range 0–3)
VAS (last control)	
Pre-treatment	2.48 (range 0–8) (SD 2.42)
Post-treatment (1 and 3 months)	0.97 (range 0–5) (SD 1.75)

Note. Median and range (minimum and maximum, between brackets) are displayed for continuous variables. Percentage of cases are displayed for categorical variables. RT = radiotherapy. BED = biologically equivalent dose. KPS = Karnofsky performance status scale. CI = conformational index. HI = homogeneity index. VAS = visual analogue scale.

Table 4 displays the statistics derived from studying univariate relationships between the pain outcomes and the variables of interest. Regarding the clinician assessment of pain at the first follow-up, despite two factors being univariately significant (the time from bone metastasis to SBRT initiation and prescribed dose), none of them showed a significant effect.

Four covariates were univariately associated with the clinician's assessment at the last follow-up point: female gender (OR = 1.43); histology (OR = 1.59)—observation of higher pain scores in patients with other malignant tumors (compared to adenocarcinomas); absence of visceral progression (OR = 0.68); and lack of previous surgery (OR = 0.65). All these covariates were entered into a multivariate regression model. This model (AIC = −607.91) fitted the data better than a model without covariates (AIC = −590). Regarding the covariates, the following three were significant within this multivariate model: female gender (OR = 1.35, CI95 = (1.06, 1.71), $p < 0.05$); histology—observation of higher pain scores in patients with other malignant tumors compared to adenocarcinomas (OR = 1.32, CI95 = (1.04, 1.67), $p < 0.05$); and lack of previous surgery (OR = 0.73, CI95 = (0.58, 0.93), $p < 0.01$).

Table 4. Univariate relationships between pain outcomes and sociodemographic and RT-related factors.

	First Control				**Last Control**							
	Clinician Assessment				**Clinician Assessment**				**VAS**			
	OR	**CI_{95} (LB)**	**CI_{95} (UB)**	**Wald's Test**	**OR**	**CI_{95} (LB)**	**CI_{95} (UB)**	**Wald's Test**	**OR**	**CI_{95} (LB)**	**CI_{95} (UB)**	**Wald's Test**
Sex (ref.: female)	1	0.92	1.1	0	1.43	1.43	1.43	3379.05 **	1.01	0.82	1.24	0.11
Age (at treatment start)	1	1	1	0.09	1	1	1	0	0.99	0.98	0.99	−3.74 **
Cancer type (ref.: adenocarcinoma)	1.02	0.92	1.12	0.33	1.59	1.59	1.59	8124.04 **	1.01	0.83	1.24	0.11
Non-spinal bone metastasis (ref.: no)	1.01	0.94	1.09	0.31	1	1	1	0	0.95	0.95	0.96	−19.41 **
Spinal metastasis location (ref.: cervical)	1.03	0.92	1.15	0.49	1	1	1	0	0.97	0.96	0.98	−4.05 **
Visceral metastasis (ref.: no)	0.96	0.87	1.05	−0.91	0.68	0.55	0.83	−3.72 **	1.06	0.87	1.29	0.58
Time from diagnosis to bone metastasis	1	1	1	−0.07	1	1	1	0	1	1	1	−0.31
Time from metastasis to RT start	1	1	1	2.47 *	1	1	1	0	1	1	1	−3.08 **
Time from RT end and first pain control	1	0.99	1.01	−0.01	1	1	1	0	0.99	0.99	0.99	−36.15 **
Time from RT end and last pain control	1	1	1	−0.52	1	1	1	0	1	1	1	3.66 **
KPS	1	1	1.01	0.86	1	1	1	0	1	0.99	1.01	0.26
Previous infield radiation (ref.: no)	0.99	0.92	1.08	−0.13	1	1	1	0	1	0.96	1.05	0.01
Previous surgery (ref.: no)	1.01	0.92	1.12	0.28	0.65	0.51	0.84	−3.27 **	1.02	0.82	1.29	0.21
Prescribed dose	1	1	1	2.8 **	1	1	1	0	1	1	1	2.07 *
Treatment fraction	1	0.96	1.03	−0.24	1	1	1	0	1.02	1.02	1.03	11.8 **
Dose per fraction	1	1	1	−0.73	1	1	1	0	1	1	1	−6.15 **
BED10	1	0.99	1	−1.43	1	1	1	0	0.99	0.99	1	−6.39 **
Curve prescription (ref.: <80%)	0.99	0.93	1.06	−0.24	1	1	1	0	1	0.98	1.02	−0.04
RT Coverage (ref.: <95%)	1.04	0.96	1.12	0.87	1	1	1	0	1	0.98	1.02	−0.01
Mean dose	1	0.99	1	−1.43	1	1	1	0	0.99	0.99	1	−6.39 **
CI	1.05	0.59	1.87	0.17	1	1	1	0	0.99	0.98	1.0	−2.07 *
HI	1.09	0.54	2.23	0.24	1	1	1	0	1	0.72	1.39	0.01
Mean dose in spinal cord [1]					1	1	1	0				
Clinician assessment of pain (first control) [1]					1	1	1	0	1	0.97	1.04	0.16
VAS score of pain (pre-treatment)	1.01	0.99	1.03	0.85	1	1	1	0	0.99	0.98	1	−2.98 **

Note: RT = radiotherapy. BED10 = biologically equivalent dose con $\alpha/\beta = 10$. KPS = Karnofsky performance status. CI = conformal index. HI = homogeneity index. VAS = visual analogue scale. OR = odds ratio. CI95 (LB) = confidence interval of the OR at 95% (lower bound). CI95 (LB) = confidence interval of the OR at 95% (upper bound). [1] Lack of model convergence for two outcomes (blank cells). * $p < 0.05$; ** $p < 0.01$. Finally, 13 covariates were univariately associated with the VAS score at the last follow-up point: younger age (OR = 0.98); absence of non-spinal bone metastasis (OR = 0.95); development of spinal metastasis in upper spinal locations (OR = 0.97); interval from metastasis to RT initiation (OR = 1.00); interval between RT and pain assessment (first control, OR = 0.99; last control, OR = 1.00); treatment fraction (OR = 1.00); dose per fraction (OR = 1.02); lower mean dose of RT (OR = 0.99), lower BED (OR = 0.99), lower CI (OR = 0.99); and lower pre-treatment pain using the VAS (OR = 0.99). Due to the limited sample size and the small magnitude of covariate effects, a multivariate analysis was conducted by entering covariates with a higher OR: spinal metastasis location, CI, and pre-treatment pain. As a result, the model with covariates (AIC = −40.34) fitted the data better than a model without covariates (AIC = −23). Again, all the covariates were significant within this multivariate model. In this regard, patients with metastasis in lower spinal regions showed lower VAS scores compared to those with cervical lesions (for dorsal lesions: OR = 0.96, CI95 = (0.94, 0.97), $p < 0.01$; for lumbar or sacral lesions: OR = 0.96, CI95 = (0.95, 0.98), $p < 0.01$). On the other hand, individuals with lower pre-treatment VAS scores showed higher scores after the treatment, OR = 0.98, CI95 = (0.96, 0.99), $p < 0.01$. Finally, patients with higher CI showed increased pain scores on the VAS, OR = 1.02, CI95 = (1.01, 1.03), $p < 0.01$.

4. Discussion

In this series, while investigating the effectiveness of SBRT with respect to pain control of spinal metastases, we found a reduction in the VAS score (last control data between one and three months after radiotherapy) of more than 1.5 points (2.48 VAS pre-treatment vs. 0.97 VAS post-treatment, $p < 0.01$). It is relevant to note that 17 lesions were asymptomatic before treatment. We also found two factors that were variably significant: the time elapsed from bone metastasis to the start of SBRT and the prescribed dose. In this regard, the longer the interval between bone metastasis and SBRT initiation, the worse it is for pain relief ($p < 0.01$), and a higher prescribed dose is better for pain relief ($p < 0.01$).

Three covariates were significant within this multivariate model: female sex ($p < 0.05$); histology, observation of higher pain scores in patients with other malignancies compared to adenocarcinomas ($p < 0.05$); and the lack of previous surgery ($p < 0.01$). Thus, female sex, adenocarcinoma tumors, and the lack of previous surgery were associated with a better response to SBRT in our study. Of note, female gender is related to adenocarcinoma tumor type in our study ($p < 0.0007$), and it is not related to previous surgery.

Patients with metastases in lower spinal regions also showed lower VAS scores compared to those with cervical lesions. Individuals with lower VAS scores before treatment showed higher scores after treatment. Finally, patients with a higher CI showed higher pain scores (exacerbation effect due to peripheral tissue inflammation). In addition, SBRT can be administered with very low toxicity (only one patient experienced grade III radiodermatitis).

In the study conducted by Yeung and colleagues, the median age was similar (62 years; range 27–88) to that of our own series (56 years; range 28–80). The gender distribution also exhibited similarities: 15 female and 11 male patients in both studies. However, there were differences in the number of spinal metastatic lesions treated. Yeung et al. addressed 32 lesions, while our series involved 43 lesions. Notably, the most frequently treated lesions in their study were pulmonary metastases (n = 19), whereas our series predominantly focused on breast metastases. Regarding treatment locations, both studies emphasized the thoracic spine as the most common site (n = 18 in Yeung et al. vs. n = 21 in our study). The lumbosacral spine followed closely (n = 12 in Yeung et al. vs. n = 14 in our study), and the cervical spine was less frequently treated (n = 2 in Yeung et al. vs. n = 8 in our study) [2].

In terms of dose fractionation, Yeung et al. primarily used 24 Gy in 3 fractions, whereas our study employed 27 Gy in 3 fractions. Acute toxicity, mainly characterized by pain flare, occurred in 16% of the treated lesions and could be managed with analgesics and steroids. Interestingly, in our series, the flare effect was observed in patients with a higher CI. Importantly, no radiation-induced myelopathy was reported by Yeung et al., and only one case of grade III dermatitis occurred in our study. Based on these findings, we can confidently conclude that SBRT is a safe treatment [2].

Several studies have reviewed SBRT's pain control and other clinical benefits in the literature.

In their study, Zeng et al. compared SBRT and cEBRT in patients with spinal metastatic lesions with palliative intent. The median follow-up was almost one year. Median survival was 21.6 months for SBRT and 18.9 months for cEBRT ($p = 0.428$). The risk of local failure of SBRT vs. cEBRT was 2.8% vs. 11.2% at 6 months, 6.1% vs. 28.4% at 12 months, and 14.8% vs. 35.6% at 24 months. Time to re-irradiation was favorable in the SBRT group (2.2% vs. 15.8% ($p = 0.002$) and 22.9 months vs. 9.5 months, respectively). However, the rate of vertebral fractures was higher in SBRT (8 of 12 vs. 4 of 12). Therefore, this study evidences a benefit in the antalgic response with SBRT in 2 fractions up to a total of 24 Gy, less local failure, and less need for re-irradiation in favor of SBRT [27]. These findings encourage us to indicate SBRT in oligometastatic spinal lesions, such as those in our series.

A recent study by Patel and colleagues demonstrated that while SBRT is an excellent treatment method for LC in patients with spinal metastases, the risk of vertebral body fracture (VBF) remains significant. In their series, the 12% VBF rate one year after SBRT aligns with previous publications reporting VBF rates ranging from 11% to 39%. Notably,

their study stands out as the largest investigation to date that explored the role of antiresorptive drugs in mitigating VBF frequency after SBRT. Their data indicate that patients who received antiresorptive medication before SBRT had a significantly lower incidence of VBF at 1 year and 2 years post-treatment compared to those not taking antiresorptive drugs. Remarkably, the cumulative incidence of VBF remained at 4% among patients who initiated antiresorptive medication before SBRT, a notably lower rate than that historical data would predict. These findings suggest that antiresorptive drugs may serve as a noninvasive and low-risk preventive solution to reduce the risk of VBF following spinal SBRT [28]. Furthermore, in the study conducted by Patel et al., local tumor control (LC) at 1 year and 2 years was reported as 83% and 71%, respectively. The median overall survival (OS) was 30.6 months. Specifically, OS rates at 1 year and 2 years were 88% and 59%, respectively. Univariate analysis revealed that worse outcomes were associated with the presence of visceral metastases ($p = 0.001$), uncontrolled primary disease ($p = 0.02$), and having more than three vertebral metastases ($p = 0.04$). In the multivariate analysis of OS, only the presence of visceral metastases remained statistically significant ($p = 0.002$) [28]. In our study, we did not administer antiresorptive drugs, but it is something that should be recommend in present and future clinical practice.

Sprave et al. also found, in their randomized study, that SBRT has a faster and better pain response than cEBRT [29]. We cannot compare the results of our series with cEBRT, but acute form pain relief at 1–3 months was very statistically significant.

The planned phase 3 component of RTOG 0631 analyzes pain relief at 3 months without finding superiority of cEBRT for its primary endpoint of patient-reported pain response at 3 months, and there were no spinal cord complications at 2 years after cEBRT. This finding may serve as a basis for future research on the use of spinal radiosurgery in the setting of oligometastases, where durability of cancer control is essential [30]. Nevertheless, we advocate that pain relief could be more rapid with SBRT, but this needs to be demonstrated, and further prospective randomized studies are necessary.

Sahgal et al. also demonstrated that a dose of 24 Gy in 2 daily fractions is superior to cEBRT to a dose of 20 Gy in 5 daily fractions with a better complete response rate for pain. More awareness of specialized multidisciplinary involvement is needed for palliative patients and their end-of-life care [31]. Pain relief—by administering few sessions and even in a single day—is very convenient for patients, and that is why we have chosen this treatment with SBRT in our patients.

On the other hand, Singh et al. found that single fraction SBRT is better for LC than multi-fraction SBRT in their systematic review and meta-analysis (SAFFRON). However, these results are hypothesis-generating, and prospective randomized clinical trials are needed [32].

Due to the advancements in immunotherapies and systemic targeted treatments, disease control and overall survival have improved significantly. Additionally, the growing utilization of CT scans and MRI surveillance for spinal evaluation has led to an increase in the number of patients presenting both asymptomatic and symptomatic spinal metastases. The crucial focus now is on identifying patients with painful spinal metastases who would derive the greatest benefit from this essential therapeutic option [33].

In carefully selected cases, SBRT is an effective treatment to achieve adequate disease control, either as a single treatment or in combination with surgery. Thus, SBRT is currently the treatment of choice when local ablation of a metastatic lesion is indicated. Thus, there has been a paradigm shift in the treatment of patients with metastatic disease, which is even more evident in patients who are oligometastatic, i.e., those patients with fewer than 5 foci of metastases, where data suggest adequate disease control at 2–5 years in approximately 20% of patients when all foci have been eliminated [20].

Vertebral metastases require a multidisciplinary approach, involving radiation oncologists, spine surgeons, medical oncologists, and radiologists, for their evaluation and appropriate treatment. In the context of this treatment, decision making becomes intricate, involving multiple considerations. These include the following: (1) patient-dependent

factors (such as neurological function, pain presence and severity, age, comorbidities, functional status, estimated life expectancy, and patient preferences); (2) oncologic factors (such as tumor histology, molecular characteristics, tumor burden, and systemic treatment options), and (3) treatment-specific factors (such as location, spinal level, epidural disease presence and degree, radiographic appearance, previous surgical or radiotherapeutic treatment, and spinal instability). Before the advent of spinal SBRT and minimally invasive surgical techniques, the Tomita scoring system and the Tokuhashi scoring system were developed for the prognostic/pre-operative assessment of spinal metastases. More recently, the neurologic, oncologic, mechanical instability, and systemic disease (NOMS) framework and the spinal instability neoplastic score (SINS) have been developed [20].

In this regard, the SINS scoring system is a tool developed to assist the different medical specialties involved in the treatment of the spine to categorize and assess spinal instability, and to facilitate communication and referrals between medical specialists. In addition, SINS serves to identify and select patients who may benefit most from RT and may even be useful in predicting survival in patients with metastatic spinal disease [34].

Physicians face challenges in identifying patients with spinal metastatic disease who exhibit mechanical instability of the spine. For effective stabilization, it is crucial to involve a spine surgeon, as stereotactic body radiotherapy (SBRT) does not specifically target this issue. Recently, Fisher and colleagues introduced the SINS to evaluate the extent of spinal instability in these patients [20].

Over the recent 15 years, the multidisciplinary spine team at the Memorial Sloan Kettering Center has devised a framework called NOMS. This framework integrates four essential assessments for making decisions regarding metastatic spine tumors: neurological status, oncologic tumor behavior, mechanical stability, and systemic disease burden/medical co-morbidities. NOMS facilitates decision making and patient care by incorporating advances in interventional radiology, radiation therapy, systemic treatments, and surgical techniques to optimize outcomes and provides a common language to develop individualized treatment plans and encourage interinstitutional analysis of outcomes. Radiation therapy has become the treatment of choice to achieve a durable tumor outcome, and the goals of surgery have shifted from attempting to resect the maximum amount of tumor to attempting to separate the tumor from the spinal cord to optimize the radiation dose [35]. Compared to more aggressive surgical methods, the concept of separation surgery, combined with advancements in RT and the utilization of SBRT for treating spinal metastases, has demonstrated promising outcomes. This approach aims to achieve effective LC while minimizing surgery-related complications and morbidities [36].

It is important to treat patients before the onset of symptoms, such as pain. Moreover, our patients had a low initial pain assessment, with a mean VAS of 2.48, and 17 lesions were asymptomatic. In addition, SCC could appear to make surgery necessary. If surgery is required, it should be minimally invasive surgery (MIS) so that robotic SBRT can be administered within 7–10 days.

In our study, three factors were associated with improved pain control using SBRT: female gender, adenocarcinoma tumor type, and lack of previous surgery. Notably, this finding reinforces the concept of initiating SBRT treatment promptly upon diagnosis.

In addition, patients who are asymptomatic exhibit better tolerance to SBRT treatments. The duration of these treatments typically ranges between 30 and 45 min, depending on the lesion size and the number of beams utilized. Notably, the introduction of more advanced Cyberknife® S7 technology is expected to further reduce treatment time to just 15 min, significantly enhancing patient comfort during the procedure.

Survival expectancy is one of the main selection criteria when considering surgery in a patient. Multiple prognostic scoring scales exist to help clinicians determine post-operative life expectancy (Takuhashi, Sioutos, van der Linden, Tomita, and Bauer scales). In general, patients with a life expectancy of less than three months should be treated non-surgically, as the morbidity associated with surgical treatment outweighs the potential therapeutic benefits. However, MIS reduces morbidity and surgery may become an option in patients

for whom conventional approaches are considered too morbid [1]. Specifically, in our series, 7 patients were operated on with 12 different interventions per location.

Predictive factors described in the literature that may influence local control include spinal instability after surgery, large tumor volumes, and non-elevated BEDs. Other factors that may influence SBRT failure include adjacent bone, epidural space, and paraspinal tissue involvement. These factors increase treatment volume and thus result in an increased risk of recurrence. Epidural involvement may decrease overall survival and local control, and paraspinal involvement predicts recurrence and worse local control [18].

In our series, the response to SBRT was better in the non-surgical group. Obviously, surgical treatment causes acute bone and nerve trauma that may increase pain. On the other hand, surgery is also indicated because compressed nerve tissue could be relieved. Although a subgroup analysis could be very interesting, the small number of patients with surgery (only nine in our series) makes its elucidation negligible.

The location of spinal metastases is also important, as cervical metastases are more painful than dorsal, lumbar, and sacral metastases. And, for example, sacral metastases respond worse than thoracolumbar metastases due to lesions with >2 vertebrae and epidural and paraspinal involvement [18]. In our series, we only treated one patient with sacral metastases, making it irrelevant to assess/support this result.

It would also be interesting to know if pain correlates with tumor location (vertebral body, vertebral arch, intraspinal parts), but this was not recorded in our series.

Contouring of patients' lesions following expert consensus, both operated and non-operated lesions, is essential to treat patients correctly. Several articles with recommendations for contouring metastatic spinal lesions can be found in the literature [26,37–39].

Especially when the treatment is performed in a single session, the time patients must spend on it is obviously reduced. This is very important for patients with palliative care. Better results have been reported in patients treated with a single fraction in terms of LC, as in the study by Ehret et al. with a 1-year LC rate of 85%, which is in line with the patients treated by Hashmi et al., where better LC rates were reported for single-fraction treatments compared to multi-session irradiations. Since most published series only report 1-year LC rates due to the poor overall survival of the study cohorts, the respective median follow-ups are around 1 year. Therefore, not much data are known about LC beyond that period after SBRT treatment. In this case, many patients were still alive after two years, with 73% LC at that time. After three years, the LC rate was 73%. Thus, despite the limited data available and the small sample size, SBRT can achieve satisfactory local control rates at 2 and 3 years [40].

We must acknowledge certain limitations in our study, such as that it is a retrospective, single-institutional study with a small number of patients. We did not use the Brief Pain Inventory (BPI), which quickly assesses pain severity and its impact on functioning. The use of the BPI by nursing staff is increasingly recommended.

It is very important to offer more radical and effective treatments for disease and symptom control early on since patients' QoL is crucial until the end of their lives and since many patients with vertebral metastases are long survivors.

Physicians and nursing staff should be trained in pain assessment, at least with the VAS, before and after treatments (at each follow-up visit) to determine the efficacy of treatments.

In our opinion, it is also important to record the reduction of analgesic consumption, as it influences the quality of life of patients and the cost-effectiveness of health care.

In our series, except for grade 3 radiodermatitis, there were no major toxicities. Toxicities of SBRT could be myelopathy (0.4%) and CVF (11–39%). Myelitis has not appeared in our series because the fractionations used were safe, are recommended in the literature (1 to 5 fractions), and all of them were dosed higher than 6 Gy. We could explain the absence of FVC by the short follow-up period in most of our patients.

5. Conclusions

The use of SBRT for treating spine metastases with the CyberKnife® system is both feasible and safe. Notably, patients do not exhibit progression on imaging within the treatment field, and side effects are minimal. Additionally, a significant number of patients experience pain relief after treatment. We recommend early treatment for patients experiencing pain during procedures in the clinic.

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