Role of epidural disease in local control of spinal metastases treated with stereotactic body radiation therapy

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Abstract. Spinal metastases can be contained in the bone or have epidural spread. Whether the extent of epidural involvement changes tumor response to therapy is unknown. The decision of when to treat disease progression with focal radiation therapy with or without surgery vs. systemic therapy is debated. The present study compared outcomes and local tumor control after stereotactic body radiation therapy (SBRT) between patients with spine metastases localized to the bone (Bilsky 0) vs. patients with mild epidural spread (Bilsky 1). A retrospective analysis of a prospectively maintained database of adult oncological patients who underwent SBRT to the spine at a single, large, tertiary care facility from August 2010 to January 2021 was performed. Patients with Bilsky grades 1a, 1b and 1c were grouped and compared. Approximately half (53.7%) of the 255 patients identified had Bilsky grade 1 epidural disease. Of the 311 spine treatment sites, 86 (27.7%) had a radiosensitive histology, 116 (37.3%) had intermediate radiosensitivity and 109 (35.0%) had a radioresistant histology. Patients with Bilsky grade 1 were more predisposed to receive surgery followed by SBRT compared with those with Bilsky grade 0 (21.0% vs. 6.3%; P=0.0002). Patients with Bilsky grade 0 compression had 92.0% local control at 12 months and 85.8% local control at 24 months; patients with Bilsky grade 1 compression had 85.6% local control at 12 months and 77.6% local control at 24 months. Biologically effective dose and infield progression between patients presenting with Bilsky grade 0 and 1 compression were not statistically different. Local control rates did not differ significantly between Bilsky grade 0 and grade 1 patients following treatment with spinal SBRT. However, patients with grade 1 disease were more likely to receive surgery before SBRT. Overall, evidence indicates that patients may benefit from treatment with SBRT before epidural disease progresses to requiring separation surgery.

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Introduction

As cancer therapies have improved, spinal metastases have become increasingly common in the course of oncologic disease (1). Spinal metastases are symptomatic in approximately 15% of patients with solid primary tumors (2,3). Complications arising from spinal metastases have a significant impact on patient quality of life. The most common complications include pain (4-6) and neurological disability (7-11). Treatment is complicated and usually the purview of a multidisciplinary team. Numerous treatment algorithms for metastatic spine disease are available (12). Major considerations regardless of algorithm are spinal stability, neurologic risk of the patient, and tumor sensitivity to radiation. The main treatment for good local control for most tumors is high dose conformal radiation stereotactic body radiation therapy (SBRT). Indeed, most treatment algorithms uphold the premise that if the tumor does not respond to low dose external beam radiation therapy (EBRT; 30 Gy in 10 fractions) than SBRT is standard.

Therefore, from a neurosurgical standpoint, indications for a surgical intervention include: (1) the presence of radioresistant tumors that are too close to the spinal cord to receive the full dose of radiation, (2) neurologic risk (how compressed the cord is), (3) spinal instability, and (4) the need for a tissue diagnosis. Neurological compromise from metastatic disease to the spine is often the result of spinal cord compression from the invading tumor; this may be the most significant indication for a surgical intervention. Approximately 10% of patients with spinal metastases develop spinal cord compression (3).

Bilsky *et al* (13) created a grading system for epidural spinal cord compression: Grade 0 disease is confined to the

bone without any epidural spread; grade 1a indicates that there is epidural impingement without significant deformation of the thecal sac; 1b indicates that the thecal sac has been deformed without abutment of the spinal cord; 1c indicates that there is spinal cord abutment without cord compression; 2 indicates spinal cord compression with visible cerebrospinal fluid (CSF) around the cord; and 3 indicates that there is spinal cord compression without any CSF visible around the spinal cord. With improved diagnostic imaging and increased utilization of surveillance imaging in patients with metastatic cancer, more patients with early grade epidural disease, Bilsky grade 0 or 1, are being identified. Unfortunately, limited data exists to guide the preferred management of patients with low-grade epidural disease with potential options, including local therapies such as radiation therapy with or without surgery vs. systemic therapies. It is unknown how the presence of grade 1 epidural disease impacts local control following spinal stereotactic body radiation therapy compared to spine metastasis confined to bone.

We compared outcomes and local tumor control after SBRT between patients with disease localized to the bone (Bilsky 0) vs. patients with mild epidural spread (Bilsky 1) to emphasize the importance of timing of SBRT in patients with metastatic spread prior to progression of pathology to include the central canal. Given the mechanism of SBRT as an intervention, this minimally invasive approach in patients without thecal sac involvement ensures high dose delivery of radiation with maximal precision and sparing of normal tissue, and thus improved symptom control and reduced progression risk. Soltys *et al* (14) showed improved tumor control probability with high dose regimens, but emphasized weighing the benefits with the risks of increased toxicity; meanwhile, the probability of toxicity is reduced the farther the pathologic locus is from the thecal sac, further substantiating the importance of intervening at Bilsky 0.

Materials and methods

Study design and patient selection. We performed a retrospective analysis of a prospectively maintained database of consecutive adult patients with spine metastases who received spine SBRT at Michigan Medicine-a single, large tertiary care facility in Ann Arbor, Michigan, USA-from August 2010 to January 2021. All included patients received SBRT based on an established treatment algorithm (12). No patients underwent conventional EBRT. It was determined that patients who had a sufficiently high functional status were appropriate candidates for SBRT therapy, and often had systemic treatment options. Patients with poor performance status or advanced disease with limited treatment options did not receive SBRT and were not included in this dataset. We only included patients who had a presenting Bilsky score of 0 or 1 (includes 1a, 1b, and 1c) and excluded patients with a presenting Bilsky score of 2 or 3 (13). Pediatric patients (≤18 years old) were excluded. Approval for this study was obtained from the University of Michigan (Ann Arbor, Michigan, 48109, USA) Institutional Review Board (ID HUM00139855); patient consent was not required.

Clinical data. Demographic data were prospectively entered for each patient as the patient began SBRT. Variables included age at treatment, sex, body mass index, race (White, African American, Asian, other, unknown), marital status (single, married, divorced, widowed, unknown), insurance type (private, Medicare, Medicaid, uninsured, unknown), and whether the patient had a primary care physician. Other prospectively maintained variables included if the patient underwent surgery, the histology of the tumor, whether there were contiguous spinal levels of disease, if the patient had previously undergone radiation therapy at the level of interest, and the dose of radiation, converted to a biologically effective doses (BED) for standardization. Tumor histology was grouped into radiation sensitive, intermediate, and radiation resistant groups based upon the available literature and expert opinion (JRE & WCJ; Table I) (15-22). Radiosensitivity, or the responsiveness to EBRT, traditionally describes the impact that radiation therapy of this nature can have on a specific histology compared to another. Additional variables retrospectively gathered included the Bilsky score of the lesion at the level of worst compression being treated, post-SBRT infield progression of cancer, date of infield progression before death, and survival.

Table I. Breakdown of cancer histologies by radiosensitivity.

Radiosensitive	Intermediate	Radioresistant
Breast cancer	Adrenal cancer	Blood vessel tumor
Prostate cancer	Bladder cancer	Colorectal cancer
	Esophageal cancer	Melanoma
	Head/neck cancer	Pancreatic cancer
	Liver cancer	Primary bone tumor
	Neuroendocrine cancer	Renal cell carcinoma
	Non-small cell lung carcinoma	Sarcoma
	Salivary cancer	
	Thyroid cancer	

This table classifies how different histologies respond to radiation therapy (for example, external beam radiation therapy), which can influence treatment planning and expected outcomes. Of note, radiosensitivity has not been defined by responsiveness to stereotactic body radiotherapy, which is the mode of radiation therapy administered in this study.

Clinical treatment. The goal of SBRT for all patients was to maximize the radiation dose given to the treated tumors. While not all treatment regiments were uniform, all obtained an appropriate dose of radiation to treat the tumor. When sufficiently high doses of radiation could not be administered because of proximity of the tumor to the spinal cord, separation surgery was performed. As previously described, separation surgery consists of transpedicular decompression at the level of the tumor with circumferential decompression of the thecal sac as assessed by intraoperative ultrasound. Once sufficient decompression is achieved, pedicle screws are placed two levels above and below the decompression (23).

Clinical follow-up in a multidisciplinary spinal oncology clinic. Patients who received spinal SBRT were followed in

Table II. Demographics of patients presenting with Bilsky grade 0 compared with 1 compression.

Characteristic	Patients with Bilsky grade 0 compression (n=144), no (%)	Patients with Bilsky grade 1 compression (n=167), n (%)	P-value
Age, years	63.6 (10.8)	61.7 (13.5)	0.19
Sex			0.19
Female	45 (31.3%)	64 (38.3%)	
Body mass index	28.3 (7.0)	26.7 (5.3)	0.05
Race			0.23
White	125 (86.8%)	150 (89.8%)	
Black	9 (6.3%)	6 (3.6%)	
Asian	2 (1.4%)	5 (3.0%)	
Other	5 (3.5%)	1 (0.6%)	
Unknown	3 (2.1%)	5 (3.0%)	
Marital status			0.21
Married	80 (55.6%)	113 (67.7%)	
Divorced	11 (7.6%)	7 (4.2%)	
Single	16 (11.1%)	16 (9.6%)	
Widowed	7 (4.9%)	4 (2.4%)	
Unknown	30 (20.8%)	27 (16.2%)	
Insurance type			0.53
Private	81 (56.3%)	97 (58.1%)	
Medicare	56 (38.9%)	57 (34.1%)	
Medicaid	0 (0.0%)	2 (1.2%)	
Uninsured	5 (3.5%)	6 (3.6%)	
Unknown	2 (1.4%)	5 (3.0%)	
Presence of primary care physician			0.63
No	5 (3.5%)	6 (3.6%)	
Yes	137 (95.1%)	156 (93.4%)	
Unknown	2 (1.4%)	5 (3.0%)	
Surgical intervention			0.01
No	135 (93.8%)	132 (79.0%)	
Yes	9 (6.3%)	35 (21.0%)	

a multidisciplinary spinal oncology clinic where their care was coordinated between their neurosurgical team, radiation oncologists, medical oncologists, physical therapists, and other ancillary teams. Patients were seen in clinic at 1 and 3 months for examination and assessment of treatment effects as well as every 3 to 6 months for a surveillance total spine MRI. The need for additional treatment was determined in the multidisciplinary clinic.

Statistical analysis. We examined the association of each variable against patients presenting with Bilsky grade 0 compared to Bilsky grade 1 epidural disease using the chi-square test, Fisher exact test, or *t*-test, depending on the sample size and whether the variable was continuous or categorical. Continuous variables are presented as mean with standard deviations. Survival analyses were utilized to examine the associations between infield progression and survival against patients with Bilsky 0 vs. 1 compression. An additional stratified log rank analysis was performed for infield progression to test between Bilsky grade while stratifying based on levels of radiation sensitivity. Finally, a subgroup analysis was performed by removing patients who underwent surgery, leaving patients who only underwent SBRT. A two-sided P<.05 was considered statistically significant. All data were analyzed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Demographics. A total of 311 spine treatment sites in 255 patients were included. The average age of our population was 62.4±12.8 years and 34.1% were female. Other demographic data are provided in Table II.

Among the 311 spine treatment sites, 167 (53.7%) exhibited Bilsky grade 1 compression while the remaining sites had bone-only disease (Bilsky grade 0). Tumor histologies, detailed in Table III, revealed that certain cancers were significantly more prevalent in patients with Bilsky grade 0 compression, such as prostate or breast cancer. Conversely, renal cell carcinoma, non-small cell lung cancer, and sarcoma were more commonly associated with Bilsky grade 1 compression.

Table III. Demographic information of tumors of patients.

Characteristic	Patients with Bilsky grade 0 compression (n=144), no (%)	Patients with Bilsky grade 1 compression (n=167), n (%)	P-value
Histology categories			<0.01
Prostate cancer	42 (29.2%)	19 (11.4%)	
Renal cell carcinoma	16 (11.1%)	32 (19.2%)	
Non-small cell lung cancer	9 (6.3%)	34 (20.4%)	
Sarcoma	8 (5.6%)	18 (10.8%)	
Breast cancer	19 (13.2%)	6 (3.6%)	
Melanoma	5 (3.5%)	9 (5.4%)	
Thyroid cancer	9 (6.3%)	5 (3.0%)	
Bladder cancer	7 (4.9%)	5 (3.0%)	
Liver cancer	5 (3.5%)	2 (1.2%)	
Oropharyngeal cancer	2 (1.4%)	7 (4.2%)	
Colorectal cancer	5 (3.5%)	3 (1.8%)	
Neuroendocrine tumor	2 (1.4%)	6 (3.6%)	
Pancreatic cancer	3 (2.1%)	2 (1.2%)	
Esophageal cancer	3 (2.1%)	4 (2.4%)	
Blood vessel tumors	1 (0.7%)	1 (0.6%)	
Salivary cancer	2 (1.4%)	4 (2.4%)	
Primary bone tumor	2 (1.4%)	1 (0.6%)	
Adrenal cancer	0 (0.0%)	1 (0.6%)	
Other	4 (2.8%)	8 (4.8%)	
Radiation sensitivity of tumor			<0.01
Sensitive	61 (42.4%)	25 (15.0%)	
Intermediate	42 (29.2%)	74 (44.3%)	
Resistant	41 (28.5%)	68 (40.7%)	
Prior radiation therapy to site	7 (4.9%)	22 (13.2%)	0.01
Biologically effective dose	51.4 (8.7)	53.6 (10.6)	0.05

Of the 311 treatment sites, 86 (27.7%) were radiosensitive histologies, 116 (37.3%) had intermediate radiosensitivity, and 109 (35.0%) were radioresistant histologies. Patients with Bilsky grade 1 compression were significantly more likely to have tumors with intermediate (44.3% 29.2%) or resistant (40.7% vs. 28.5%; P<.0001) radiation sensitivity compared to those with Bilsky grade 0 compression (Table III).

Infield progression. Patients with Bilsky grade 1 were more frequently treated with surgical intervention followed by SBRT, rather than SBRT alone, compared to those with Bilsky grade 0 (21.0% vs. 6.3%, P=.0002). Patients with Bilsky grade 0 and grade 1 compression (51.4±8.7 vs. 53.6±10.6; P=.05; see Table III) received similar BEDs. Local control rates for patients with Bilsky grade 0 compression were 92.0% at 12 months and 85.8% at 24 months, whereas for patients with Bilsky grade 1 compression, the rates were 86.0% at 12 months and 77.6% at 24 months. Infield progression between patients presenting with a Bilsky grade 0 and 1 compression was not statistically different (Fig. 1A). A stratified log rank analysis showed that no significant difference between infield progression between Bilsky grade 0 and 1 compression when accounting for the different levels of sensitivity to radiation (P=0.22). We performed a sensitivity analysis to determine if radiosensitivity of the tumor impacted local control; no significant difference between infield progression when comparing radiosensitive and radioresistant histologies (Fig. 1B and D) resulted. However, patients with intermediate radioresistant histologies and Bilsky grade 0 compression had significantly better local control compared to patients with Bilsky grade 1 compression (Fig. 1C).

We performed an in-depth analysis of the specific histologies that were within the intermediate radioresistant group with infield progression (Table IV) and found a trend towards more patients with non-small cell lung cancer who had infield progression compared to no infield progression (53.3% vs. 34.7%; P=.16). However, this was not statistically significant.

Survival. Patients with Bilsky grade 0 compression had significantly longer survival compared to patients with Bilsky grade 1 compression (P=.006; Fig. 2A), likely driven by the larger proportion of patients with metastatic breast and prostate cancer in the Bilsky grade 0 group (Table III). Patients with Bilsky grade 0 compression had 66.6% survival at 12 months and 48.4% survival at 24 months; patients with Bilsky grade 1 compression had 53.4% survival at 12 months and 34.1% survival at 24 months. We performed a sensitivity analysis to determine if radiosensitivity of the tumor impacted

Table IV. Infield progression in patients with histologies of intermediate radioresistance.

Histology categories	Patients with infield progression (n=15), n (%)	Patients without infield progression (n=101), n (%)	P-value
Cancers			0.16
Non-small cell lung	8 (53.3%)	35 (34.7%)	
Thyroid	0 (0.0%)	14 (13.9%)	
Bladder	0 (0.0%)	12 (11.9%)	
Liver	0 (0.0%)	7 (6.9%)	
Oropharyngeal	1 (6.7%)	8 (7.9%)	
Neuroendocrine tumor	2 (13.3%)	6 (5.9%)	
Esophageal	1 (6.7%)	6 (5.9%)	
Salivary	2 (13.3%)	4 (4.0%)	
Adrenal	0 (0.0%)	1 (1.0%)	
Other	1 (6.7%)	8 (7.9%)	

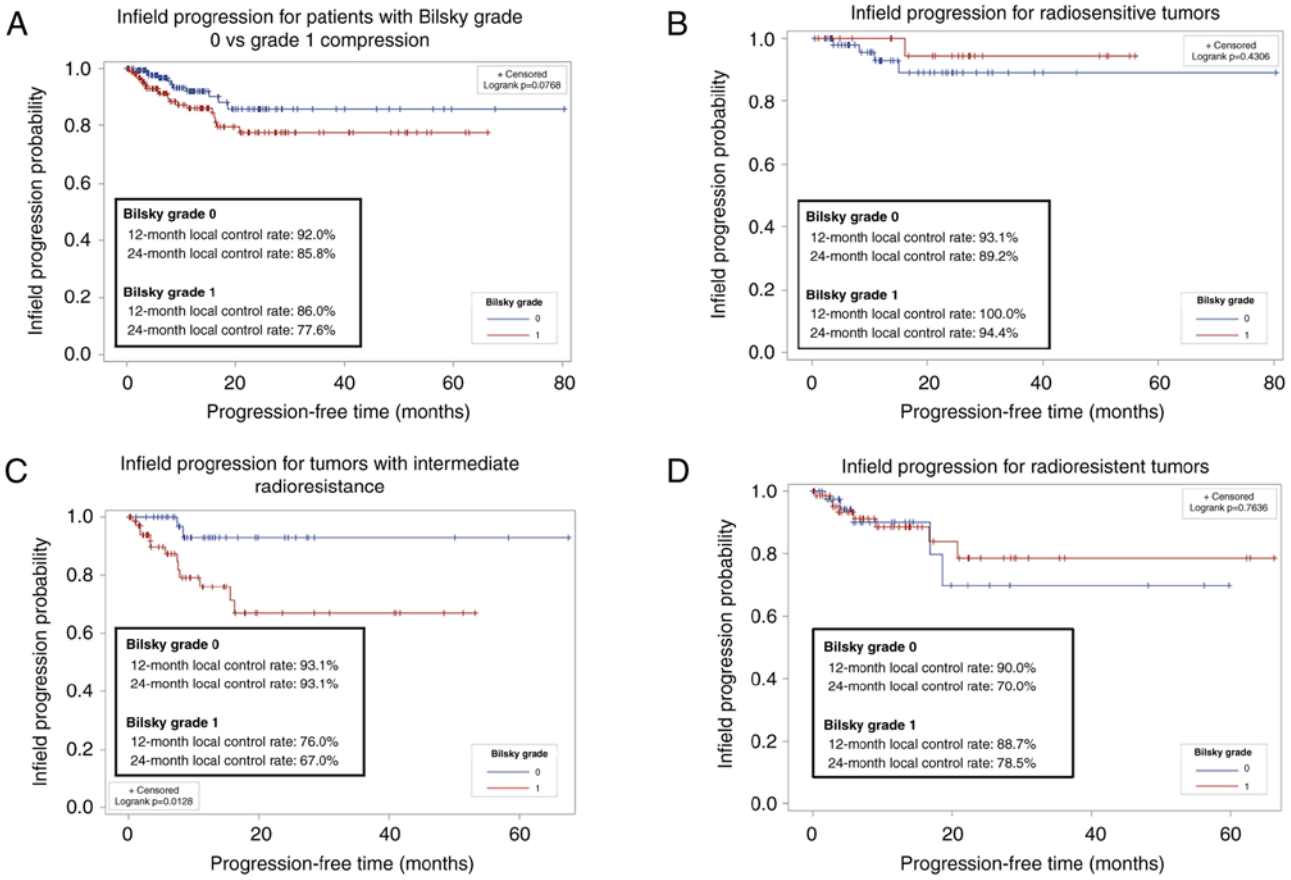

Figure 1. Survival plots for infield progression for patients with (A) Bilsky grade 0 vs. grade 1 compression, (B) radiosensitive tumors, (C) tumors of intermediate radioresistance, and (D) radioresistant tumors.

survival and found no significant difference between survival in radiosensitive and radioresistant tumors (Fig. 2B and D). However, patients who had tumors with an intermediate radioresistance and Bilsky grade 0 compression had significantly better survival compared to patients with Bilsky grade 1 compression (Fig. 2C).

We performed an in-depth analysis of the specific histologies that were within the intermediate radioresistance group (Table V) and found more patients with non-small cell lung cancer who had Bilsky grade 1 compression compared to bone-only disease (45.9% vs. 21.4%; P=.04). Conversely, thyroid, bladder, and liver cancers were more common in patients with grade 0 compression.

Subanalysis of patients with SBRT only treatment. When the same analyses were performed for patients with SBRT only (patients who underwent surgery were excluded) results were

Table V. Histologies of patients with intermediate radioresistance.

Histology categories	Patients with Bilsky grade 0 compression (n=42), n (%)	Patients with Bilsky grade 1 compression (n=74), n (%)	P-value
Histology			0.04
Non-small cell lung cancer	9 (21.4%)	34 (45.9%)	
Thyroid cancer	9 (21.4%)	5 (6.8%)	
Bladder cancer	7 (16.7%)	5 (6.8%)	
Liver cancer	5 (11.9%)	2 (2.7%)	
Oropharyngeal cancer	2 (4.8%)	7 (9.5%)	
Neuroendocrine tumor	2 (4.8%)	6 (8.1%)	
Esophageal cancer	3 (7.1%)	4 (5.4%)	
Salivary cancer	2 (4.8%)	4 (5.4%)	
Adrenal cancer	0 (0.0%)	1 (1.4%)	
Other	3 (7.1%)	6 (8.1%)	

Within the data collected the frequency of Bilski 0 vs. Bilski 1 cases was dependent on the histological distribution of primary metastasis.

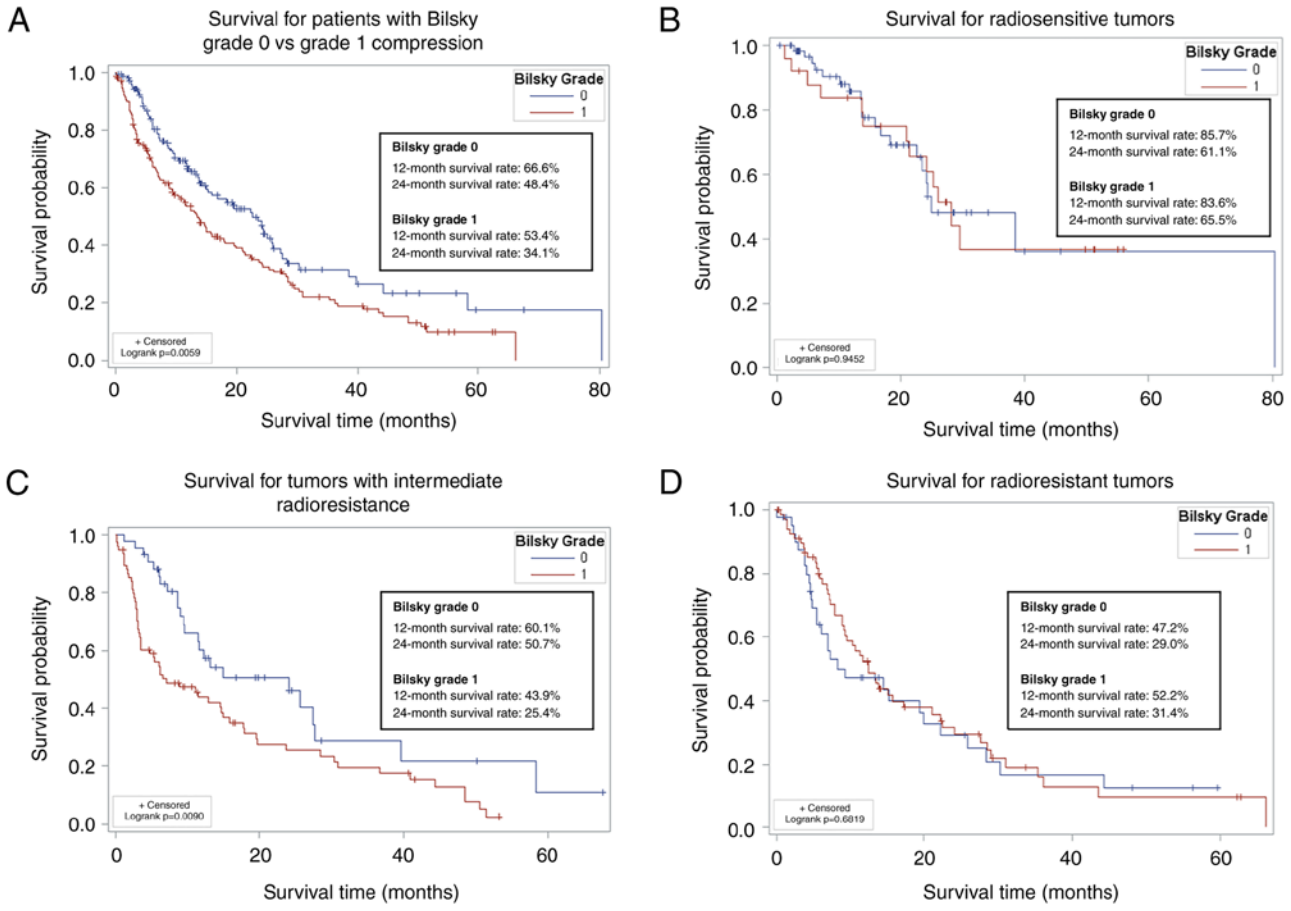

Figure 2. Survival plots for patients with (A) Bilsky grade 0 vs. grade 1 compression, (B) radiosensitive tumors, (C) tumors of intermediate radioresistance and (D) radioresistant tumors.

similar compared to when surgical patients were included. Infield progression also remained similar between patients with Bilsky grade 0 and grade 1 (P=0.06). Additionally, patients with Bilsky grade 0 compression had significantly longer survival compared to patients with Bilsky grade 1 compression (P=0.01; Fig. S1).

Discussion

As spinal metastases are becoming increasingly common in the course of oncologic disease, physicians are continuing to search for treatment modalities and algorithms that both minimize patient symptoms and improve outcomes (1). Nearly

10% of patients with spinal metastases develop spinal cord compression (3), which can cause significant pain and neurological disability, ultimately affecting quality of life (4-11). As diagnostic imaging has improved, spinal metastases are detected earlier in the disease course (as opposed to historically when most patients presented with symptomatic high-grade spinal cord compression). With earlier detection, data are needed to guide the preferred management for an individual patient. Ideally it would be possible to know when to aggressively treat spinal metastases with SBRT and possibly separation surgery if there is not frank, symptomatic epidural spinal cord compression.

We examined patient outcomes and local control rates in patients treated with SBRT for either Bilsky grade 0 or 1 compression. While some variation existed in local control rates between the two groups, the difference was not statistically significant overall. Patients with Bilsky grade 1 compression more often underwent separation surgery prior to SBRT. Despite the use of different SBRT dose and fractionation schemes for treating spinal metastases, the BED between the two groups was not significantly different, and infield progression rates were similar. However, patients with Bilsky grade 1 compression were more commonly treated with separation surgery before SBRT therapy (24-26). Separation surgery is often necessary to achieve sufficiently high doses of SBRT when the epidural spread does not allow a safe distance of CSF around the spinal cord (27). While patients with Bilsky grade 1 and 0 compression achieved statistically similar local control, patients with Bilsky grade 1 compression, on average, underwent more treatment with the additional surgery to achieve a similar result.

Overall, infield progression did not differ between Bilsky grade 0 or 1 compression; however, when examining the trend of infield progression between Bilsky grade 0 or 1 compression of radiosensitive, intermediate radioresistant, and radioresistant histologies, patients with intermediate radioresistance tumors had significantly worse infield progression if they had Bilsky grade 1 compression compared to grade 0 compression. We performed a sensitivity analysis examining the specific histologies and found no significant difference between infield progression between the different histologies. It is likely that our cohort is too small to detect more nuanced reasons for why patients with Bilsky grade 1 compared to grade 0 compression with an intermediate radioresistant tumor would have significant differences of infield progression when radiosensitive and radioresistant tumors did not. It is possible that operative patterns for these tumors are different, representing an area for future research.

We found that patients with Bilsky grade 0 compression had significantly longer survival compared to patients with Bilsky grade 1 compression. We performed a sensitivity analysis to examine if this difference was driven by Bilsky grade or histology. Our data suggested that tumors that were grouped into intermediate radioresistance had worse survival. When looking specifically at the histologies within that group, we found that patients with non-small cell lung cancer were more likely to have Bilsky grade 1 compression compared to bone-only disease, which may account for the difference in survival. Lung cancer has highly variable responses to radiation treatments (28,29).

While not born out in the sensitivity analysis, the possibility remains that the improved survival rate is at least partially driven by the larger number of breast and prostate cancer patients in the Bilsky grade 0 group and that the small numbers of our study do not allow for statistical differences. Overall, it is realistic that both Bilsky grade and tumor histology are jointly critical in determining survival outcomes in patients with spinal metastases. In fact, these variables are unlikely to be independent in predicting survival. We did not test for correlation between Bilsky grade and tumor histology, so this is only a logical assumption. Meanwhile, Shah and Schwab (30) attempted to close the gap between the ability to predict prognosis and patient-specific survival probability. Tumor histology was a standout factor in survival prediction (30). Bendfeldt *et al* (31) found poor survivability at the higher Bilsky scores (2-3), but the same finding was not observed at lower grades of epidural spinal cord compression. The combination of findings from these studies (30,31) are consistent with expectations, but are not granular enough to distinguish between Bilsky 0 and Bilsky 1. A larger sample size is required for granularity

Alternatively, the difference could be related to anatomical differences between Bilsky grade 0 and 1 compression. We postulate that this may be due to (1) later diagnosis and thus more advanced systemic disease in patients with Bilsky grade 1 compression compared to patients with grade 0 compression, and (2) longer periods of time off systemic therapy for patients who underwent separation surgery before SBRT was performed. Our findings suggest that appropriate patients may obtain similar levels of benefit or infield progression if they are treated when the disease is bone-only, which would minimize the risk of needing to undergo separation surgery with associated operative complications and possible delays in obtaining or continuing systemic therapies.

This study is limited by the utilization of a single center, prospectively maintained database, but many of the variables were retrospectively obtained, potentially introducing bias into the analysis. Since these data come from a large, academic institution with a multidisciplinary spinal oncology clinic, these findings may not be generalizable to all centers. While the BED for the two patient populations was not significantly different, multiple different SBRT dose and fraction schemes were utilized, which introduces some minor heterogeneity into the analysis. In addition to the BED being statistically similar between the patient groups, all radiation doses achieved appropriate treatment levels. Because we split the data into specific histologies to attempt to understand infield progression and survival patterns, the size of our data may be a limiting factor, emphasizing the need for future, larger, multicenter studies to obtain robust data.

In conclusion, patients with low-grade Bilsky spinal cord compression did not have significantly different local control rates when compared to patients with bone-only spinal metastases following treatment with spinal SBRT. However, patients with grade 1 disease were more likely to need surgery before SBRT. In patients with radioresistant histologies, earlier treatment before epidural spread may eliminate the need for separation surgery and the consequences associated with this procedure.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JRL conception and design, acquisition of data, analysis and interpretation of data, drafting the article, critically revising the article, statistical analysis. MJS, VGK, PEG, LRT, JL, AT, SK, ALW, OO, MMK, and RSJ acquisition of data, critically revising the article. SK analysis and interpretation of data, statistical analysis. JRE and WCJ analysis and interpretation of data, critically revising the article. NJS conception and design, analysis and interpretation of data, critically revising the article, reviewed submitted version of the manuscript, study supervision. JRL and MJS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The University of Michigan Institutional Review Board (Ann Arbor, USA) approved this study (approval no. HUM00139855).

Patient consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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