North American Spine Society Journal (NASSJ) 6 (2021) 100066

Contents lists available at ScienceDirect

North American Spine Society Journal (NASSJ)

journal homepage: www.elsevier.com/locate/xnsj

Clinical Studies

Phase 1 study of spinal cord constraint relaxation with single session spine stereotactic radiosurgery in the primary management of patients with inoperable, previously irradiated metastatic epidural spinal cord compression

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ARTICLE INFO

Keywords:
Radiosurgery
Phase 1
Spine
Cord compression
Metastases
SBRT

ABSTRACT

Background: Patients with previously irradiated metastatic epidural spinal cord compression (MESCC) who are not surgical candidates are at high risk of neurologic deterioration due to disease in the setting of limited treatment options. We seek to establish the feasibility of using salvage spine stereotactic radiosurgery (SSRS) allowing for spinal cord dose constraint relaxation as the primary management of MESCC in inoperable patients monitoring for radiation related toxicity and radiographic local control (LC).

Methods: Inoperable patients with previously irradiated MESCC were enrolled on this prospective Phase 1 single institution protocol. Single fraction SSRS was delivered to a prescription dose of 18 Gy. Spinal cord constraint relaxation was performed incrementally from an initial allowable Dmax cohort of 8 Gy to 14 Gy in the final planned cohort. Patients were monitored every 3 months with follow-up visits and MRI scans.

Results: The trial was closed early due to slow accrual. From 2011 to 2014, 11 patients were enrolled of which 9 patients received SSRS. Five patients were in the 8 Gy cord Dmax cohort and 4 in the 10 Gy cord Dmax cohort.

The median overall survival (OS) was 11.9 months (95% CI 7.1, 22 months). Of the 9 patients treated with SSRS, 1 died prior to post-SSRS evaluation. Of the remaining 8 patients, 5 experienced a local failure. Three of the five were treated with surgery while two received systemic therapy. Two of the five failures ultimately resulted in loss of neurologic function. The median LC was 9.1 months (95%CI 4.8, 20.1 months). With a median clinical follow-up of 6.8 months, there were no cases of RM.

Conclusions: Despite the limited life expectancy in this high-risk cohort of patients, strategies to optimize LC are necessary to prevent neurologic deterioration. Larger prospective trials exploring optimal dose/fractionation and cord constraints are required.

Introduction

Spine metastases account for 70% of all involved bony sites and leads to significant morbidity including pain, neurologic injury, instability or fracture [1]. In addition, metastatic epidural spinal cord compression (MESCC) is an oncologic emergency best managed with a combination of surgical decompression with external beam radiotherapy to preserve ambulatory function [2].

Cord dose escalation spine SBRT

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https://doi.org/10.1016/j.xnsj.2021.100066
Received 3 February 2021; Received in revised form 23 April 2021; Accepted 24 April 2021
Available online 1 May 2021

However, for patients with MESCC who are inoperable due to rapidly progressive systemic disease, patient refusal or medical co-morbidities, external beam radiotherapy alone is typically offered. For sites previously irradiated, though, treatment options historically have been limited to palliation with systemic therapy, further conventionally fractionated re-irradiation, pain medications and steroids. These patients are at particularly high risk of neurologic compromise from disease progression.

Spine stereotactic radiosurgery (SSRS) is a form of stereotactic body radiotherapy (SBRT) optimized for spinal targets. Intensity modulated radiation treatment planning techniques are combined with precise image guidance and rigid immobilization to deliver ablative radiation doses to the target while sparing nearby critical structures such as the spinal cord. Phase I/II prospective single arm trials have been performed at MD Anderson Cancer Center to establish the safety and efficacy of salvage SSRS for previously irradiated spine metastases demonstrating 1-year actuarial local control rates of 76% [3].

Nonetheless, patients with MESCC receiving SSRS alone are at high risk for local failure secondary to deliberate under-dosing of the epidural disease in order to prioritize spinal cord dosimetry [4,5]. Ideally, surgery followed by SSRS has been used in this cohort with success to optimize local control with minimal toxicities [6–8]. It is clear that local failure following suboptimal local treatment delivery may place the inoperable patient at significant risk of disease progression related spinal cord injury.

On the other hand, the risk of radiation related spinal cord myelopathy (RM) following SSRS is generally <1%. Given that a minimum dose to gross disease of 14 Gy to 15 Gy in a single fraction has been correlated with optimal local control by multiple institutions, the clinical strategy to selectively relax spinal cord dose constraints for high risk inoperable patients is thought to be reasonable. In so doing, it is felt that one can better balance the risks of RM against disease related compressive myelopathy [5,9]. Moreover, the lack of prospective data to define the safety of single fraction SSRS in MESCC as well as the maximum re-irradiated cord tolerance also motivated the design and execution of the Phase 1 clinical trial reported here. The primary goal of this trial was to evaluate the role of spinal cord dose constraint relaxation in inoperable patients with previously irradiated MESCC undergoing single fraction SSRS.

Patients and methods

Study design and participants

Eligibility criteria were as follows: age ≥18 years; no more than 2 contiguous spinal levels involved with metastasis at the target; MRI documented MESCC within 4 weeks of registration which may range from minimal canal compromise to actual displacement of the spinal cord; pathologic confirmation of cancer diagnosis; motor strength ≥ 4 out of 5 in extremity affected by the involved spinal level; Karnofsky performance status ≥ 40; patients deemed to be inoperable by patient refusal, by neurosurgical evaluation, or for any other reason; 1 prior course of spine radiotherapy >3 months prior to registration and maximum cord dose less than 45 Gy in 25 fractions conventional fractionation or similar normalized biologically effective dose (nBED) to the site of interest (e.g., 20 Gy in 5 fractions, 30 Gy in 10 fractions, 37.5 Gy in 15 fractions, 40 Gy in 20 fractions); signed informed consent.

Exclusion criteria included inability to lay flat on the treatment table for > 30 min, inability to undergo an MRI of the spine, pregnancy or cord compression secondary to bone retropulsion.

Written informed consent was obtained from trial participants prior to enrollment. We planned to enroll 36 patients in one of four cohorts defined by the spinal cord dose constraint. At the time the trial was designed, limited data were available establishing the safety of single fraction spinal cord constraints in the setting of re-irradiation. As such, we started at a conservative dose level and escalated from there. Four spinal cord Dmax levels (defined as dose to 0.01 cc) were considered (8 Gy, 10 Gy, 12 Gy and 14 Gy) with enrollment starting in the lowest spinal cord Dmax cohort (8 Gy) and advancement to the subsequent cord dose cohort occurring only if a tumor progression was noted at a given level.

The trial was monitored by the MD Anderson Cancer Center Data Safety Monitoring Board. Prospectively defined stopping rules were established based on the occurrence of RM at a given level. A cohort was deemed unsafe if there were more RM events than tumor progression events and there was more than one RM event. If a spinal cord Dmax was deemed unsafe, accrual would be halted and the trial completed. It was recognized that a lower dose constraint cohort may be deemed unsafe even while a higher dose constraint cohort appeared to be safely accruing. Nonetheless, all dose cohorts at or above the unsafe dose would be deemed unsafe and accrual stopped. Dose to a larger volume of the cord was restricted at the discretion of the treating physician.

The trial was approved by the institutional review board and registered at the US National Institutes of Health (ClinicalTrials.gov) #XXX.

Simulation and treatment procedures

All patients underwent image-guided intensity modulated stereotactic radiosurgery with computed tomography (CT)-guidance using the EXaCT targeting system CT-on-rails or Trilogy treatment delivery system with On-board Imager Cone Beam CT (Varian Medical Systems, Palo Alto, CA) as previously described [10,11]. Briefly, patients were immobilized in an Elekta BodyFix stereotactic body frame system (Elekta, Stockholm, Sweden) and aligned using a stereotactic localizer and target positioning frame (Integra-Radionics, Burlington, MA). Treatment planning was performed using intensity modulated radiation therapy inverse-treatment software (Pinnacle, Philips Medical Systems, Andover, MA). Verification of target positioning and quality assurance procedures for each case was performed by the radiation oncologist and a dedicated radiation physicist, respectively.

The gross tumor volumes (GTVs) were prescribed to receive 18 Gy in a single fraction. The clinical target volume (CTV) as defined by the international consensus guidelines was treated to 16 Gy using simultaneous integrated boost technique [12]. Biologic dose escalation to 24 Gy was not allowed on the trial. MRI-CT fusion was used to define the true spinal cord. No planning target volume or cord planning organ at risk volume were applied per institutional practice.

Patients were clinically evaluated by the treating radiation oncologist at 1 month, then every 3 months for 2 years, then every 6 months thereafter, with MRI of the spine at each visit. Toxicity was assessed using NCI CTCAE version 4.0 with only grade 2 and above radiation related toxicity documented. Neurological assessment was performed by the treating physician and RM determined primarily based on clinical assessment and scored using a modified McCormick Scale as follows: A) No abnormality, B) Focal minor symptom (e.g., pain), C) Functional paresis (≥4/5 muscle power), D) Non-functional paresis (≤3/5 muscle power), E) Paralysis or incontinence. RM was assessed for at least 12 months or until death of the patient. Patient reported outcomes, including the Brief Pain Inventory, MDASI and SF-12v2 were obtained at baseline and at each follow-up. The study neuroradiologist (N.G.) blinded to the treatment cohort determined local control and assessed for radiographic evidence of RM. The MESCC scale described by Bilsky et al. was used to grade the degree of epidural extent (Table 1) [13].

Statistical methods

Patient characteristics were summarized using the median and interquartile range (IQR) for continuous variables and counts and percentages for categorical variables. Time-to-event (TTE) variables were measured from the time of the metastatic epidural spinal cord compression (MESCC) procedure. Four TTE variables were recorded, TLF = time to local failure, TNP = time to neurological paralysis, TRM = time to

Table 1
Metastatic epidural spinal cord compression (MESCC) Grading System.

Grade	Description
0	Bone only disease
1a	Epidural impingement without deformation of the thecal sac
1b	Deformation of the thecal sac without spinal cord abutment
1c	Deformation of the thecal sac with spinal cord abutment but without cord compression
2	Spinal cord compression but with CSF visible around the cord
3	Spinal cord compression, no CSF visible around the cord

RM, and TD = time to death. We assumed that the distribution of each event time was exponential and that, under a Bayesian model, the prior distribution of the mean m was inverse gamma (IG), which implies by conjugacy that the posterior of m was IG[14].

For each TTE outcome's mean, the parameters of a non-informative IG prior were derived by using the empirical mean TTE, defined as the total TTE divided by the number of events if the number of event>0, or the total TTE if the number of events=0) and a given variance[10], 100, 500, and 1000. The posterior distribution, median, mean m, and 95% credible interval (ci) for m were estimated and plotted for each of the four means, which we denote by mLF, mNP, mRM, and mD. The values of TD also were summarized by received RT dose (8 or 10), along with the mean and the standard deviation. For regression of TD on dose(14), it was assumed that the mean time to death at dose 8 was mD8 = exp(α-β/2), and the mean time to death at dose 10 was mD10 = exp(α+β/2), so β = the 10-versus-8 dose effect on mD. Normal priors with large variances (sd=1000) were assumed for alpha and beta.

The posterior distributions of alpha, beta, mD8, and mD10 were estimated using Markov Chain Monte Carlo (MCMC). MCMC trace plots, autocorrelation plots, and posterior density plots were used to ensure a good fit to the data. The posterior distribution of mean TD by received dose was plotted along with the mean and 95% ci. The Kaplan-Meier method[15] was used to estimate unadjusted survival probabilities for the entire sample. An event time plot[16] was constructed, including the times to local failure, neurologic paralysis, and death, starting from time of MESCC (time 0). SAS 9.4 (SAS Inc, Cary, NC) was used for all statistical computations.

RESULTS

The trial was prematurely closed due to slow accrual. Between 2011 and 2014, a total of 11 patients were enrolled (Fig. 1). Of the 11 patients who registered on the study, 2 did not receive the single fraction SSRS treatment. The demographic information for the 9 patients who received treatment on protocol are provided in Table 2. TNP, TRM, and TD each was evaluated for all 9 patients, with TLF evaluated for 8 of the 9, The median age of those treated is 57.8 years, and the most common primary site was lung (n = 4). The most common grade of epidural spinal cord compression was MESCC Grade 2 (n = 4) and 7 of the 9 patients had MESCC Grade 1C or higher disease. Five patients were enrolled on the 8 Gy cord dmax cohort and 4 patients on the 10 Gy cord dmax cohort.

Of the 9 patients who received SSRS on protocol, all returned for at least one clinical assessment but 1 patient did not return for repeat imaging. The median overall survival time was 11.9 months (95% posterior credible interval from the 2.5th to 97.5th percentile of the distribution, CI, 7.1–22 mo) and the 1 year overall survival probability was 33% (Fig. 2). An event time plot for each patient is illustrated in Fig. 3. With a median clinical follow-up of 6.8 months (range 1–29 months), there were no radiation myelopathies.

Local tumor progression occurred in 5 of the 8 evaluable patients. The median time to local failure was 9.1 months (95% CI 4.8–20.1 mo). Of the 5 local failures, 3 were treated with salvage surgery, 1 with systemic therapy and 1 with SSRS for a marginal component followed by systemic therapy. Of the 9 clinically evaluable patients, 3 suffered irreversible neurological deterioration directly attributable to local failure

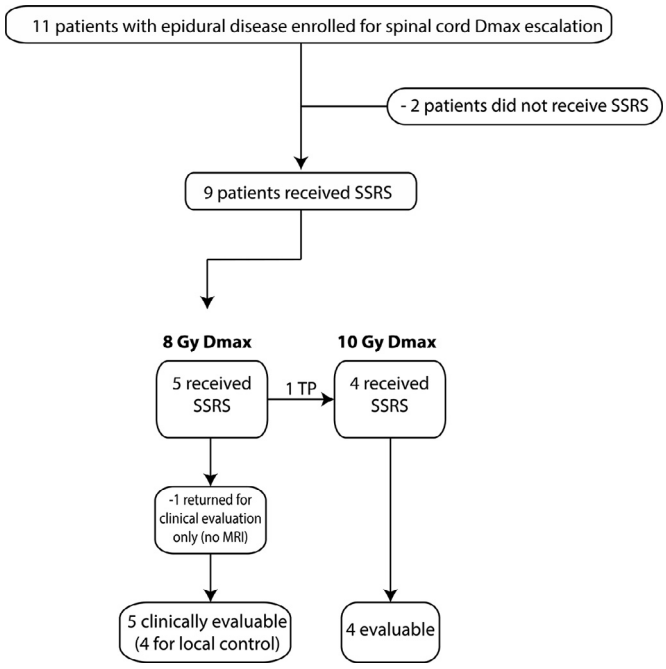

Fig. 1. CONSORT Flowchart.

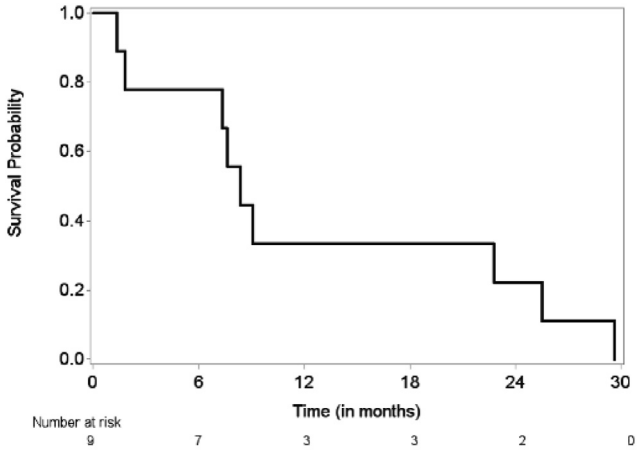

Fig. 2. Kaplan-Meier estimated overall survival.

at the site of SSRS. Neurologic deterioration occurred at 0.9 months, 6.7 months and 21.9 months in the three patients, respectively (Fig. 3). There were no Grade 2 or greater radiation related CTCAE v4.0 toxicities noted.

Bayesian modeling was performed to illustrate the differences in probability between neurologic deterioration secondary to disease progression versus radiation related myelopathy. As illustrated in Fig. 4, the risk of neurologic deterioration secondary to disease progression far

Table 2
Patient demographics.

			Cord Dmax Cohort	
		Total	**8 Gy**	**10 Gy**
Patients		9	5	4
Gender				
	Male	3	0	3
	Female	6	5	1
Primary site				
	Lung	4	4	0
	Colon	1	0	1
	Prostate	1	0	1
	Liver	1	0	1
	Uterus	1	0	1
	Brain	1	1	0
Histology				
	Adenocarcinoma	6	3	3
	Squamous cell carcinoma	1	1	0
	Hepatocellular carcinoma	1	0	1
	Hemangiopericytoma	1	1	0
Levels involved				
	1	5	3	2
	2	4	2	2
MESCC Grade				
	1B	2	0	2
	1C	2	2	0
	2	4	2	2
	3	1	1	0

MESCC, Metastatic epidural spinal cord compression.

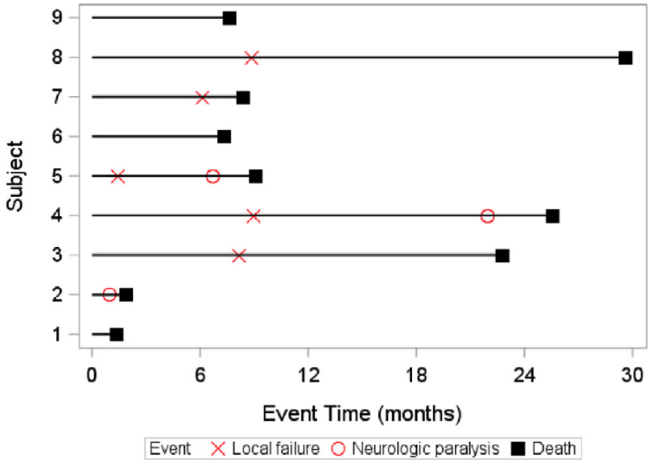

Fig. 3. Event time plot.

exceeds the risk of myelopathy in this study even if one assumes a single hypothetical radiation myelopathic event (Posterior median 32.2 mo (95% CI, 16.8–73.6) vs 116 mo (95% CI, 72.3–203.2)).

Discussion

SSRS is an effective treatment technique in the management of select patients with spinal metastases. Prospective as well as retrospective clinical data from multiple institutions have demonstrated not only durable radiographic local control but also durable pain relief with reduced symptom burden in patients receiving SSRS for radioresistant disease, oligometastatic disease and/or previously irradiated disease [3,5,17–23]. However, patients with metastatic disease extending into the epidural space are at an increased risk of local failure within the epidural space [4]. This is largely due to deliberate under dosing of epidural tumor to respect established spinal cord dose constraints.

On the other hand, RM is an exceedingly rare event following SSRS with most studies citing a less than 1% risk with standard spinal cord dose constraints and recent studies suggesting that traditional constraints may be overly conservative [24,25]. Moreover, applying a de-

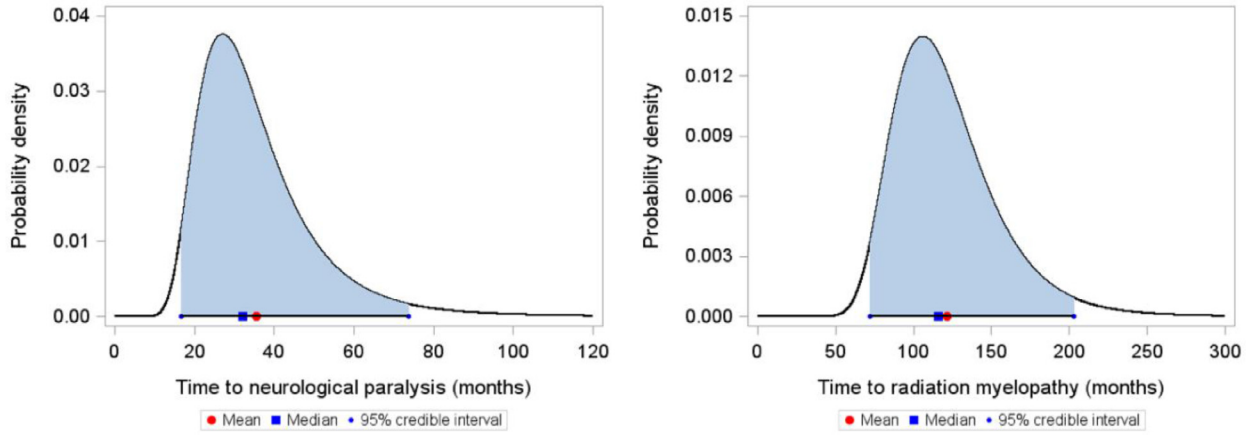

Fig. 4. Bayesian model of risk for neurologic progression and radiation myelopathy.

fined minimal dose to the gross tumor (i.e., GTV Dmin of 14 Gy to 15 Gy in 1 fraction) has been correlated with superior local control [5,19]. Current treatment strategies to optimize local control in patients with MESCC undergoing SSRS include separation surgery(7) as well as laser interstitial thermotherapy(26). Surgical resection of epidural disease followed by SSRS yields excellent 1-year local control rates ranging from 84% to 90% in retrospective studies [6,27]. Ryu et al. demonstrated that single fraction SSRS may be utilized safely for patients with unresected, previously unirradiated metastatic epidural spinal cord compression with the most common pattern of failure as epidural [28]. However, therapeutic strategies for previously irradiated inoperable patients remain limited leading to the development of the current trial. We demonstrate in this trial, closed early due to slow accrual, that inoperable patients were more likely to develop disease related neurological deterioration than radiation myelopathy from salvage single fraction SSRS.

Recently, our group published the results of a Phase 1 study investigating the role of spinal cord constraint relaxation in inoperable patients with metastatic epidural spinal cord compression and no prior history of radiation at the site of interest [29]. Patients received single fraction radiosurgery with the GTV receiving either 24 Gy or 18 Gy depending on histology. The median survival for the 28 evaluable patients was 29 months. With escalating spinal cord constraints ranging from a Dmax of 10 Gy to 16 Gy, and a median follow-up of 17 months, no myelopathy events were noted. The 1- year local control rate was 89% and no disease related neurologic progression was noted. The current companion trial investigated the same concept within the setting of prior irradiation at the site of interest; however, the median survival was only 11.9 months on this study with a median local control of only 9 months. In addition, 3 of 9 patients suffered disease progression related neurological deterioration.

Multiple factors likely contribute to the relatively limited efficacy of SSRS in this study. For instance, in the current study, patients were prescribed single fraction radiosurgery to a dose of 18 Gy regardless of histology in contrast to the radiation naïve trial whereby patients received either 24 Gy or 18 Gy based on histology. Multiple institutions have demonstrated that biologic dose escalation particularly for radioresistant disease yields better local control [9,21,30]. One multi-institutional retrospective analysis of salvage spinal SBRT following prior conventional radiotherapy demonstrated improved local control with single fraction treatment versus multi-fraction treatment [31]. However, the rate of local control in this study is much lower than a prior prospective clinical trial performed at our institution using multi-fraction radiosurgery for previously irradiated disease without cord compression suggesting additional factors at play [23].

The current cohort of patients included inoperable patients with previously irradiated MESCC, a high risk cohort of patients with poor prognoses as reflected by the relatively limited median survival of 11.9 months (compared with 29 months in the radiation naïve companion trial). Of note, inoperability was determined after a multi-disciplinary tumor board discussion and could include reasons such as patient refusal, neurosurgery evaluation or minimizing a delay in systemic therapy initiation in patients without rapid neurological compromise. As such, some patients deemed inoperable at the time of trial registration were salvaged with surgery after receiving the protocol treatment and suffering a local failure.

Furthermore, the spinal cord constraint in this trial was limited to 8 Gy and 10 Gy prior to the trial closing early due to poor accrual. Under dosing of the epidural space is correlated with a higher risk of local failure with GTV Dmin doses of 14 Gy associated with optimal local control [5]. As such, optimizing local control for high risk patients with inoperable MESCC may require more liberal spinal cord constraints.

The clinical ramifications of local failure in this study of inoperable, previously irradiated MESCC was demonstrated by the high risk of disease progression related neurologic sequelae. Three of the 9 patients enrolled on the study experienced paralysis due to local progression at the treated site. However, no patient on the study suffered a radiation related myelopathy. This suggests that there may be a role for more aggressive approaches to controlling previously irradiated disease to include spinal cord constraint relaxation and/or biologic dose escalation.

There are significant limitations to this single institution, single arm, prospective clinical trial. The study did not meet accrual and was terminated prematurely. The small sample size lends to an increased variance in patient characteristics limiting the generalizability of the results. During protocol enrollment, laser interstitial thermotherapy (LITT) was developed at our institution offering a minimally invasive option for surgical separation of epidural tumor [26,32,33]. As such, more patients were eligible for operative intervention with this minimally invasive approach reducing the number of patients eligible for the current study. The limited enrollment on this study limits our ability to perform secondary analyses to investigate factors which may correlate with local control in this setting. Also, escalated spinal cord tolerance was not assessable as patients were only enrolled in the Dmax 8 Gy and 10 Gy cohorts. It is unclear whether the planned spinal cord relaxation to 12 Gy or 14 Gy would have yielded improved local control. Furthermore, as a single institution, single arm clinical trial, the results may not be generalizable to other practice settings depending on institution experience and population of patients.

Despite these limitations, this prospective clinical trial demonstrates that inoperable patients with MESCC have a poor prognosis and high risk of clinically significant neurologic sequelae from spinal disease progression. Future clinical trial designs may focus on more aggressive local therapy approaches for inoperable MESCC including biologic dose escalation, spinal cord constraint relaxation and exploring radiosensitizers for this high risk cohort.

Declarations of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding disclosure

Supported by the NIH/NCI under award number P30CA016672.

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