

# The Impact of Histologies On Clinical Outcomes of Spinal Metastases Treated With Stereotactic Body Radiotherapy.

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## Research Article

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# Abstract

## Background

With the life expectancy prolonging, more cancer patients occurred spinal metastases. To evaluate the impact of histologies on outcomes of spinal metastases treated with stereotactic body radiotherapy (SBRT) and identify the correlated prognostic factors.

## Methods

The authors retrospectively reviewed the records of all patients who underwent SBRT with no prior radiation for spinal metastases between October 2015 and October 2020 at Sun Yat-sen University Cancer Center. Propensity score matching (PSM) was applied to balance the distribution of related baseline characteristics. The endpoints included overall survival (OS), local control (LC), pain relief, and time to pain relief.

## Results

A total of 202 consecutive patients with 345 spinal metastases were treated with a median follow-up time of 16.02 months (range, 0.73–57.90 months). The 1- and 2-year OS rates were 57% and 50%, respectively. The median survival was 35.63 months. A higher Karnofsky Performance Scale (KPS) score at consult predicted for better OS ( $P=0.020$ ). The presence of pain at enrollment assessed by the Brief Pain Inventory (BPI) predicted for worse OS ( $P=0.038$ ). The 1-year LC rate was 92.0%. The pain relief rate was 76.30% (103/135 patients). Younger age was identified to be prognostic for better pain relief ( $P=0.037$ ). In the univariate and multivariate analysis, no variable was independently associated with time to pain relief. As for toxicity, no Grade  $\geq 3$  toxicity was observed.

## Conclusions

SBRT is feasible and appears to be an effective treatment paradigm for patients with spinal metastases, with limited accepted toxicities.

## Background

Following lung and liver metastases, bone metastases are regarded as the most common tumor metastases, mostly in the spine(1, 2). According to the estimation, up to 40% of cancer patients will develop spinal metastases during their life-time (3). Over 70% of spinal metastases are situated in the thoracic or lumbar spine; cervical spine metastases and sacrum are included in 4–18% and 5% of the sample in recent series, respectively (4, 5). More than 10% of cancer patients with spinal metastases will develop metastatic epidural spinal cord compression (MESCC) (6, 7). Apparently, the occurrence of spinal metastases can confer significant morbidity and mortality, especially in patients with advanced cancer, with some adverse events (pain, neurological deficit, spinal instability, etc) having negative influences on patients' quality of life. For patients with spinal metastases, the conventional treatment paradigm includes chemotherapy, targeted therapy, surgery, radiotherapy, and immunotherapy, which need multidisciplinary cooperation. Additionally, with the development of surgical techniques and implementations, more and more clinicians choose to treat patients with adjuvant radiation therapy. In the meanwhile, stereotactic body radiotherapy (SBRT) has emerged as an attractive alternative for spinal metastases. In particular, SBRT can deliver high doses of radiation to the target lesions with high accuracy, while sparing the critical organs at risk (OARs) to the great extent.

The goal of treatment for patients with spinal metastases remains palliative, in order to prevent the progression or retreatment, delaying it at any rate. Therefore, a better understanding of long-term efficacy and safety about these treatment modalities is essential. Traditionally, histologies (renal cell carcinoma [RCC], melanoma, sarcoma) were regarded as radioresistant, indicating a poor local tumor control treated with conventional external beam radiotherapy (cEBRT). A study (8) exploring the impact of histology and dose on local control (LC) of spinal metastases treated with stereotactic radiosurgery (SRS), it demonstrated that SRS can provide durable tumor control, irrespective of the histology or tumor size. The actual dose of radiation given was the only significant predictive factor for LC.

Therefore, this study aimed to assess the influence of tumor histology on the effect of SBRT to patients with spinal metastases, and attempt to elucidate indications for patient selection. Categorizing tumors with different radiosensitivity (radiosensitive, radioresistant) and using propensity score matching (PSM), we specifically examined pain relief, time to pain relief, overall survival (OS), durable LC, and toxicities after SBRT for spinal metastases.

## Methods

### Patient population and selection criteria

We retrospectively reviewed a consecutive series of 547 lesions in 314 patients who were treated with SBRT for spinal metastases at Sun Yat-Sen University Cancer Center between October 2015 and October 2020, and gathered outcomes until December 2020. All patients had histologically proven primary cancer diagnosis. Spinal metastases were diagnosed by CT and/or MRI and/or PET-CT. Institutional Review Board (IRB) approval was obtained at the Sun Yat-Sen University Cancer Center, Guangzhou, China.

Eligibility criteria included: Age > 18 years; a pathological diagnosis of primary cancer, preferably oligometastasis; KPS score of  $\geq 70$ ; lesions treated with radiographic or clinical follow-up; a maximum of 3 separate sites of treatment, up to two contiguous levels within one radiation field. Patients were ineligible if they had acute spinal cord compression or presence of overt spinal instability.

### Outcomes assessment

Outcomes of interest were imaging-based LC, OS, and toxicities (specifically vertebral compression fracture [VCF], and myelopathy). Time to event was calculated from the start of treatment to the date of local failure for LC, death for OS, and/or last follow-up date, and last MRI for local failure if the event had not yet occurred. LC was defined as no progression within the treated vertebral body level on following CT or MRI. Local failure was defined by radiographic progression in the treated lesion. OS was defined as the time from the start date of SBRT to death from any cause. VCF was defined as de novo and progressive preexisting fractures. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (9). For assessment of pain palliation, the four-point verbal rating scale (VRS-4) (10) was administrated, along with a categorical scale representing different levels of pain intensity: "none," "mild," "moderate," "severe". Epidural extent was graded utilizing criteria by Bilsky et al (11).

### Data collection

A retrospective review of the hospital records and radiographic studies of these patients was performed. Data on each patient including age, sex, date of initial diagnosis of primary cancer, histology of primary cancer, date of diagnosis of first spinal metastasis, location of the spinal metastasis, radiation sites, further radiotherapy to other sites, presence of paraspinal extension, further systemic treatment, number of the spinal metastasis, previous treatments (including surgery, chemotherapy, immunotherapy, targeted therapy, and radiation therapy [RT]) and KPS score, pre-SBRT pain as

assessed by the Brief Pain Inventory (BPI) (when available), epidural spinal cord compression (ESCC) grade pre-SBRT, and SBRT information (including RT dose, and number of RT fractions delivered) were gathered.

## PSM analysis

In order to minimize the confounding influences of measured covariates on assessed outcomes those consecutive patients, PSM was performed. The matched study was created by matching as closely as possible using the following variables: age, paraspinal extension, KPS score, previous treatment (chemotherapy, immunotherapy, targeted therapy).

## Statistical Analysis

Both continuous and categorical variables were summarized. The Kaplan-Meier product-limit method was used to estimate OS, and survival curves were compared using the log-rank test. Factors associated with OS after SBRT were assessed using univariate and multivariate Cox proportional hazards analyses, as well as LC. Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were computed. Factors associated with pain palliation and the incidence of SBRT complications were assessed using univariate and multivariate logistic regression analyses. Factors associated with the time of pain palliation were assessed using linear regression. All mean values are presented as mean  $\pm$  standard error. All *P*-values were 2-sided. Here, a *P*-value  $< 0.05$  was considered statically significant. Statistical analysis was performed using SPSS software (version 26.0, IBM).

# Results

## Patient demographics

During the study period, 314 patients treated with SBRT were included between October 2015 and October 2020. The demographic, tumor, and treatment characteristics are summarized in **Table 1**. After using PSM, a total of 202 patients with 345 lesions were analyzed eventually (Fig. 1). The characteristics of these patients are presented in Table 2. One hundred and thirty-six patients (67.33%) were male, 66 (32.67%) were female. The median age was 56 years (range, 19–86 years). The median KPS score was 90 (range, 70–100). The median follow-up for all patients was 16.02 months (range, 0.73–57.90 months).

Table 1  
Baseline patient demographic, tumor, and treatment characteristics before PSM

Baseline characteristics	Number of patients (overall n = 314 patients, 548 lesions)	% of patients
<b>Sex</b>		
Male	228	72.61%
Female	86	27.39%
<b>Age at time of SBRT(y)</b>		
Range	19–89	
Median	57	
Mean	56.65	
<b>Follow-up(mo)</b>		
Range	0.33–59.03	
Median	15.93	
<b>Primary tumor</b>		
Non-small-cell lung cancer	69	21.97%
Prostate cancer	66	21.02%
Renal cell cancer	60	19.11%
Liver cancer	39	12.42%
Head and neck cancer	18	5.73%
Breast cancer	14	4.46%
Gastrointestinal cancer	9	2.87%
Genitourinary cancer	8	2.55%
Esophagus cancer	7	2.23%
Melanoma	7	2.23%
Sarcoma	4	1.27%
Small-cell lung cancer	3	0.96%
Canvical cancer	1	0.32%
Endometrial cancer	1	0.32%
Thymoma	1	0.32%
Other	7	2.23%
<b>Histologic type</b>		
Radiosensitive metastases	183	0.58
Radioresistant metastases	131	0.42
<b>Surgery</b>		

<b>Baseline characteristics</b>	<b>Number of patients (overall n = 314 patients, 548 lesions)</b>	<b>% of patients</b>
Yes	48	0.15
No	266	0.85
<b>Karnofsky performance status</b>		
Range	70–100	
Median	90	
<b>Spine location/level</b>		
Cervical	33	10.51%
Thoracic	151	48.09%
Lumbar	106	33.76%
Sacral	24	7.64%
<b>Bilsky epidural Grade</b>		
0	226	71.97%
1a	11	3.50%
1b	37	11.78%
1c	11	3.50%
2	22	7.01%
3	7	2.23%
<b>Paraspinal extension</b>		
Yes	111	35.35%
No	203	64.65%
<b>Systemic therapy</b>		
Prior immunotherapy	48	15.29%
Prior chemotherapy	198	63.06%
Prior targeted therapy	114	36.31%
Bisphosphonate therapy	194	61.78%
<b>Other radiation</b>		
Yes	90	28.66%
No	224	71.34%
<b>Total dose (Gy)</b>		
Range	800–4800	
Median	3000	
<b>Fractions</b>		

<b>Baseline characteristics</b>	<b>Number of patients (overall n = 314 patients, 548 lesions)</b>	<b>% of patients</b>
Range	1–6	
Median	5	
<b>Time to diagnosis of spinal metastases from primary cancer</b>		
Range	0-201.50	
Median	6.82	

Table 2  
Baseline patient demographic, tumor, and treatment characteristics after PSM

Baseline characteristics	Number of patients (overall n = 314 patients, 548 lesions)	% of patients
<b>Sex</b>		
Male	136	67.33%
Female	66	32.67%
<b>Age at time of SBRT(y)</b>		
Range	19–86	
Median	56	
Mean	54.76	
<b>Follow-up(mo)</b>		
Range	0.73–57.90	
Median	16.02	
Mean	13.20	
<b>Primary tumor</b>		
Other lung cancer	51	25.25%
Renal cell cancer	36	17.82%
Liver cancer	34	16.83%
Prostate cancer	15	7.43%
Head and neck cancer	15	7.43%
Gastrointestinal cancer	9	4.46%
Breast cancer	9	4.46%
Other	6	2.97%
Melanoma	6	2.97%
Genitourinary cancer	6	2.97%
Non-small-cell lung cancer	5	2.48%
Sarcoma	4	1.98%
Esophagus cancer	3	1.49%
Thymoma	1	0.50%
Small-cell lung cancer	1	0.50%
Endometrial cancer	1	0.50%
<b>Histologic type</b>		
Radiosensitive metastases	40	19.80%
Radioresistant metastases	162	80.20%

<b>Baseline characteristics</b>	<b>Number of patients (overall n = 314 patients, 548 lesions)</b>	<b>% of patients</b>
<b>Surgery</b>		
Yes	41	20.30%
No	161	79.70%
<b>Karnofsky performance status</b>		
Range	70–100	
Median	90	
<b>Spine location/level</b>		
Cervical	22	10.89%
Thoracic	92	45.54%
Lumbar	74	36.63%
Sacral	14	6.93%
<b>Bilsky epidural Grade</b>		
0	136	67.33%
1a	8	3.96%
1b	27	13.37%
1c	7	3.47%
2	17	8.42%
3	7	3.47%
<b>Paraspinal extension</b>		
Yes	82	40.59%
No	120	59.41%
<b>Systemic therapy</b>		
Prior immunotherapy	34	16.83%
Prior chemotherapy	116	57.43%
Prior targeted therapy	92	45.54%
Bisphosphonate therapy	120	59.41%
<b>Other radiation</b>		
Yes	44	21.78%
No	158	78.22%
<b>Total dose (Gy)</b>		
Range	800–4800	
Median	3000	

Baseline characteristics	Number of patients (overall n = 314 patients, 548 lesions)	% of patients
<b>Fractions</b>		
Range	1–6	
Median	5	
<b>Time to diagnosis of spinal metastases from primary cancer (mo)</b>		
Range	0-201.50	
Median	6.82	

Among all treated lesions, 22 (10.89%) were cervical, 92 (45.54%) thoracic, 74 (36.63%) lumbar, and 14 (6.93%) sacral. The most common lesions treated were metastatic tumors of lung (n = 52) or from the kidney (n = 36), followed by liver cancer (n = 34) and others. The ESCC grades were 0 in 136 (67.33%), 1a in 8 (3.96%), 1b in 27 (13.37%), 1c in 7 (3.47%), 2 in 17 (8.42%), and 3 in 7 (3.47%). Of the 24 patients with epidural disease compressing the spinal cord (Bilsky grade 2 and 3), 12 underwent surgery. Because of the medical comorbidities and not tolerating for surgery, the other 12 patients were treated with SBRT alone. The spinal metastases with paraspinal extension were 82 (40.59%). 34 (16.83%) patients experienced prior immunotherapy, 116 (57.43%) prior chemotherapy, 92 (45.54%) prior targeted therapy, 120 (59.41%) prior bisphosphonate therapy. Patients treated with radiation therapy on other sites were 44 (21.78%). Systemic therapy included chemotherapy, immunotherapy, targeted therapy, and bisphosphonate therapy. Of the 202 patients, 23 (11.39%) patients had not undergone previous therapy before treatment. In this consecutive series, 69 (28.16%) lesions were from radiation-sensitive tumors, 276 (80.0%) from radiation-resistant malignancies.

The median interval from the initial diagnosis of primary cancer to the diagnosis of spinal metastases was 6.92 months (range, 0-201.50 months). Of the 345 lesions, 41 (20.30%) were treated with SBRT postoperatively. The median total dose delivered was 30 Gy (range, 8–48 Gy), with a median fraction number of 5 (range, 1–6).

### Local Control

The 1-, 3-, 6-, 9-month LC rates were 86.9% (53/61), 86.8% (33/38), 92.8% (64/69), and 92.5% (49/53), respectively. After 1 month, in the univariate analysis, paraspinal extension ( $P = 0.046$ ) was the only factor associated with the 1-month LC rate. However, in the multivariate analysis, there were no significant factors associated with 1-month LC rate. Of those 25 patients with radiographic follow-up, 2 experienced local failure, and the 1-year LC rate was 92.0%.

### Overall Survival

The OS rates at 1- and 2-year were 57% and 50%, respectively (**Figure 2**). The mean survival was 35.98 months (95% CI, 30.61-41.35 months). The median survival was 35.63 months. On univariate analysis, the factors that significantly affected OS were KPS score at consult ( $P = 0.020$ ) and presence of pain at enrollment assessed by the BPI ( $P = 0.038$ ). On multivariate analysis, presence of pain at enrollment was the only significant factor of worse OS ( $P = 0.031$ ), but primary cancer, gender, age, treating site, paraspinal extension, other metastases, other radiation, Bilsky grade, use of surgery, use of bisphosphonate, use of chemotherapy, and use of immunotherapy were all not significant predictors of OS. There was no statistically significant difference in radiosensitivity associated with OS ( $P = 0.532$ ) (**Figure 3**).

### Pain Relief

Of these 143 patients with baseline pain, 135 patients were assessable. We reported a 76.30% (103/135 patients) of pain relief. Univariate analysis identified age ( $P = 0.037$ ) to be prognostic for better pain relief. In the multivariate analysis, age

retained its significance in terms of pain relief ( $P = 0.042$ ). The others were not significant factors including primary cancer, treating site, paraspinal extension, KPS score at consult, the degree of radiosensitivity, the number of metastases, dose, fractions, time to spinal metastases, other metastases, Bilsky grade, use of surgery, use of bisphosphonate, use of chemotherapy, use of immunotherapy, and use of target therapy. The median time to pain relief was 0.80 months (range, 0-14.67 months). In the univariate and multivariate analysis, there were no significant factors with time to pain relief.

### **The Treatment after SBRT**

Radiotherapy is considered as a local treatment. Therefore, after SBRT, there were several people experienced systemic therapy for primary cancer, including chemotherapy in 71 (35.15%) patients, immunotherapy in 33 (16.34%) patients, and targeted therapy in 81 (40.10%) patients. Obviously, almost these treatments were for primary cancer. In addition, other local treatments were applied, including 6 (2.97%) patients of surgery and 36 (17.82%) patients of radiation for other sites. In the meanwhile, there were 105 patients (51.98%) received bisphosphonate. Bisphosphonates were mainly used in reducing the incidence of bone disease, bone pain, and fracture.

### **Toxicity**

Totally, all patients tolerated SBRT well with minimal complications or toxicity, with no grade  $\geq 3$  toxicities observed in any patient. And there were no cases of myelopathy or radiculopathy. Overall, 19 (9.41%) patients experienced VCFs. Of these patients, two were surgically stabilized before SBRT, with 17 VCFs occurring after SBRT in the nonsurgical sites. 17 of 19 were de novo VCFs and others were the progression of an existing VCF. As for the rate of VCF, there was no statistically significant difference between surgery and no surgery before SBRT ( $P = 0.233$ ). On the univariate analysis, the time to spinal metastases was a predictor for the occurrence of VCF ( $P = 0.049$ ). Two patients experienced pain flare after SBRT that required hospitalization. Grade 1/2 toxicity consisted of fatigue during treatment for 9 patients treated, and 1 patient had decreasing smelling after SBRT not requiring treatment. No patient had persistent or worsening neurological symptoms.

## **Discussion**

In 1995, spinal radiosurgery was first applied to patients with spinal metastases, who were demonstrated radiographically recurrence or progression after treated with conventional external beam radiotherapy (12). When spinal metastases are presented with symptomatic vertebral compression fracture, mechanical instability, and acute epidural spinal cord compression, surgery is regarded as the first-line treatment (13). For patients not requiring surgery or unbearable to surgery, cEBRT is taken into consideration (low- to intermediate-dose in 1 or more fractions) (14). With imaging and treatment technology developing, SBRT has increasingly established its role in the treatment for spinal metastases. Selecting patients treated with spinal SBRT is of great significance, which can avoid the catastrophic consequences of failure. For carefully selected patients, SBRT could be a standard treatment modality.

There were few patients with radiographic follow-up in our study. Therefore, we cannot evaluate the LC rate of all patients. Of patients with radiographic follow-up, the 1-year LC rate was 92.0%. The result was consistent with several previous analysis (15–19). In addition, 6- and 9-month LC rates were 92.8% and 92.5%, respectively. Another study (20) about a median follow-up of 6 months (range, 3–12 months), 6- and 9-month LC rates were 86% and 86%, respectively. The rates were consistent with our result. The 2-year LC rate ranged from 73%-83.9% (15, 16, 19). In our study, for most patients, there was a lack of long-term radiographic follow-up. Therefore, the 2-year LC rate was not reported. Furthermore, for different treating aims, LC rates were 90% and 88% in patients as a primary treatment modality and treated for radiographic tumor progression (21). With regard to different histologies, LC rate varied from 80% (breast cancer with one local failure at 57 months) to 100% (cervical cancer and hepatobiliary cancer), while no statistically

significant difference was found (8). According to above studies, we can think that SBRT could provide durable local tumor control.

Chang et al. (22) reported that LC was observed in 75 of 83 lesions. Of those 8 lesions regarded as local failure, they were hepatocellular carcinoma (5 cases), lung cancer (1 case), breast cancer (1 case) and RCC (1 case). For our study, 8 patients experienced local failure with a 1-month follow-up. Among these, there were breast cancer (1 patient), liver cancer (2 patients), melanoma (2 patients), small cell lung cancer (SCLC) (1 patient), esophagus cancer (1 patient), and urinary tract tumors (1 patient). No significant difference was observed in primary cancer with LC ( $P = 0.247$ ).

As for 1-month LC, we reported that paraspinal extension ( $P = 0.046$ ) was the only statistically significant factor. In the study (23), on univariate and multivariate analysis, the presence of epidural mass was also identified as a significant prognostic factor for LC ( $P = 0.026, 0.002$ , respectively). The significant prognostic factors correlated with LC rate included colorectal cancer ( $P < 0.01$ ), spinal metastases from colorectal cancer ( $P < 0.01$ ), radiation histology ( $P = 0.02$ ), dosimetric data of delivered maximum dose ( $P < 0.01$ ) (17). Moreover, an interval between primary diagnosis of cancer and SBRT of  $\leq 30$  months ( $P = 0.01$ ; HR = 0.27) and histology of primary disease (NSCLC, RCC, melanoma, other) ( $P = 0.01$ ; HR = 0.21) (16), a rapidly growing primary tumor ( $P = 0.047$ ), and poor performance status ( $P = 0.035$ ) were found to be significant predictors of worse LC (24). Nevertheless, there was no statistically significant difference correlated with LC in our findings. In some degree, it might be due to that there were fewer patients experienced radiographic follow-up and analyzed on the univariate and multivariate analysis eventually.

We also pay attention to the survival outcomes. We reported that the OS rates at 1- and 2-year were 57% and 50%, respectively. These results are consistent with prior reports in the literature. The 1- and 2-year OS rates were 64.9% and 43.7%, respectively (16). The 1-year OS rate was 65.0% (17). The 1- and 2-year OS estimates were 80% and 57%, respectively (19). The 1- and 2-year overall survival rates were 77.2 and 49.4 %, respectively (25). We reported a better overall survival than previous studies. Compared with previous results (8, 16, 17, 25, 26), there were the favorable median and mean survival periods demonstrated in our study, 35.63 and 35.98 months (95% CI, 30.61–41.35 months), respectively. In some degree, it suggested appropriate patient selection via definite inclusion and exclusion criteria.

On univariate analysis, the factors that significantly affected OS were KPS score at consult ( $P = 0.020$ ) and baseline pain assessed by the BPI ( $P = 0.038$ ). KPS score was used to evaluate general condition of patients. Obviously, higher KPS score, and better general condition. With better general condition, patients with spinal metastases would accomplish the treatment and gain the survival benefit from SBRT. On multivariate analysis, baseline pain was the significant factor for worse OS ( $P = 0.031$ ). As is known to us, for bone metastases, including spinal metastases, the most common symptom was pain. Therefore, with regard to patients with baseline pain, optimal analgesia treatment modality was critical before SBRT. Controlling pain well might predict longer overall survival. Another study (16) about the multivariate analysis for overall survival, performance status  $< 90$  ( $P < 0.001$ ; HR = 0.46) and  $> 1$  vertebra treated with SBRT ( $P = 0.04$ ; HR = 0.62) were significant predictors for worse OS. Chao et al. (27) reported that there was no statistical difference in histologies with OS ( $P = 0.54$ ). This was consistent with our result ( $P = 0.28$ ).

Furthermore, median OS intervals for favorable, radioresistant, and other histologies were 14, 11.2, and 7.3 months ( $P = 0.02$ ), respectively (27). However, in our study, we didn't note a significant difference in the radiosensitivity associated with OS ( $P = 0.54$ ). Through the statistical analysis, there was no significant difference found in histologies with LC and overall survival. It could be predicted that spinal SBRT provides a satisfying LC and overall survival, regardless of histologies.

The most common symptom is pain for patients with spinal metastases. For these patients, SBRT aims to achieve the pain palliation and delay or even prevent the retreatment. In our study, no pain intensity score was applied to evaluate the pain intensity. We just assess the degree of pain relief depending on the subjective feeling. Of these 143 patients with

baseline pain, 135 patients were assessable. We reported 76.30% (103/135 patients) of pain relief rate. According to previous studies (15, 17, 22, 28), the range of pain relief rate was 79.5%-92.3%. Among these studies, for rate of 92.3% (15), there were 48 of 51 patients experienced complete pain relief after SBRT, and 3 had partial pain relief. Moreover, in the malignant epidural compression (MEC) and without MEC group, complete pain relief rates were 90% and 93.75%, respectively. However, no statistically significant difference was noted ( $P = NS$ ) in the study. Thus, the presence of MEC might not show an adverse influence on the outcomes of lesions treated with SBRT. In these patients with MEC, spinal SBRT could be a choice.

In addition, the pain-free rates of mild, moderate and severe pain were 76.8%, 56.3% and 43.8%, respectively (16). After single-dose radiosurgery (10–16 Gy), the median duration of pain relief was 13.3 months (29). The 1-year pain progression-free rate was 61.7% (17). During a follow-up ranging from 3 to 53 months (median, 21 months), long-term pain improvement occurred after SBRT (21). Univariate analysis identified age ( $P = 0.037$ ) to be a prognostic factor for pain relief. In the multivariate analysis, age retained its significance in terms of pain relief ( $P = 0.042$ ). Another study reported that there was no factor correlated with improved pain relief (16). Younger age could achieve better pain relief. When selecting patients to be treated with SBRT, age might be taken into consideration.

Of the study with reliable and valid measures of pain intensity, compared with three-dimensional conformal radiation therapy (3DCRT) group, SBRT patients illustrated shorter decreased time ( $P = 0.01$ ) and lower value ( $P = 0.002$ ) (30). As a traditional treatment paradigm, conventional external beam radiotherapy played a critical role in treating spinal metastases. With respect to the treatment of cancer pain, it is critical to administrate a drug coordinated with three-step analgesia ladder principle. In most of cases, pain flare was due to localized issue edema, which usually didn't last so long. In general, it could be controlled by use analgesic. Pain flare was reported in 2 patients, which was successfully controlled by increasing doses of analgesic without interrupting the radiotherapy. Our result was consistent with the study, pain flare controlled well (20).

To our knowledge, there are no uniformly accepted indications in patient selection for spinal SBRT. The above factors might provide instructions in selecting patients. Moreover, the neurologic, oncologic, mechanical, and systemic (NOMS) framework (31) and the location of disease in the spine, mechanical instability, neurology, oncology, and patient fitness, prognosis and response to prior therapy framework (LMNOP) (32) might play an important role in patient selection.

As for the toxicity of patients treated with SBRT, we demonstrated a risk of VCF of 9.41% (19/202), which is consistent with previous spinal SBRT literatures reporting rates ranging from 5–42% (33). As for time to VCF, a multi-institutional study on renal cell carcinoma spinal metastases reported that the median time to VCF was 2.35 months (range, 0.03–43.01 months) (26). The median time to VCF was 2.26 months (range, 0.87–14.39 months) in our study. Therefore, it is necessary to take some protective measures to avoid the occurrence of VCF after SBRT. In the meanwhile, factors associated with VCF should be taken into consideration, before or after SBRT.

With respect to predictors of VCF post-SBRT, baseline fracture ( $P < 0.001$ ), dose per fraction of  $\geq 20$  Gy ( $P = 0.005$ ), and spinal misalignment ( $P = 0.002$ ) (26), age  $\geq 65$  years ( $P = 0.008$ ), ESCC grade 1a and 1b ( $P = 0.006$ ), dose per fraction ( $P = 0.05$ ), tumor progression ( $P = 0.045$ ), and a Spinal Instability Neoplastic Score (SINS) of  $\geq 7$  ( $P < 0.001$ ) (25) were confirmed as significant predictors. Prior conventional radiation was found to be significant and protective ( $P = 0.029$ ) (26) and the primary tumor site of the breast ( $P < 0.001$ ) (34) were found to be significant and protective of VCF. We identified time to spinal metastases as the only significant predictor for VCF ( $P = 0.049$ ). A study about (25) predicting vertebral body compression following spinal SRS, 32 of 79 patients developed VCF, 20 (62.5%) of de novo fractures and 12 (37.5%) of progression. On univariate and multivariate analysis, 2-year fracture-free rates were 78.7% and 33.7% between low and high SINS group.

The most common toxicity for spinal metastases treated with SBRT was the occurrence of vertebral compression fracture. For patients, VCF would have an influence on the quality of life, such as intolerable bone pain. Hence, fracture prevention is of great importance. Up to date, to our knowledge, there was no case of radiculopathy or myelopathy during the follow-up.

## Strengths And Limitations

Several strengths of this study deserve mention. First, after our selection of 314 patients, we used PSM dealing with characteristics before data statistics, which could result in a decrease of heterogeneity on baseline characteristics. Second, we categorized tumors with different radiosensitivity (radiosensitive, radioresistant). Although there was no statistically significant difference found in histologies with OS, LC, pain relief, and time to pain relief. Our results might provide a reference to the future research. Third, in the study, we analyzed the aspects including OS, LC, pain relief rate, and time to pain relief. Obviously, it included and analyzed comprehensive outcomes. Fourth, without limited in 1 fraction, we reported 1–6 fraction, the results were consistent with previous studies. Moreover, as is known to us, our study was the first to report the outcomes of spinal metastases treated with SBRT in China.

There were a number of limitations in this study. Given the retrospectively collected data, selection biases inevitably existed. Furthermore, assessment of pain response was not prospectively collected, and the degree of pain at enrollment was assessed by the BPI. However, during the period of follow-up, we cannot accurately assess the pain score as BPI. In our study, it just depended on the subjective feelings of patients themselves. Assessing the degree of pain when using a standard pain scale, which might promote the consistence of the outcome index. The study is limited because of the experience of single institution, which is needed to be validated in other institutions.

## Conclusions

In conclusion, regardless of tumor histology, SBRT is a noninvasive intervention that seems to be viable, safe, and effective for patients with spinal metastases. With minimal accepted toxicities, a good overall survival was achieved. Furthermore, patients can be expected to develop durable LC and pain relief on treated lesions. To confirm late toxicities and define patient selection, further studies with large sample sizes and a longer follow-up are required.

## List Of Abbreviations

SBRT, stereotactic body radiotherapy; PSM, propensity score matching; OS, overall survival; LC, local control; KPS, Karnofsky Performance Scale; BPI, Brief Pain Inventory; MESCC, metastatic epidural spinal cord compression; OARs, organs at risk; RCC, renal cell carcinoma; cEBRT, conventional external beam radiotherapy; SRS, stereotactic radiosurgery; IRB, Institutional Review Board; VCF, vertebral compression fracture; CTCAE, Common Terminology Criteria for Adverse Events; VRS-4, four-point verbal rating scale; ESCC, epidural spinal cord compression; HRs, hazard ratios; CIs, confidence intervals; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; MEC, malignant epidural compression; 3DCRT, three-dimensional conformal radiation therapy; NOMS, neurologic, oncologic, mechanical, and systemic; LMNOP, location of disease in the spine, mechanical instability, neurology, oncology, and patient fitness, prognosis and response to prior therapy framework; SINS, Spinal Instability Neoplastic Score.

## Declarations

### [Ethical Approval and consent to participate]

This study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center. Patient representatives have not been involved in the present study design, due to its retrospective nature.

### **[Consent for Publication]**

All authors have read the paper and given consent for publication.

### **[Availability of data and materials]**

The retrospective data and materials used to support the findings of this study are available from the corresponding author upon request.

### **[Competing interests]**

Competing interests: none.

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### **[Authors' Contributions]**

Study concept and design: Lixia Lu and Lei Chen.

Acquisition of data: all authors.

Analysis and interpretation of data: Lanlan Guo and Qingqing Xu.

Drafting the manuscript or revising it critically for important intellectual content: all authors.

Given final approval of the version to be published: Lixia Lu.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Lanlan Guo and Qingqing Xu contributed equally to this study.

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### **[Authors' information]**

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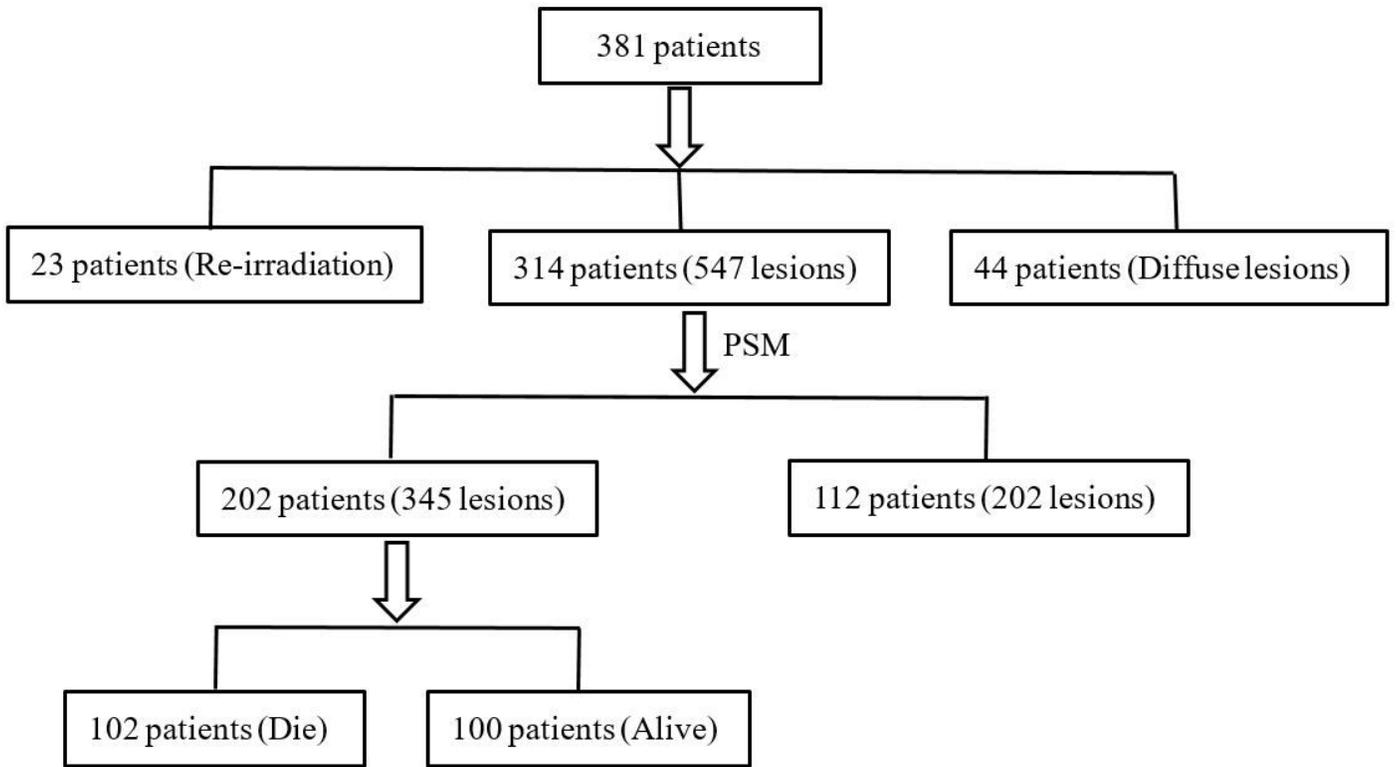
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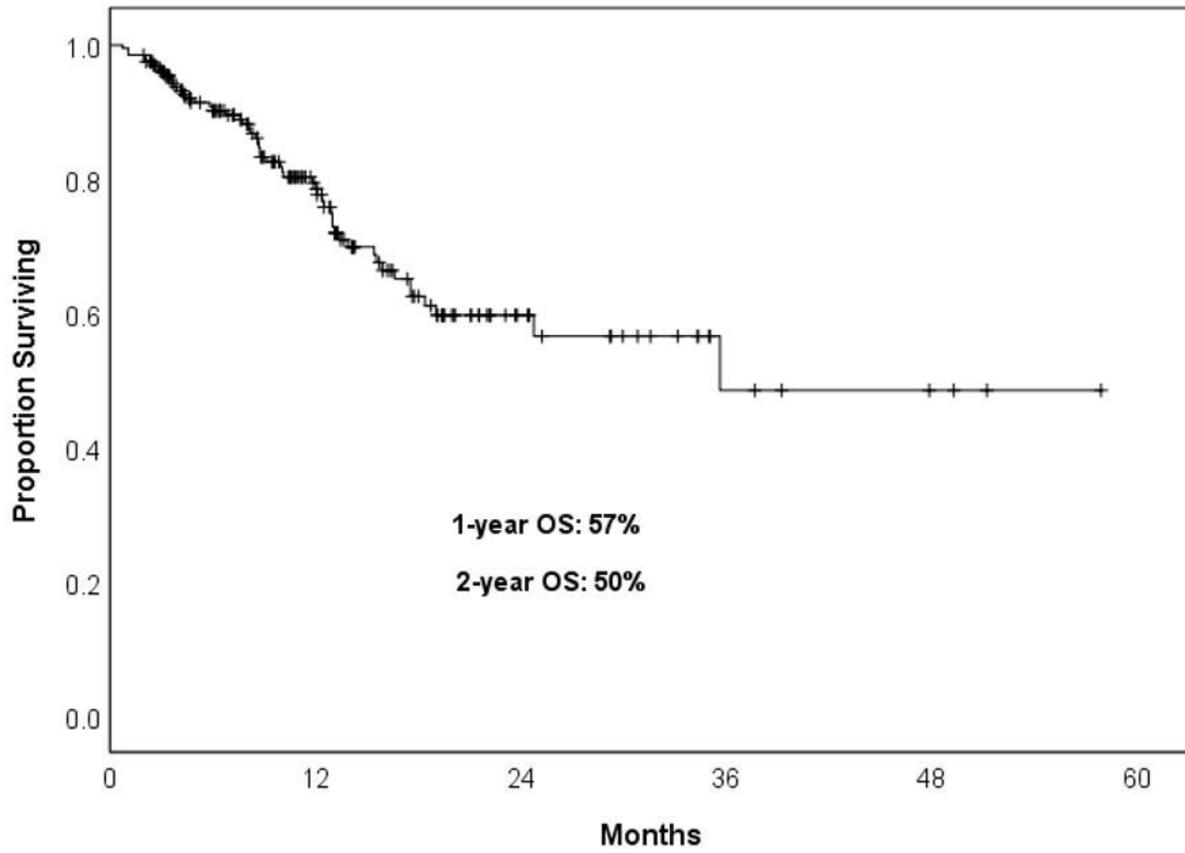
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## Figures



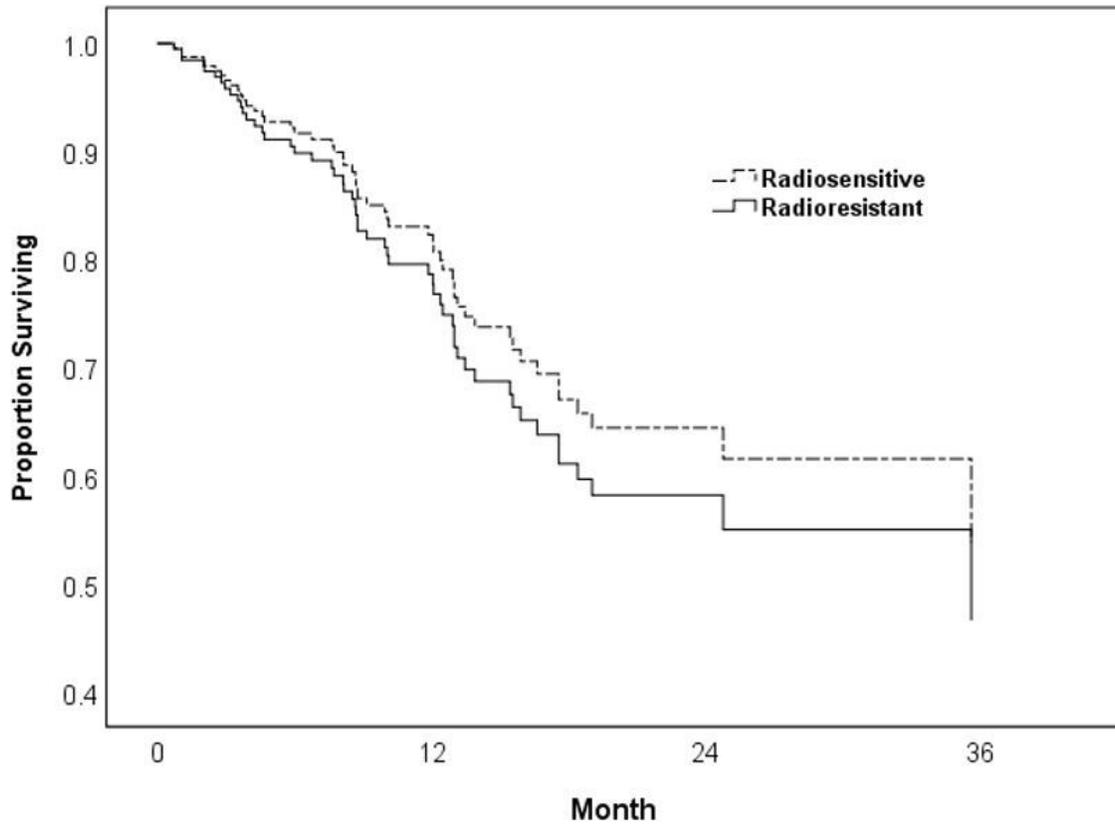
**Figure 1**

Flow chart of the patients included and treated with SBRT at our center.



**Figure 2**

Kaplan-Meier chart showing overall survival after SBRT in spinal metastases.



**Figure 3**

Overall survival for radiosensitive vs. radioresistant spinal metastases.