Risk factors for wound-related reoperations in patients with metastatic spine tumor

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OBJECTIVE Resection of metastatic spine tumors can improve patients' quality of life by addressing pain or neurological compromise. However, resections are often complicated by wound dehiscence, infection, instrumentation failures, and the need for reoperation. Moreover, when reoperations are needed, the most common indication is surgical site infection and wound breakdown. In turn, wound reoperations increase morbidity as well as the length and cost of hospitalization. The aim of this study was to examine perioperative risk factors associated with increased rate of wound reoperations after metastatic spine tumor resection.

METHODS A retrospective study of patients at a single institution who underwent metastatic spine tumor resection between 2003 and 2013 was conducted. Factors with a p value < 0.200 in a univariate analysis were included in the multivariate model.

RESULTS A total of 159 patients were included in this study. Karnofsky Performance Scale score > 70, smoking status, hypertension, thromboembolic events, hyperlipidemia, increasing number of vertebral levels, and posterior approach were included in the multivariate analysis. Thromboembolic events (95% CI 1.19–48.5, p = 0.032) and number of levels involved were independently associated with increased wound reoperation rates in the multivariate model. For each additional spinal level involved, the risk for wound reoperations increased by 21% (95% CI 1.03–1.43, p = 0.018).

CONCLUSIONS Although wound complications and subsequent reoperations are potential risks for all patients with metastatic spine tumor, due to adjuvant radiotherapy and other medical comorbidities, this study identified patients with thromboembolic events or those requiring a larger incision as being at the highest risk. Measures intended to decrease the occurrence of perioperative venous thromboembolism and to improve wound care, especially for long incisions, may decrease wound-related revision surgeries in this vulnerable group of patients.

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KEY WORDS reoperation; spine tumor; metastasis; wound dehiscence; infection; instrumentation failure; oncology

THE most common indications for surgical treatment of metastatic spine lesions include spinal instability, local tumor control, management of intractable pain, and prevention of neurological deterioration.^{22,25} Although surgery for metastatic spine disease is primarily palliative in nature, recent studies have demonstrated that this intervention can significantly improve patients' quality of life.³³ Despite the benefits of treatment, the potential

complications associated with surgery for metastatic spine disease represent a significant source of morbidity and mortality.^{15,19,33} These include wound infections, wound dehiscence, hematomas, neurological impairments, deep venous thrombosis, and instrumentation failure, among others.^{15,33}

In patients with metastatic spine tumors, overall complication rates range between 19% and 28%,^{30,33,34} whereas

ABBREVIATIONS BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; EBL = estimated blood loss; KPS = Karnofsky Performance Scale; RT = radiation therapy; VEGF = vascular endothelial growth factor; VTE = venous thromboembolism.

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the incidence of surgical site infection and wound breakdown is 4%–20%.^{8,20,23,26} Crucially, the most common reason for reoperation after the resection of spinal metastases is surgical site infection, which commonly leads to wound breakdown.²⁶ Spinal tumor resections are further complicated by the fact that many patients have had previous radiotherapy or repeated surgeries, which diminish the capacity for wound healing following tumor resection.^{10,13} Patient demographic information and comorbidities such as body mass index (BMI), diabetes mellitus (DM), smoking status, end-stage renal disease, and a recently created frailty index have also been shown to increase the risk of postoperative complications after spine surgery.^{2–4,6,7,12,21}

Given the risk for possible neurological damage as well as exposed or infected hardware, wound breakdown is a particularly serious complication for patients with spine tumors. Therefore, for patients who underwent resection of metastatic spine tumor, we aimed to identify factors associated with wound dehiscence that required reoperation. Demographics, medical comorbidities, and surgical variables were analyzed.

Methods

Study Design and Patients

This study was a retrospective review of patients with metastatic spine disease and was approved by our institutional review board. Included patients were seen at our institution (Johns Hopkins) and treated within the neurosurgery department over a 10-year period (2003–2012). Patients who were included in the study satisfied the following criteria: 1) age 18–100 years at the time of surgery; 2) minimum of 3 months of follow-up after their initial operation; 3) complete electronic medical record; and 4) resection of a metastatic spine lesion with the primary consisting of lung, breast, kidney, bone marrow (multiple myeloma or plasmacytoma), prostate, colorectal, gynecological (uterus or cervix), or skin (melanoma)—as these were more frequent tumor types seen in this cohort ($n \geq 5$ patients).

Study Variables

The primary outcome variable in this study was wound breakdown that required reoperation. To capture possible effects of postoperative radiation treatments or chemotherapy regimens, we included any wound reoperation that occurred during the patient's life. Predictor variables considered in this study included demographic variables (age, BMI, race); medical variables (smoking status, hypertension, coronary artery disease [CAD], thromboembolic events, renal disease, DM, preoperative albumin, hyperlipidemia, chronic obstructive pulmonary disease [COPD]); surgical variables (previous spine irradiation, approach [anterior, posterior, combined], estimated blood loss [EBL], number of spinal levels involved in operation); steroid administration; topical and parenteral antibiotics; vascular endothelial growth factor (VEGF) inhibitor treatment; postoperative radiation therapy (RT); chemotherapy; and Karnofsky Performance Scale (KPS) score.

Statistical Analysis

General demographic data are presented as the mean

$\pm$ SD. Wound reoperations are presented as the percentage of patients with at least one wound reoperation. Frequencies were compared via the chi-square test and means were compared via 1-way ANOVA. For time to wound reoperation failure–event analysis, failure was defined as wound reoperation, and the log-rank test was used to compare curves stratified by tumor type. Additionally, survival with just wound reoperation as the primary end point was analyzed. A multivariate Cox proportional hazards model was used to identify independent factors associated with wound reoperation; factors with a p value < 0.200 on univariate analysis were included in a multivariate model. The confidence interval was set to 95%; results of this model are presented as odds ratios with 95% CIs. Statistical significance was defined as a p value < 0.05 . All analyses were done in Stata/SE 12 (StataCorp LP) or GraphPad Prism 6 (GraphPad Software, Inc.).

Results

Demographic Information

A total of 159 patients were included in the study. The average age for the overall cohort was 59.6 ± 11.7 years, and 85 (53.5%) of the patients were men. Surgery was performed by a neurosurgeon in all cases. General demographic information is presented in Table 1. Of the 159 patients included, 22 underwent wound reoperation. Six of the 22 surgeries were related to wound dehiscence, and the remaining 16 were for wound infections. There were no significant factors in comparisons between the 2 groups requiring wound reoperation.

Factors Associated With Reoperation

Univariate Analysis

Patients with a KPS score ≥ 70 were 67% less likely to have a reoperation due to wound breakdown than were patients with a KPS score < 70 ($p = 0.025$). Additionally, patients with an increasing number of spinal levels involved in the operation were at a higher risk for reoperation, such that for every increase in spinal levels involved, the risk of reoperation increased by 20% ($p = 0.008$). Presence of a venous thromboembolism (VTE) approached significance for an increased risk for reoperation ($p = 0.06$). Other factors with a p value < 0.200 that met inclusion criteria for the multivariate model were smoking status, hypertension, hyperlipidemia, and a posterior surgical approach (Table 2).

Multivariate Analysis

All 7 factors with a p value < 0.200 in univariate analysis were included in the multivariate model. In the multivariate analysis, KPS score, smoking status, hypertension, hyperlipidemia, and posterior surgical approach dropped out of the model—leaving VTEs and increasing number of levels as independent risk factors for a significantly higher rate of wound-related reoperations (Table 3). Patients with a VTE had wound reoperations 7.61 times more often than patients without a VTE (95% CI 1.19–48.5, $p = 0.032$). For each additional spinal level involved in the tumor resection surgery, the risk for wound reoperation increased by 21% (95% CI 1.03–1.43, $p = 0.018$).

TABLE 1. Demographic data in 159 patients who underwent surgery for metastatic spine tumor

Parameter	No Wound Reop, n = 137	Wound Reop, n = 22
Mean age in yrs (range)	59.79 (27–89)	58.45 (42–80)
Male sex, no. (%)	74 (54.0)	11 (50.0)
Race, no. (%)		
Caucasian	97 (70.8)	17 (77.3)
African American	29 (21.2)	5 (22.7)
Other	11 (8.0)	0 (0)
Mean BMI (no. of patients)	27.7 (74)	27.6 (19)
Mean preop albumin, g/L (no. of patients)*	3.87 (112)	3.81 (14)
Topical antibiotics/vancomycin, no. (%)†	130 (100)	20 (100)
Parenteral antibiotics, % (no.)‡	98.6 (69/70)	92.9 (13/14)
EBL in mL§	1648	2240
Duration of symptoms, days¶	95	90
VEGF inhibitor treatment, no. (%)**	19 (14.5)	0 (0)
Primary tumor type, no. (%)		
Breast	25 (18.2)	6 (27.3)
Cervix	2 (1.5)	0 (0)
Colorectal	8 (5.8)	6 (27.3)
Uterus	5 (3.6)	0 (0)
Melanoma	7 (5.1)	0 (0)
Multiple myeloma/plasmacytoma	20 (14.6)	1 (4.5)
Lung	31 (22.6)	4 (18.2)
Prostate	14 (10.2)	4 (18.2)
Kidney	25 (18.2)	1 (4.5)
Spine lesion location, no. (%)		
Cervical	32 (23.4)	2 (9.1)
Thoracic	83 (60.6)	18 (81.8)
Lumbar	34 (24.8)	5 (22.7)
Sacral	2 (1.5)	1 (4.5)
Combined	14 (10.2)	4 (18.2)
Metastases & recurrence, no. (%)		
Extraspinal bony metastases	51 (37.2)	11 (50.0)
Visceral metastases	57 (41.6)	7 (31.8)
Brain metastases	17 (12.4)	3 (13.6)
Recurrence of spine lesion	13 (9.5)	4 (18.2)
Presentation, no. (%)		
Preop motor deficit	74 (54)	14 (63.6)
Preop sensory deficit	65 (47.4)	11 (50.0)
Preop pain	125 (91.2)	18 (81.8)
Preop gait dysfunction	55 (40.1)	12 (54.5)
Preop bladder dysfunction	10 (7.3)	0 (0)
Preop bowel dysfunction	5 (3.6)	1 (4.5)
Comorbidities, no. (%)		
Smoker††	53 (42.4)	10 (50.0)
Hypertension	50 (36.5)	6 (27.3)
CAD	16 (11.7)	4 (18.2)
Cardiovascular disease	9 (6.6)	6 (27.3)

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TABLE 1. Demographic data in 159 patients who underwent surgery for metastatic spine tumor

Parameter	No Wound Reop, n = 137	Wound Reop, n = 22
Comorbidities, no. (%) (continued)		
Thromboembolic disease	8 (5.8)	4 (18.2)
Renal disease	3 (2.2)	1 (4.5)
DM	22 (16.1)	3 (13.6)
Hyperlipidemia	31 (22.6)	2 (9.1)
COPD	13 (9.5)	2 (9.1)
Preop functional status, no. (%)‡‡		
KPS score ≥70	106 (79.7)	15 (68.2)
KPS score ≥40	20 (15.0)	6 (27.3)
KPS score <40	7 (5.3)	1 (4.5)
Surgery		
Mean no. of levels instrumented (range)	5.02 (0–14)	7.05 (0–14)
Approach, no. (%)		
Anterior	39 (28.5)	2 (9.1)
Posterior	87 (63.5)	18 (81.8)
Combined	11 (8.0)	2 (9.1)
Periop complications, no. (%)	64 (46.7)	12 (54.5)
Radiation, no. (%)		
Preop radiation to primary tumor	41 (29.9)	10 (45.5)
Preop radiation to spine	51 (37.2)	12 (54.5)
Postop radiation to spine	69 (50.4)	6 (27.3)
Postop cEBRT	64 (46.7)	6 (27.3)
Postop SRS	5 (3.6)	0 (0)
Steroids, no. (%)		
Preop steroids	80 (58.4)	9 (40.9)
Postop steroids	46 (33.6)	7 (31.8)
Chemotherapy, no. (%)		
Preop chemotherapy	60 (43.8)	12 (54.5)
Postop chemotherapy	66 (48.2)	10 (45.5)
Survival from surgery		
Mean survival in mos (range)§§	13.3 (0.1–73)	9.2 (1.1–41.8)

cEBRT = conventional external-beam RT; SRS = stereotactic radiosurgery.

* Preoperative albumin was known for 14 patients requiring wound reoperations and 112 not requiring wound reoperations.

† Topical antibiotics were known for 130 patients not requiring wound reoperations and 20 requiring wound reoperations.

‡ Status of parenteral antibiotics was known for 70 patients not undergoing wound reoperations and 14 undergoing wound reoperations.

§ The EBL was known for 81 patients not requiring wound reoperations and 10 requiring wound reoperations.

¶ Duration of symptoms was known for 118 patients not requiring wound reoperations and 18 requiring wound reoperations.

** Treatment with VEGF inhibitors was known for 131 patients not requiring wound reoperations and 14 requiring wound reoperations.

†† Smoking status was known for 125 patients not undergoing wound reoperations and 20 undergoing wound reoperations.

‡‡ Baseline KPS score available for 133 of 137 patients not undergoing wound reoperations.

§§ Survival known for 87 patients not undergoing wound reoperations and 9 undergoing wound reoperations.

TABLE 2. Univariate analysis of factors associated with wound reoperation

Parameter	OR (95% CI)	p Value
Increasing age	0.99 (0.96–1.03)	0.870
Age >65 yrs	1.26 (0.50–3.15)	0.612
Male sex	0.85 (0.34–2.09)	0.726
Race		
Caucasian	Reference	
African American	0.71 (0.22–2.26)	0.564
Other	1.0	—
KPS score ≥70	0.33 (0.12–0.86)	0.025*
Comorbidities		
Smoker	2.17 (0.83–5.70)	0.113*
Hypertension	0.47 (0.16–1.37)	0.172*
CAD	1.62 (0.48–5.40)	0.429
VTE	3.47 (0.94–12.71)	0.060*
Renal disease	2.04 (0.20–20.62)	0.543
DM	0.79 (0.21–2.92)	0.732
Hyperlipidemia	0.32 (0.07–1.48)	0.149*
COPD	1.57 (0.40–6.11)	0.509
Previous spine RT	1.58 (0.66–3.78)	0.299
Increasing no. of levels	1.20 (1.04–1.38)	0.008*
Approach		
Anterior	Reference	
Posterior	2.44 (0.67–8.84)	0.172*
Combined	2.30 (0.34–15.56)	0.392

* p < 0.200.

Discussion

Wound reoperations in this cohort of patients with metastatic spine tumor are potentially devastating due to potential risk for hardware exposure, delay in the administration of systemic treatments, increased costs, and prolonged hospitalizations. To stratify patients' risk and improve outcomes, a better understanding of the factors that predict wound reoperation rates is needed. In a multivariate model, we found that thromboembolic events and number of spinal levels involved are both independently associated with a higher risk for wound reoperation.

Patients undergoing spinal tumor resection are at a high risk for VTE due to the length of the operations and limitations in ambulation function perioperatively. Furthermore, patients with cancer in general experience more hypercoagulability than do patients without cancer, and that predisposes the former group to postoperative VTE. Hemostatic abnormalities that lead to a high incidence of VTE include increased fibrin formation and tumor expression of tissue factor and cancer procoagulant, which can both activate the coagulation cascade.⁹ For patients with metastases, the primary cancer site has been shown to be a significant predictor of the development of a VTE. In terms of absolute numbers, VTEs are most prevalent in patients with lung cancer, with the highest rates in lymphoma, ovarian, and pancreatic carcinoma.¹⁷ The incidence of asymptomatic VTE after spine surgery approaches 20%,

TABLE 3. Multivariate analysis of factors associated with wound reoperation

Parameter	OR (95% CI)	p Value
KPS score ≥70	0.36 (0.11–1.13)	0.082
Smoking	2.15 (0.73–6.27)	0.161
Hypertension	0.28 (0.07–1.07)	0.064
VTE	7.61 (1.19–48.5)	0.032*
Hyperlipidemia	0.61 (0.11–3.23)	0.567
Increasing no. of levels	1.21 (1.03–1.43)	0.018*
Approach		
Anterior	Reference	
Posterior	1.38 (0.32–6.00)	0.651
Combined	1.34 (1.14–12.66)	0.796

* p < 0.05.

whereas symptomatic pulmonary embolism and deep venous thrombosis typically occur in < 1% of patients.^{27,31}

Increasing age, preoperative walking disability, congestive heart failure, and staged surgeries increase the risk of a VTE after spine surgery.^{14,28,32} Previous studies have shown that the development of VTE after spine surgery is associated with poor outcomes. In a sample of 8617 patients who underwent thoracic or thoracolumbar spinal fusion, VTE was associated with higher hospital costs, longer hospitalizations, and increased morbidity.¹⁴ In this current study, VTE after spine surgery was associated with an increased risk for wound reoperations by 7.61-fold. One explanation for this increased risk for wound reoperations could be that it is due to the fact that patients who develop a VTE are aggressively treated with anticoagulants, which may delay wound healing and can predispose patients to wound complications, as has been shown in previous studies.^{11,29} Thus, to reduce the incidence of wound reoperations, early VTE prophylaxis, which may include early administration of subcutaneous heparin and compression devices, is crucial.⁵

The greater risk for more extensive spinal tumor resections is well known. For instance, although en bloc spondylectomy is not as frequently applicable in the metastatic spine tumor population, in patients who received 4- or 5-level en bloc spondylectomy for the treatment of malignant spine tumors, Luzzati et al. reported at least one major complication in 7 of the 9 patients (77.8%).¹⁸ Furthermore, in a series of 134 en bloc spinal tumor resections, the number of resected spine segments was a significant predictor of major complications.¹ Although existing literature has established that the number of spinal levels involved is associated with major complications in general, it was unknown whether multilevel resections were also associated with wound-related complications. In this study, we show that the number of spinal levels involved in the operation is significantly associated with higher rates of wound reoperations, such that for each additional level involved, the risk for wound-related reoperations increased 21%.

Because the metastatic tumor involves more spinal levels, the incision will clearly need to be lengthened to complete the resection. Thus, the length of the incision seems to be an independent risk factor for wound reop-

eration. One factor that could contribute to the adverse effect of wound lengthening is adjuvant radiation, which disrupts every phase of wound healing. Previous work has demonstrated that adjuvant RT is associated with a higher rate of deep wound infections, wound dehiscence, and delayed wound healing.^{1,24} During the inflammatory and proliferative stages of wound healing, radiation alters levels of transforming growth factor- β , VEGF, and nitrous oxide, leading to uncontrolled matrix accumulation and impaired strength of wounds.¹⁶ Furthermore, irradiated wounds have a decreased rate of collagen deposition due to the toxic effects on fibroblasts as well as less tolerance of bacterial contamination.²⁰ These combined factors lead to delayed healing and a higher incidence of infections. Given that this cohort may already experience diminished wound healing from previous spine radiation (39.0%) as well as smoking (43.5%) and DM (16.1%), lengthening the wound exaggerates this inherent vulnerability and leads to higher rates of wound breakdown. In patients with spine tumors, wound complications typically require reoperation for irrigation, debridement, and soft-tissue coverage. Because most patients are preparing for or have already started postoperative radiotherapy, interrupting treatment for a wound reoperation could interfere with their ability to fight against their malignancy.²²

In addition to thromboembolic events and multilevel resections, previous studies have also identified preoperative RT, preoperative corticosteroid administration, nutritional deficiencies, previous spine surgeries, DM, length of hospitalization, and posterior approach as some of the other risk factors for wound complications in metastatic spine surgery.^{8,20,22,23} To mitigate risks for wound complications, a recent review by Mesfin et al. recommended involving a plastic surgeon to perform soft-tissue reconstruction, using intrawound vancomycin, and placing percutaneous pedicle screws.²² Since we show that thromboembolic events and increasing number of levels are independently associated with a higher risk for wound reoperations, other ways to prevent wound breakdown after metastatic spine surgery include implementing early multimodal VTE prophylaxis and making only the minimum incision length needed for resection.

Our study has several limitations that warrant discussion. Because our study is retrospective, we have limited ability to make causal conclusions regarding factors associated with wound reoperations. However, this is the largest study to date examining factors associated with wound reoperations after metastatic spine surgery. The heterogeneity of past treatments in our cohort could further limit the conclusions of our study. Finally, additional studies are needed to examine whether wound reoperations are associated with other adverse events such as readmissions, explanted instrumentation, or death.

Conclusions

Patients who undergo metastatic spine tumor resection are at an inherently high risk for wound-related reoperations due to high rates of adjuvant radiation, various medical comorbidities, and potentially long incisions. In this study, we found that thromboembolic events and number

of levels resected are independently associated with a greater risk for wound reoperations. To lower the risk for wound reoperations in this highest-risk subgroup, initiating aggressive VTE prophylaxis and providing meticulous and timely wound care to the longest incisions in particular are crucial interventions.

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Disclosures

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Conception and design: Goodwin, Carl, Abu-Bonsrah, De la Garza Ramos, Sciubba. Acquisition of data: Goodwin, Ahmed, Abu-Bonsrah, De la Garza Ramos, Sankey, Pennington. Analysis and interpretation of data: Goodwin, Carl, Ahmed, Abu-Bonsrah, De la Garza Ramos, Sankey, Bydon, Witham, Wolinsky, Gokaslan, Sacks. Critically revising the article: Goodwin, Carl, Ahmed, Abu-Bonsrah, De la Garza Ramos, Bydon, Witham, Wolinsky, Gokaslan, Sacks, Sciubba. Reviewed submitted version of manuscript: Goodwin, Carl, Abu-Bonsrah, Sankey, Bydon, Witham, Wolinsky, Gokaslan, Sacks, Sciubba. Statistical analysis: Goodwin, Carl, Ahmed, De la Garza Ramos. Administrative/technical/material support: Sciubba. Study supervision: Goodwin, Bydon, Witham, Wolinsky, Gokaslan, Sacks, Sciubba.

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