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## Predictors of Quality of Life Improvement after Surgery for Metastatic Tumors of the Spine: Prospective Cohort Study

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### Abstract

**Background Context**—Surgical decompression and stabilization followed by radiosurgery represents an effective method for local tumor control and neurologic preservation for patients with metastatic epidural spinal cord compression. We have previously demonstrated improvement in HrQOL after this combined modality treatment (“hybrid therapy”).

**Purpose**—The current analysis focuses on delineation of patient-specific prognostic factors predictive of HrQOL change after combined surgery-SRS treatment of MESCC.

**Study Design**—This is a prospective, single-center, cohort study.

**Patient Sample**—One hundred and eleven patients with MESCC who underwent separation surgery followed by SRS were included.

**Outcome Measures**—Prognostic factors associated with improved patient reported outcome (PRO) measures.

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**Methods**—PRO tools, i.e. Brief Pain Inventory (BPI) and MD Anderson Symptom Inventory – Spine Tumor (MDASI-SP), both validated in the cancer population, were prospectively collected. Numeric prognostic factors were correlated with PRO measures using the Spearman rank correlation coefficient. Categorical prognostic factors were correlated with PRO measures using the Wilcoxon two-sample test (for two categories) or the Kruskal-Wallis test (for three or more categories). All statistical tests were two-sided with a level of significance  $<0.05$  for correlation of prognostic factors with PRO constructs and a level of significance  $<0.0014$  for correlation of prognostic factors with PRO items. Statistical analyses were done in SAS (version 9.4, Cary, NC).

**Results**—One hundred and eleven patients were included in this analysis. Patients with lower pre-operative Medical Research Council (MRC) motor scores experienced a greater decrease in symptom interference (BPI Interference construct ( $p=0.03$ ), and individual functional measures including general activity ( $p=0.001$ ), walking ( $p=0.001$ ) and normal work ( $p=0.006$ )). Lumbar location was associated with better outcomes than cervical or thoracic as noted on the BPI pain experience construct ( $p=0.03$ ) and MDASI-SP interference ( $p=0.01$ ) and core symptom ( $p=0.002$ ) constructs. Patients with ASIA scores of C or D benefit more than those with ASIA E on BPI Interference construct ( $p=0.04$ )). Patients with higher ECOG scores at presentation benefit more than those with low ECOG scores on MDASI-SP interference construct, ( $p=0.03$ )). Women benefit more than men on BPI interference ( $p=0.03$ ) and pain experience ( $p=0.04$ ) constructs. Patients with prior spinal surgery at the current level of interest benefit less than those which are naïve surgical patients in MDASI-SP interference construct, ( $p=0.04$ ).

**Conclusions**—Delineation of patient characteristics associated with HrQOL improvement provides crucial information for patient selection, patient education and setting treatment expectations. For patients with MESCC treated with hybrid therapy using surgery and radiosurgery, the presence of neurological deficits and diminished performance status, lumbar tumor level and female gender were associated with greater PRO improvement.

### Keywords

MESCC; HRQoL; Separation surgery; Spine tumor; PRO

### Introduction

Metastatic spinal tumors frequently occur in the cancer population as they are found in up to 40% of cancer patients[1]. These tumors often require surgical intervention for decompression of the spinal cord or nerve roots, for mechanical stabilization or a combination of both. Surgical decompression and stabilization followed by radiotherapy represents the established therapy for patients with high-grade epidural tumor extension and has been shown to result in pain relief, restoration or preservation of neurologic function and spinal column stability and improvement in HrQOL[2].

Symptom relief serves as an important surgical goal and identifying patients who are most likely to experience symptom relief is critical for surgical decision-making. PRO measures serve as an important method for analyzing the effect of disease and therapy on the symptoms that the patients experience. In our recent prospective study[3], we used validated PRO measurements and demonstrated that hybrid therapy consisting of separation surgery

and radiosurgery provides significant and durable pain relief and reduction in disease interference with daily activities. Optimization of patient selection and the setting of reasonable treatment expectations provide better physician-patient relationships and ultimately better cancer care. Delineating prognostic factors that influence PRO measures following this treatment is an important addition to treating physician's body of knowledge and is the object of the current analysis.

## Materials and Methods

This is a prospective, single center, observational cohort study. The study was performed at a tertiary cancer center. The local institutional review board (IRB) approved this study. The methods of this study have been described in detail elsewhere[3] and hence will be described here in brief.

### Population

One hundred and eleven patients were included in the current analysis. All patients were treated with separation surgery followed by radiosurgery for spinal tumors between October 2013 and July 2016. Patients who were treated with other spinal surgical procedures (i.e. percutaneous stabilization, minimal access decompression, etc.) were excluded. Patients whose pre-operative evaluation was conducted more than 30 days prior to surgery were likewise excluded.

Patient Reported Outcomes were collected electronically either in clinic or using an electronic link to fill out surveys in the outpatient setting. Written surveys were provided when necessary and data were subsequently manually transferred to the electronic database. All data were kept in accordance with HIPAA regulations. The change in PRO measures was compared pre-operatively; 3 months post operatively (2–4.5 months) and at long term follow up (4.5–12 months).

*Brief Pain Inventory (BPI)* is a cancer validated tool[4] which assesses pain and disease interference[5]. Four pain-related items generate a pain construct and 8 disease interference items generate a disease interference construct. Combining the pain and disease interference constructs generates a patient pain experience construct.

*MD Anderson Symptom Inventory (MDASI)* is another cancer validated tool[6] and has a spine specific module (MDASI-sp)[7]. Thirteen combined items comprise the MDASI core symptom construct, six disease interference items combined generate a MDASI disease interference construct and 5 spine tumor-specific items combined generate an MDASI spine tumor-specific construct.

### Treatment

The detailed method for separation surgery has been previously described elsewhere[8]. Briefly, it is a postero-lateral approach allowing for circumferential decompression and stabilization of the spine. No attempt to completely resect the tumor is made and generally the anterior column tumor is left intact. Typically, instrumented stabilization is achieved prior to decompression. Laminectomy, facetectomy and transpedicular approach to the

ventral epidural space is accomplished with a high-speed drill in order to provide circumferential access for 360° decompression. The posterior longitudinal ligament (PLL) is resected to provide a margin on the anterior dura and epidural tumor is excised until spinal cord decompression is achieved. Adequate tumor excision provides a 2–3mm separation between the tumor and the spinal cord, allowing re-constitution of the thecal sac.

In this patient series, 101 patients underwent spinal separation surgery with posterior instrumented fusion followed by SRS and an additional 10 patients had previously placed instrumentation and therefore underwent salvage tumor separation surgery followed by radiosurgical treatment with no additional instrumentation. Following surgical intervention, all patients underwent simulation with CT myelogram for SRS contouring and planning. The time interval from surgery to radiation was at a median of 20 days. SRS planning and contouring was carried out according to consensus guidelines[9, 10]. The radiosurgery treatment plans were then reviewed by neurosurgery and radiation oncology teams. Radiosurgery was delivered in 17 patients with a median dose of 24 Gy single fraction (range, 9 to 27 Gy), in 70 patients at a median dose of 27 Gy in 3 fractions (range, 24 to 36GY) and in 24 patients at a median dose of 30 Gy in 5 fractions (range 20 to 40 Gy).

### Statistical Analysis

Descriptive statistics such as frequencies, medians, means, and standard deviations were used to characterize the cohort. Numeric prognostic factors were correlated with individual PRO measures and constructs using the Spearman rank correlation coefficient. Similarly, categorical prognostic factors were correlated with individual PRO measures and constructs using the Wilcoxon two-sample test (for two categories) or the Kruskal-Wallis test (for three or more categories). Age was dichotomized at the median for correlation analyses. Surgical treatment level was categorized as cervical, thoracic, lumbar, cervico-thoracic, and thoracolumbar for correlation analyses. All statistical tests were two-sided. For correlation of prognostic factors with PRO constructs (n=6), a level of statistical significance of <0.05 was used. For correlation of prognostic factors with individual PRO items (n=36), Bonferroni correction was used for statistical significance with a level <0.0014 considered statistically significant. Statistical analyses were done in SAS (version 9.4, Cary, NC).

### Results

One hundred and eleven patients were included in this analysis of which 67 (60%) were male and the median age was 63.9. The most common histologies treated were non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC) and sarcoma. Patient and tumor variables are summarized in table 1.

The majority of cases were performed on the thoracic spine (48%) or junctional levels (24%). Fifty-nine surgeries (53%) required 3 level and 26(23%) required 2 level posterolateral decompression. The most common stabilizing construct length was 5 levels typically stabilizing with screw-rod constructs 2 levels above and below the index level. Treatment variables are summarized in table 2.

### BPI Constructs

Patients with an ASIA score of C or D benefit statistically significantly more with regard to BPI interference construct than those with an ASIA score of E ( $p=0.04$ ). Patients with lower pre-operative medical research council (MRC) scores benefit statistically significantly more than those with high scores representing normal muscle strength ( $p=0.03$ ) in regards to BPI interference construct. Women benefit statistically significantly more with regard to patient-reported BPI interference ( $p=0.03$ ) and pain experience ( $p=0.04$ ) constructs than men. There were statistically significant associations between treatment level and BPI Patient Pain Experience ( $p=0.03$ ) demonstrating that patients with lumbar disease benefit more than those with cervical, thoracic or junctional disease.

### MDASI Constructs

Patients with prior spinal surgery benefit statistically significantly less with regard to patient-reported MDASI spine tumor specific construct than those without prior spinal surgery ( $p=0.04$ ). Those with higher ECOG (lower functional status) benefit statistically significantly more with regard to patient-reported MDASI interference construct than those with lower ECOG ( $p=0.03$ ). Similarly to the BPI constructs, there were statistically significant associations between treatment level and MDASI Core symptom severity ( $p=0.002$ ), and MDASI Interference ( $p=0.01$ ) constructs demonstrating that patients with lumbar spine disease benefit the most.

No significant associations were found with length of stabilizing construct, number of levels decompressed, age or the delivery of concurrent radiation treatment.

### Individual Items

Patients with lower pre-operative MRC scores benefit more than those with high scores in BPI general activity ( $p=0.001$ ) and walking ability ( $p=0.001$ ).

All BPI and MDASI significant construct and individual item results are summarized in table 2.

### Discussion

The current analysis identifies patient-specific factors prognostic of improvement in health related quality of life (HrQOL) after surgical treatment of MESCC. “Hybrid therapy” (separation surgery and concomitant radiosurgery) is an effective method for tumor control and neurologic preservation for patients with metastatic epidural spinal cord compression[2] and was uniformly applied in the study patient population. We have previously demonstrated the benefit of this combined modality treatment on HrQOL PRO measures in a prospective study[3] and now identify specific factors associated with patient-perceived benefit of this treatment paradigm. Symptomatic relief plays a key role in decision making and thus delineation of favorable patient characteristics facilitates patient selection. Furthermore, informing patients and setting realistic treatment goals and expectations are crucial in cancer care.

Patient reported outcome measures have become an important tool in the assessment of spine oncology outcomes. Outcome reporting for this population is challenging compared to patients with more common spinal conditions such as degenerative spine disease or adult spinal deformity given the multifocal systemic tumor burden, concurrent treatments and psychological circumstances of metastatic cancer[11]. Objectively eliminating the inherent bias of subjective assessments such as gross measures of function (ambulatory status, Frankel Score)[11–13] and process variables including survival, local recurrence and complications is challenging. Recent prospective PRO data overcome these inherent flaws and the understanding of treatment effect on HrQOL of spine cancer patients is growing[14, 15]. There are several currently available PRO tools to assess outcomes in spine cancer patients[16]. Our current study utilized cancer validated PROs, the MDASI and BPI to determine factors associated with outcome. To note, the MDASI-sp is a unique questionnaire that has been shown to be valid and reliable in patients with spine tumors as a composite measure of disease-related symptoms[7].

In this analysis, patients with lower pre-operative functional status (i.e. high ECOG scores) as well as those with greater pre-operative neurological dysfunction (i.e. lower ASIA scores) and those with lower MRC scores (i.e. greater motor weakness) reported superior improvement in disease interference PROs following hybrid therapy than those with better pre-operative functional status and neurological examination. As expected, patients with preoperative neurologic deficits experience greater preoperative disease interference, compared to patients with intact functional and neurologic scores. Fortunately, after surgery both groups report similar post-operative symptom interference, supporting the role of surgery in patients with disability due to MESCC. Previous data shows that worse preoperative neurologic status and functional capacity places patients at risk of worse postoperative functional outcomes[17–20]. These data rely on physician-reported outcomes such as ambulation and ECOG, rather than on patient-reported symptoms. Our current data show that patients with disability due to MESCC benefit from surgery and experience significant decrease in symptom interference with daily activities, enjoyment of life, mood, distress and general activities. This finding is particularly meaningful due to the palliative nature of this treatment. The relationship between the extent of neurologic improvement and symptom relief requires further investigation and is currently the subject of a prospective multi-institutional study.

Our results show that patients who had undergone prior spinal surgery (24 patients) benefit significantly less with regard to patient-reported MDASI spine tumor specific construct than those without prior spinal surgery. All patients in the current study with history of prior surgery underwent re-operation for treatment of local tumor recurrence. Most of these patients underwent prior surgery and radiation prior to presenting to our institution and often had suboptimal post-operative radiotherapy that placed them at risk of local tumor recurrence. It has previously been shown that reoperation benefits patients with MESCC due to tumor recurrence at previously operated spinal levels, resulting in prolonged ambulation and in good functional and neurological outcomes[21]. While hybrid therapy with surgery and radiosurgery has a clear role in preservation of ambulation and in achieving local tumor control, our current data demonstrate that reoperations result in diminished improvement of spine-specific symptoms compared to first-time surgery. This finding highlights the

importance of the first operation and how critical it is to ensure that newly treated patients are offered the optimal surgical and concomitant radiation/medical therapy for durable tumor control.

Patients treated with hybrid therapy for lumbar spine disease experienced greater symptom severity prior to surgery and showed greater improvement in PROs compared to those with cervical or thoracic disease. We have previously demonstrated improvement in pain as assessed by the visual analog scale (VAS) as well as ECOG for cancer patients with lumbar mechanical radiculopathy[22]. Our current data show that cancer patients with lumbar mechanical radiculopathy are likely to experience improvement in several factors such as symptom interference, pain experience, walking ability and distress after surgery. Of note, all patients in the current study experienced diminished pain after surgery, with patients with tumors in the mobile regions of the spine (cervical and lumbar) experiencing the largest improvement. Each spine region represents a unique biomechanical and neurovascular region with region-specific symptoms and surgical considerations. Interestingly, there were no significant differences found in PRO's with regards to the extent of surgery represented by the number of levels fused and number of levels decompressed. Therefore, the location of surgery is a stronger predictor of symptom improvement than the surgical technique or extent.

Data regarding the effect of gender on spine surgery aspects are scarce. Herein, we showed that women experience greater severity of preoperative pain and symptom interference compared to men and report a significantly larger improvement in symptom severity after surgery. Both men and women have comparable post-operative PRO. In lumbar spine surgery, female gender seems to play a major role as a negative prognostic factor in different spinal disorders[23–25] possibly influenced by differences in hypothalamic-pituitary-adrenocortical responses[26]. A recent study revealed pre- and postoperative differences in pain perception between genders in an evaluation of patients with lumbar disc sequestration. Though data are limited, gender differences should likely be taken into account for outcome analysis.

## Conclusions

Among patients with MESCC requiring surgery and concomitant radiosurgery, presence of neurological deficits and diminished performance status, lumbar tumor level and female gender were associated with greater postoperative PRO improvement. Re-operated patients were associated with diminished PRO improvement compared to patients undergoing initial surgery. Delineation of favorable patient characteristics facilitates decision making as symptomatic relief plays a key role in decision making in these palliative surgeries. Knowing factors associated with outcomes is key for selecting an appropriate treatment strategy and setting realistic patient expectations.

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**Table 1**

## Patient and Treatment Characteristics

Variable	Category	N	%
Age			
<i>Median: 63.9</i>	--	111	100
<i>Mean: 61.4</i>			
Sex	Female	44	40
	Male	67	60
Surgical Treatment Level	Cervical	10	9
	Cervico-thoracic	14	13
	Thoracic	53	48
	Thoraco-lumbar	12	11
	Lumbar	22	20
Histology	NSCLC	26	23
	RCC	25	23
	Sarcoma	13	12
	Thyroid	8	7
	Prostate	7	6
	Head & Neck	6	5
	Breast	4	3
	Hepatocellular	3	3
	Melanoma	3	3
	Colorectal	3	3
	Other	13	12
# Levels Decompressed	--	111	100
<i>Median: 3</i>	1	10	9
<i>Mean: 2.8</i>	2	26	23
<i>SD: 1</i>	3	59	53
	4	11	10
	5	3	3

Variable	Category	N	%
	6	2	2
Length of Construct	--	111	100
<i>Median: 5</i>	0	10	9
<i>Mean: 5.2</i>	3	4	4
<i>SD: 2.4</i>	4	14	13
	5	43	39
	6	17	15
	7	8	7
	>7	15	14
Preoperative SINS	Stable	10	9
	Intermediate	63	57
	Unstable	19	17
	n/a	19	17
Preoperative ECOG	0	10	9
	1	88	79
	2	2	2
	3	7	6
	4	4	4
Preoperative ASIA	C	3	3
	D	12	11
	E	96	86
Prior Spinal Procedure	At surgical level	12	11
	At other level	12	11
	None	87	78

**Table 2**

Predictive Factors Associated with Change in PROs Following Separation Surgery and SSRS.

Variable of Interest	Survey	Survey Item or Construct	Variable Category	Mean Pre-Op Score	Mean Post-Op Score	Mean Score Difference	Spearman Rank Coefficient	p value <sup>d</sup>	Interpretation: Who benefits the most
MRC Muscle Scale	BPI	General Activity	Continuous	--	--	--	0.41	0.001	Patients with lower MRC scores
		Walking Ability	Continuous	--	--	--	0.33	0.001	
		Normal Work <sup>+</sup>	Continuous	--	--	--	0.35	0.006	
		Symptoms Interference <sup>*</sup>	Continuous	--	--	--	0.27	0.03	
		Work <sup>+</sup>	Continuous	--	--	--	0.38	0.005	
ECOG Score	MDASI	Limb Weakness <sup>+</sup>	Continuous	--	--	--	-0.36	0.006	Patients with higher ECOG scores
		Mood <sup>+</sup>	Continuous	--	--	--	-0.39	0.003	
		Symptoms Interference <sup>*</sup>	Continuous	--	--	--	-0.28	0.03	
ASIA Impairment Scale	BPI	Symptoms Interference <sup>*</sup>	C or D E	6.13	3.04	-3.1	--	0.04	Patients with pre operative ASIA C or D
				4.12	3.52	-0.6			
Prior Surgery	MDASI	Spine Tumor Specific Symptoms <sup>*</sup>	No prior surgery	2.80	2.13	-0.7	--	0.04	Patients with no prior spinal surgery
			Prior surgery	2.06	3.00	+0.9			
Treatment Level	BPI	Patient Pain Experience <sup>*</sup>	Cervical	26.30	17.90	-8.4	--	0.03	Patients with lumbar disease
			Thoracic	26.94	15.13	-11.8			
			Thoraco-lumbar	18.71	18.13	-0.6			
			Lumbar	20.10	18.60	-1.5			
				31.71	19.29	-12.4			
MDASI	CORE Symptom Severity <sup>*</sup>	Cervical	2.61	4.46	+1.9	--	0.002		
		Thoracic	3.22	2.76	-0.5				
		Thoraco-lumbar	2.39	3.02	+0.6				

Variable of Interest	Survey	Survey Item or Construct	Variable Category	Mean Pre-Op Score	Mean Post-Op Score	Mean Score Difference	Spearman Rank Coefficient	p value <sup>d</sup>	Interpretation: Who benefits the most
Gender	BPI	Symptoms Interference*		2.12	3.14	+1		0.01	Patients who are women
				4.02	2.66	-1.4			
			Cervico-thoracic Thoraco-lumbar Lumbar	5.07	5.69	+0.6	--		
				4.04	2.50	-1.5			
				3.68	3.82	+0.1			
				5.75	3.75	-2			
		7.39	4.05	-3.3					
		Mood <sup>†</sup>	3.43	3.40	-0.03				
			5.78	2.83	-3.0				
			Symptoms Interference*	3.69	3.26	-0.4			
5.45	3.81			-1.6	0.03				
Patient Pain Experience*	20.55	17.15	-3.4						
	28.48	19.41	-9.1	0.04					

Abbreviations: MRC=Medical Research Council, ECOG=Eastern Cooperative Oncology Group, ASIA=American Spinal Injury Association, BPI= Brief Pain inventory, MDASI= MD Anderson symptom Inventory

\* construct

<sup>†</sup>Near significant result

<sup>d</sup>P-value is for unique tests comparing mean score difference across variable of interest categories. For continuous variables of interest (MRC and ECOG), p-value is for unique tests correlating the continuous variable of interest with the continuous survey item or construct of interest.

\*\* For analysis of constructs 6 tests were performed, hence p<0.05 is statistically significant. For individual items 36 tests were performed, hence p<0.00138 is significant