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Clinical Study

Complications and reoperations after surgery for 647 patients with spine metastatic disease

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Abstract

BACKGROUND CONTEXT: Postoperative morbidity may offset the potential benefits of surgical treatment for spine metastatic disease; hence, risk factors for postoperative complications and reoperations should be taken into considerations during surgical decision-making. In addition, it remains unknown whether complications and reoperations shorten these patients' survival.

PURPOSE: We aimed to describe and identify factors associated with having a complication within 30 days of index surgery as well as factors associated with having a subsequent reoperation. Furthermore, we assessed the effect of 30-day complications and reoperations on the patients' postoperative survival, as well as described neurologic changes after surgery.

STUDY DESIGN: Retrospective cohort study.

PATIENT SAMPLE: We included 647 patients 18 years and older who had surgery for metastatic disease in the spine between January 2002 and January 2014 in one of two affiliated tertiary care centers.

OUTCOME MEASURES: Our primary outcomes were complications within 30 days after surgery and reoperations until final follow-up or death.

METHODS: We used multivariate logistic regression to identify risk factors for 30-day complications and reoperations. We used the Cox regression analysis to assess the effect of postoperative complications and reoperations on survival.

RESULTS: From 647 included patients, 205 (32%) had a complication within 30 days. The following variables were independently associated with 30-day complications: lower albumin levels (odds ratio [OR]: 0.69, 95% confidence interval [CI]=0.49−0.96, p=.021), additional comorbidities (OR=1.42, 95% CI=1.00−2.01, p=.048), pathologic fracture (OR=1.41, 95% CI=0.97−2.05, p=.031), three or more spine levels operated upon (OR=1.64, 95% CI=1.02−2.64, p=.027), and combined surgical approach (OR=2.44, 95% CI=1.06−5.60, p=.036). One hundred and fifteen patients (18%) had at least one reoperation after the initial surgery; prior radiotherapy (OR=1.56,

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Ethical review committee statement: This study was approved by our Institutional Review Board.

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95% CI=1.07−2.29, p=.021) to the spinal tumor was independently associated with reoperation. 30-day complications were associated with worse survival (hazard ratio [HR]=1.40, 95% CI=1.17−1.68, p<.001), and reoperation was not significantly associated with worse survival (HR=0.80, 95% CI=0.09−1.00, p=.054). Neurologic status worsened in 42 (6.7%), remained stable in 445 (71%), and improved in 140 (22%) patients after surgery.

CONCLUSIONS: Three or more spine levels operated upon and prior radiotherapy should prompt consideration of a preoperative plastic surgery consultation regarding soft tissue coverage. Furthermore, if time allows, aggressive nutritional supplementation should be considered for patient with low preoperative serum albumin levels. Surgeons should be aware of the increase in complications in patients presenting with pathologic fracture, undergoing a combined approach, and with any additional preoperative comorbidities. Importantly, 30-day complications were associated with worsened survival.

Keywords: Complication; Metastatic disease; Postoperative survival; Reoperation; Radiotherapy; Chemotherapy.

Introduction

The incidence of bone metastatic disease is increasing as the population ages and patients with cancer survive longer [1]. The spine is the most common site for bony metastases [2]. The goal of operative treatment for spine metastatic disease is to repair neurologic deficits, alleviate pain symptoms, and maintain—or improve—quality of life during the last phase of life [3,4]. Complications or surgical reinterventions may offset the potential benefits of surgical treatment; hence, risk factors for postoperative complications and reoperations should be taken into account during the surgical decision-making.

Numerous studies report on complications after surgery for spine metastatic disease, with rates ranging from 20% to 47% [5−11]; however, many studies are vague in their definition of complications, and study cohort sizes are often relatively small with few outcomes and therefore not able to statistically detect all risk factors [10−12]. In addition, it remains unclear—and difficult—to assess the impact of complications and reoperations on the patients' survival.

With a relatively large cohort, our primary study aim was to describe and identify factors associated with 30-day complications or reoperations. Second, we sought to assess the effect of 30-day complications or reoperations on the patients' postoperative survival. Third, we describe neurologic changes after surgery.

Methods

Study design and participants

This retrospective cohort study was approved by our institutional review board. We included patients 18 years and older who underwent operative treatment for metastatic disease in the cervical, thoracic, or lumbar spine between January 2002 and January 2014 in one of two affiliated tertiary care centers. Patients with metastases to the spine from hematologic malignancies—ie, multiple myeloma and lymphoma—were also included. We excluded patients who presented for revision surgery, or patients who had either stereotactic radiosurgery, vertebroplasty, or kyphoplasty as only procedure. In case a patient underwent multiple surgical procedures for spine metastatic disease, we only included the first procedure to not violate the statistical rule of independence.

We identified 1,330 potentially eligible patients through the ICD-9 code for pathologic fracture (733.13), and additional 796 patients by a computerized word search in operative reports of our oncology database (containing data for 52,476 patients). We manually screened medical records of the 2,126 potentially eligible patients, and 647 patients met eligibility criteria.

Treatment and follow-up

The surgeon decided on the surgical approach by accounting for the patient's estimated survival, neurologic deficits, level of pain, and spinal stability. Patients were followed up at 2 weeks, 6 weeks, and 3 months postoperatively, and subsequently every 3 months until death.

Outcome measures and explanatory variables

Our primary outcome measures were complications within 30 days after surgery and reoperations until final follow-up (or death). We graded complications according to the Clavien-Dindo classification [13]: Grade I complications were notable postoperative deviations that did not require pharmacologic treatment (eg, conservatively treated pneumothorax); Grade II complications were postoperative deviations that required pharmacologic treatment—except for commonly used postoperative medications (eg, analgesics) or blood transfusion; Grade III complications were postoperative deviations that required a surgical, endoscopic, or radiological intervention; Grade IV complications were postoperative life-threatening deviations that warranted intensive care unit admission; and Grade V complications were postoperative deviations resulting in the death of a patient. We dichotomized complications based on the Clavien-Dindo classification into minor complications (Grade I or II) and major complications (Grade III, IV, or V). We defined reoperations as unplanned surgical reinterventions to the spine directly related to the initial surgery.

Survival was the secondary outcome, defined as death from any cause—as we expected that the majority of deaths were related to metastatic disease in these terminal patients. We screened medical records and the Social Security Death Index to determine survival at the final follow-up moment (ie, October 4, 2016) [14].

We extracted the following explanatory factors from patients' medical records: age, gender, body mass index (in kg/m^2), comorbidity status, Eastern Cooperative Oncology Group (ECOG) performance status, cancer type, number of spine metastatic lesions (excluding sacrum), bone metastases outside the spine, visceral metastases (lung or liver), brain metastases, time between neurologic deficits and surgery (none, less than 14 days, or 14 days or more), location of lesion(s), pathologic fracture, preoperative back pain, prior radiotherapy to the spinal tumor, prior systemic therapy for the cancer diagnosis (all nonsurgical and nonradiotherapeutic adjuvants [chemotherapy, immunotherapy, hormone therapy, and metabolic therapy]), neurologic status before surgery and at discharge using the American Spinal Injury Association (ASIA) impairment scale, hospital, type of surgery and approach, number of spine levels operated upon, type of bone graft(s), type of instrumentation, duration of surgery (in minutes), duration of hospital stay (in days), and and estimated blood loss (in milliliters [mL]). Furthermore, we collected the following preoperative laboratory values that were closest to the date of surgery with a maximum of 7 days: hemoglobin levels (g/dL), white blood cell count ($10^3/\mu$L), creatinine levels (mg/dL), calcium levels (mg/dL), platelet count (10^3/mm^3), red blood cell count (10^6/mm^3), albumin levels (g/dL), and lymphocyte count (10^9/L).

We used a modified Charlson comorbidity index to grade comorbidity status; this index classifies 12 comorbidities that are associated with 10-year mortality (eg, diabetes, and congestive heart failure) [15]. We used a previously reported ICD-9-code-based algorithm to calculate the Charlson comorbidity index in our cohort [16]. We classified comorbidities other than the cancer as presence of additional comorbidities. We categorized cancer type into two groups based on the expected survival, as suggested by Katagiri et al. [17]: those with relatively good prognosis cancers (ie, lymphoma, multiple myeloma, breast cancer, kidney cancer, prostate cancer, or thyroid cancer), and those with relatively poor prognosis cancers (ie, lung cancer, colon cancer, rectal cancer, bladder cancer, esophageal cancer, liver cancer, melanoma, gastric cancer, or other cancers). We categorized neurologic status into complete impairment (ASIA Grade A), incomplete impairment (ASIA Grade B, C, or D), and normal neurologic status (ASIA Grade E) [18].

Statistical analysis

Categorical variables are described with frequencies and percentages, and continuous variables with medians and interquartile ranges (IQR) as histograms suggested non-normal distributions.

We used multivariate logistic regression to identify potential risk factors for 30-day complications—retaining variables with a p value below .10 in bivariate logistic regression. We used multivariate Cox regression analysis—retaining variables with a p value below .10 in bivariate cox regression—to identify risk factors for reoperations, and used the date of the first reoperation for the time to event analysis. We used Cox regression analysis to assess the effect of postoperative complications and reoperations on survival.

To retain all cases for multivariate analysis, we used multiple imputation to estimate missing data. With multiple imputation, the statistical software multiplies the existing dataset multiple times (40 in our case) and substitutes missing values based on all other variables accounting for uncertainty. The statistical software estimated missing values for preoperative albumin levels in 88 patients (14%), preoperative lymphocyte count in 89 patients (14%), and preoperative red blood cell count in 12 patients (2%). We considered p values less than .05 to be significant and used STATA 13 (StataCorp LP, College Station, TX, USA) for statistical analyses.

Patient demographics

Among 647 included patients, the median age was 60 years (IQR 52−68), 375 (58%) were men, and the median Charlson comorbidity index score was 6 (IQR 6−8; Table 1). Two hundred twenty-one patients (34%) had prior radiotherapy to the spine tumor, and 367 (57%) had prior systemic therapy. At presentation, 399 (62%) patients had a pathologic fracture, 215 (33%) had visceral metastases, and 72 (11%) had brain metastases. The thoracic spine was the most common tumor location (379 cases [59%]), and patients most commonly presented with lung cancer (115 cases [18%]) and kidney cancer (81 cases [13%]; Table 2). Surgical treatments were corpectomy with stabilization (313 cases [48%]), decompression with stabilization (230 cases [36%]), decompression alone (84 cases [13%]), and stabilization alone (20 cases [3.0%]). The median postoperative survival was 305 days (IQR 95−957, range 3−4,823).

Results

30-day complications and risk factors

Two hundred and five patients (32%) had a 30-day complication, from which 130 (20%) had a minor complication as the most severe outcome, and 75 (12%) had a major complication (Table 3). Systemic infections were encountered in 131 patients (20%), surgical site complications in 83 (13%), thromboembolisms in 49 (6.2%), pulmonary morbidities in 13 (2.0%), cardiac morbidities in 7 (1.0%), gastrointestinal morbidities in 2 (0.5%), and other morbidities in 2 patients (0.5%). Eighteen patients (2.8%) died

Table 1
Baseline characteristics

Variable Preoperative variables	All patients (n=647) Median (IQR)
Age (years)	60 (52−68)
Modified Charlson comorbidity index	6 (6−8)
Estimated blood loss (mL)*	715 (400−1500)
Duration surgery (minutes)*	385 (286−494)
Hemoglobin levels (g/dL)*	11 (10−13)
White blood cell count ($10^3/\mu L$)*	11 (7.5−14)
Creatinine levels (mg/dL)*	0.77 (0.61−0.93)
Calcium levels (mg/dL)*	8.7 (8.0−9.3)
Platelet count ($10^3/mm^3$)*	242 (179−325)
Red blood cell count ($10^6/mm^3$)*	3.8 (3.4−4.2)
Albumin levels (g/dL)*	3.8 (3.4−4.2)
Lymphocyte count (10^9/L)*	0.92 (0.59−1.5)
	Number (%)
Men	375 (58)
Body mass index (in kg/m^2)*	
< 18.5	19 (3.0)
18.5−30	402 (72)
>30	136 (24)
Hospital	
Hospital 1	368 (57)
Hospital 2	279 (43)
ECOG performance status*	
0−2	347 (79)
3−4	93 (21)
Preoperative back pain	548 (85)
Additional comorbidities†	300 (46)
Time between neurologic deficits and surgery for spine metastatic disease	
None	341 (53)
<14 days	179 (28)
≥14 days	127 (20)
Location of lesion treated for	
Cervical	87 (13)
Thoracic	379 (59)
Lumbar	142 (22)
Combined	39 (6.0)
Prognosis of cancer type‡	
Good prognosis	429 (66)
Poor prognosis	218 (34)
Pathologic fracture	399 (62)
Visceral/brain metastases	
Visceral—lung or liver	172 (27)
Brain	29 (4.5)
Visceral and brain	43 (6.6)
Number of spine metastatic lesions (excluding sacrum)	
1	176 (20)
2	98 (15)
≥3	373 (58)
Bone metastases outside the spine	341 (53)
Prior radiotherapy to the spinal tumor	221 (34)
Prior systemic therapy for the cancer diagnosis	367 (57)
Operative variables	
Type of surgery	
Corpectomy with stabilization	313 (48)
Decompression with stabilization	230 (36)
Decompression alone	84 (13)
Stabilization alone	20 (3.0)
Surgical approach	
Posterior	551 (85)
Anterior	68 (11)
Combined	28 (4.0)
Number of spine levels operated upon	
1	403 (62)
2	118 (18)
≥3	126 (19)
Implants§	
Allograft	359 (55)
Autograft	192 (30)
Cage	188 (29)
Cement	103 (16)
Plate	56 (9.0)

IQR, interquartile range; mL, milliliter; g/dL, gram per deciliter; μL, microliter; mg/dL, milligram per deciliter; mm^3, cubic millimeter; kg/m^2, kilogram per square meter; L, liter; ECOG, Eastern Cooperative Oncology Group.

* Estimated blood loss was available in 576 cases (89%), hemoglobin levels in 637 cases (98%), white blood cell count in 636 cases (98%), creatinine levels in 626 cases (96%), calcium levels in 592 cases (91%), platelet count in 635 cases (98%), red blood cell count in 635 cases (98%), albumin levels in 559 (86%), lymphocyte count in 558 cases (86%), body mass index in 557 cases (86%), and ECOG in 440 cases (68%)

† Based on comorbid conditions in Charlson Comorbidity Index.

‡ The good prognosis group includes lymphoma, breast cancer, multiple myeloma, kidney cancer, prostate cancer, and thyroid cancer. The poor prognosis group includes lung cancer, colon cancer, rectal cancer, bladder cancer, esophageal cancer, liver cancer, melanoma, gastric cancer, and other cancers.

§ Implants used are not mutually exclusive.

Table 2
Cancer type (n=647)

	Number (%)
Lung cancer	115 (18)
Kidney cancer	81 (13)
Breast cancer	77 (12)
Multiple myeloma	71 (11)
Prostate cancer	57 (8.8)
Melanoma	27 (4.2)
Colorectal cancer	25 (3.9)
Neuroendocrine cancer	21 (3.2)
Sarcomatous cancer	21 (3.2)
Unknown primary	20 (3.1)
Lymphoma	19 (2.9)
Head and neck cancer	17 (2.6)
Thyroid cancer	16 (2.5)
Hepatocellular cancer	13 (2.0)
Esophageal cancer	12 (1.9)
Endometrial cancer	11 (1.7)
Salivary carcinoma	6 (0.9)
Other*	38 (5.9)

* Other cancer types were bladder cancer five cases (0.8%), adenocarcinoma in five cases (0.8%), germ cell cancer in five cases (0.8%), pancreatic cancer in five (0.8%), ovarian cancer in three cases (0.5%), testicular in three cases (0.5%), penile cancer in three cases (0.5%), cholangiocarcinoma in three cases (0.5%), gastric cancer in two cases (0.3%), adrenal cancer in two cases (0.3%), blue round cell cancer in one case (0.2%), skin cancer in one case (0.2%), and leukemia in one case (0.2%).

Table 3
30-Days complications (n=647)

	Number (%)
At least one complication	205 (32)
Major complication	130 (20)
Minor complication	75 (12)
Number of complications	
1 complication	122 (19)
2 complications	63 (9.6)
3 complications or more	21 (3.2)
Clavien-Dindo classification	
1. No need for further intervention	8 (3.9)
2. Requiring pharmacologic treatment	122 (59)
3. Requiring surgery/endoscopy	50 (24)
4. Life-threatening complication	8 (3.8)
5. Death due to complication	17 (8.3)
Complication types	
Surgical site complication	**83 (13)**
Wound infection	48 (7.4)
Wound dehiscence	25 (3.9)
Hematoma at surgical site	2 (0.3)
Epidural hematoma	2 (0.3)
Fractured vertebra	2 (0.3)
Hardware displacement	1 (0.2)
Extravasation of cement	1 (0.2)
Active wound bleeding	1 (0.2)
Spinal fluid leak	1 (0.2)
Systemic infection	**131 (20)**
Urinary tract infection	58 (9.0)
Pneumonia	56 (8.7)
Sepsis	16 (2.5)
Viral gastrointestinal infection	1 (0.2)
Thromboembolism	**49 (6.2)**
DVT	29 (4.5)
PE	23 (3.6)
Pulmonary morbidity	**13 (2.0)**
Pneumothorax	9 (1.4)
Respiratory failure	3 (0.5)
ARDS	1 (0.2)
Cardial morbidity	**7 (1.0)**
Myocardial infarct	5 (0.8)
Atrial fibrillation	2 (0.3)
Gastrointestinal morbidity	**2 (0.5)**
Ileus	1 (0.2)
Gastric ulcer	1 (0.2)
Other	**2 (0.5)**
Cerebellar infarct	1 (0.2)
Never regained consciousness after surgery	1 (0.2)

PE, pulmonary embolism; DVT, deep vein thrombosis; ARDS, acute respiratory distress syndrome.

within 30 days of operative treatment due to the following complications: 6 (0.9%) from pneumonia, 2 (0.3%) from sepsis, 2 (0.3%) from respiratory distress after pulmonary embolism, and 1 (0.2%) from multiorgan failure. Six (0.9%) patients died with a present postoperative complication that did not seem to contribute to the death, and one patient (0.2%) never regained consciousness after surgery without a clear complication focus.

The following factors were associated with 30-day complications in bivariate analysis: lower albumin levels (odds ratio [OR]=0.56, 95% confidence interval [CI]=0.41−0.76, p<.001), additional comorbidities (OR=1.49, 95% CI=1.07−2.08, p=.018), less than 14 days between neurologic deficits and surgery (OR=1.63, 95% CI=1.11−2.38, p=.012), pathologic fracture (OR=1.47, 95% CI=1.04−2.09, p=.029), anterior surgical approach (OR=0.54, 95% CI=0.29−1.00, p=.048, and three or more spine levels operated upon (OR=1.63, 95% CI=1.07−2.47, p=.022; Appendix A). In multivariate analysis, lower albumin levels (OR=0.69, 95% CI=0.49−0.96, p=.021), additional comorbidities (OR=1.42, 95% CI=1.00−2.01, p=.048), pathologic fracture (OR=1.41, 95% CI=0.97−2.05, p=.031), three or more spine levels operated upon (OR=1.64, 95% CI=1.02−2.64, p=.027), and combined surgical approach (OR=2.44, 95% CI=1.06−5.60, p=.036) were independently associated with 30-day complications (Table 4).

Reoperations and risk factors

One hundred and fifteen patients (18%) had at least one reoperation after the initial surgery (Figure 1). The most common reasons for reoperation were recurrent tumor in 45 (7.0%), wound infection in 42 (6.5%), and wound dehiscence in 28 patients (4.3%; Table 5).

Table 4
Multivariate logistic regression assessing risk factors for 30-day complication after multiple imputation (40 imputations; n=647)

Explanatory variables	Odds ratio (95% CI)	Standard error	p value
Albumin levels (g/dL)*	0.69 (0.49−0.96)	0.12	**.021**
Lymphocyte count (10^9/L)*	0.91 (0.76−1.10)	0.09	.326
Additional comorbidities†	1.42 (1.00−2.01)	0.25	**.048**
Time between neurologic deficits and surgery for spine metastatic disease			
none	*Reference value*		
<14 days	1.28 (0.85−1.92)	0.27	.117
≥14 days	0.82 (0.51−1.33)	0.20	.540
Location of lesion treated for			
Cervical	0.69 (0.39−1.21)	0.20	.149
Thoracic	*Reference value*		
Lumbar	1.24 (0.80−1.93)	0.28	.441
Combined	0.64 (0.29−1.44)	0.26	.321
Pathologic fracture	1.41 (0.97−2.05)	0.27	**.031**
Number of spine levels operated upon			
1	*Reference value*		
2	1.25 (0.78−2.01)	0.30	.244
≥3	1.64 (1.02−2.64)	0.40	**.027**
Surgical approach			
Posterior	*Reference value*		
Anterior	0.63 (0.32−1.21)	0.21	.166
Combined	2.44 (1.06−5.60)	1.03	**.036**

Bold indicates significance (p value less than .05); g/dL, gram per deciliter; L, liter.

* Albumin levels were available in 559 cases (86%) and lymphocyte count in 558 cases (86%).

† Based on comorbid conditions in Charlson comorbidity index.

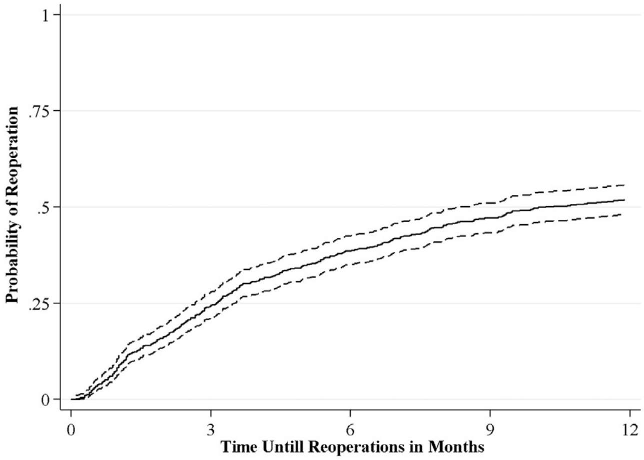

Fig. 1. Reverse Kaplan-Meier plot showing the risk of reoperation over time (this figure only accounts for first reoperations).

Table 5
Reoperations (n=647)

	Number (%)
At least one reoperation	115 (18)
Number of reoperations	
One reoperation	81 (13)
Two reoperations	22 (3.4)
Three or more reoperations	12 (1.9)
Reason for reoperations*	
Surgical site	
Wound infection	42 (6.5)
Wound dehiscence	28 (4.3)
Hematoma	5 (0.8)
Seroma	4 (0.6)
Epidural hematoma	4 (0.6)
Necrotic tissue	1 (0.2)
Epidural abscess	1 (0.2)
Cerebrospinal fluid leak	1 (0.2)
Paraspinal abscess	1 (0.2)
Hardware	
Hardware failure	10 (1.5)
Exposed hardware	4 (0.6)
Hardware displacement	3 (0.5)
Painfull hardware	3 (0.5)
Cement extravasation	1 (0.2)
Tumor	
Recurrent tumor	45 (7.0)
Remaining tumor after initial surgery	6 (0.9)
Other	
Failed anterior fusion at initial surgery	5 (0.8)
Non-union	2 (0.3)
Pseudomeningocele	2 (0.3)
Muscle flap transposition	1 (0.2)
Placement tracheostomy	1 (0.2)
Oropharyngeal fistula	1 (0.2)
Correction of spinal alignment	1 (0.2)
Further posterior stabilization	1 (0.2)
Removal of VAC dressing	1 (0.2)

VAC, Vacuum-assisted closure.
* Not mutually exclusive.

Table 6
Multivariate cox regression analysis assessing risk factors for reoperation after multiple imputation (40 imputations; n=647)

Explanatory variables	Hazard ratio (95% CI)	Standard error	p value
Red blood cell count (10^6/mm^3)*	0.79 (0.57−1.10)	0.13	*.158*
Prior radiotherapy to the spinal tumor	1.56 (1.07−2.29)	0.30	***.021***
Prior systemic therapy for the cancer diagnosis	1.20 (0.81−1.77)	0.24	*.373*

Bold indicates significance (p value less than .05). CI, confidence interval; mm^3, cubic millimeter.
* preoperative red blood cell count was available in 635 cases (98%).

Prior radiotherapy to the spinal tumor was the only factor that was associated with reoperation in bivariate (OR=1.68, 95% CI=1.16−2.43, p=.006; Appendix B) and multivariate analysis (OR=1.56, 95% CI=1.07−2.29, p=.021; Table 6).

Effect of complications and reoperations on patients' survival

A bivariate analysis showed that 30-day complications were associated with worse survival (hazard ratio [HR] =1.40, 95% CI=1.17−1.68, p<.001; Figure 2). Compared with patients who had no complications, both patients with minor complications (HR=1.29, 95% CI=1.04−1.60, p=.019), and patients with major complications had worse survival (HR=1.63, 95% CI=1.25−2.13, p<.001; Figure 3). Reoperation was not significantly associated with survival (HR=0.80, 95% CI=0.64−1.00, p=.054; Figure 4).

Neurologic changes

Before surgery, 7 patients (1.1%) presented with complete neurologic impairment (ASIA Grade A), 299 (47%) with incomplete neurologic impairment (ASIA Grade B, C, or D), and 331 (52%) with normal neurologic status (ASIA Grade E). At discharge, 6 patients (0.9%) had complete impairment (ASIA Grade A), 195 (31%) had incomplete impairment (ASIA Grade B, C, or D), and 435 (68%) had a normal neurologic status (ASIA Grade E). Neurologic status worsened in 42 (6.7%), remained equal in 445 (71%), and improved in 140 (22%) patients after surgery (Table 7).

Discussion

Despite numerous studies on complications and reoperation after surgery for spine metastatic disease [5−11], it remains unclear what risk factors attribute to these outcomes. In the present study, we (1) sought to identify patients more at risk for postoperative complications and reoperations; (2) assess the effect of complications and reoperations on survival; and (3) describe neurologic changes after surgery. Lower preoperative albumin levels,

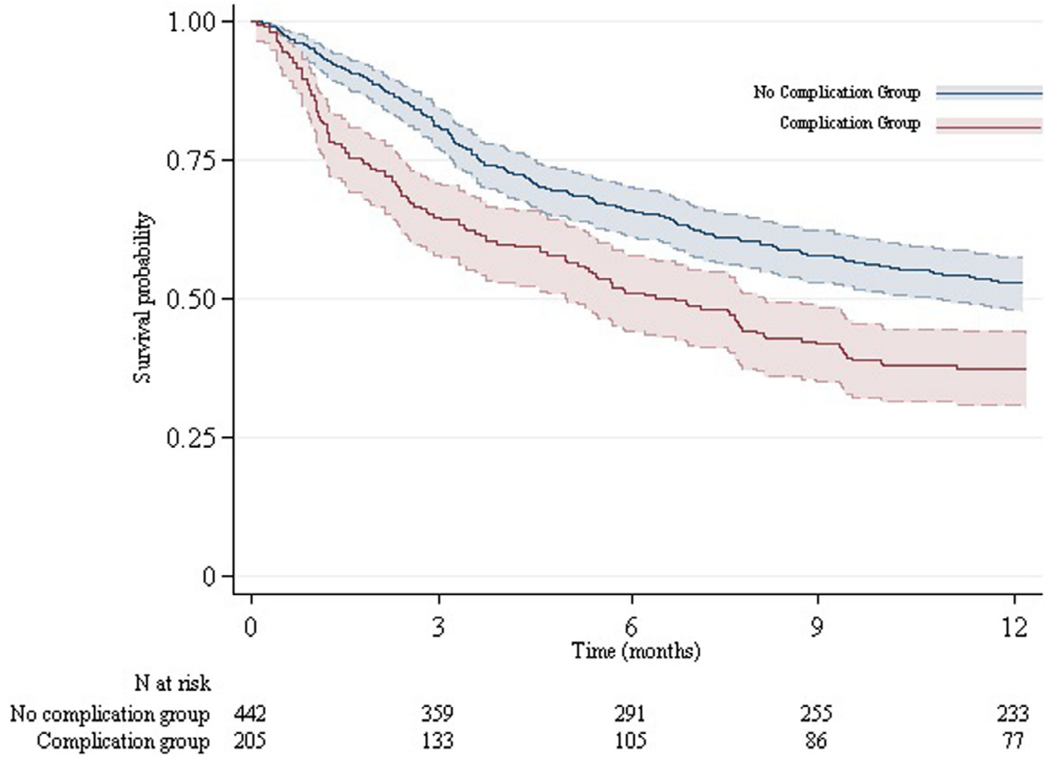

Fig. 2. Kaplan-Meier plot showing the probability of survival with 95% confidence interval for patients with (red line) and without 30-day complications (blue line). Bivariate Cox regression analysis showed a significant difference in survival (HR=1.40; 95% CI=1.17−1.68, p<0.001).

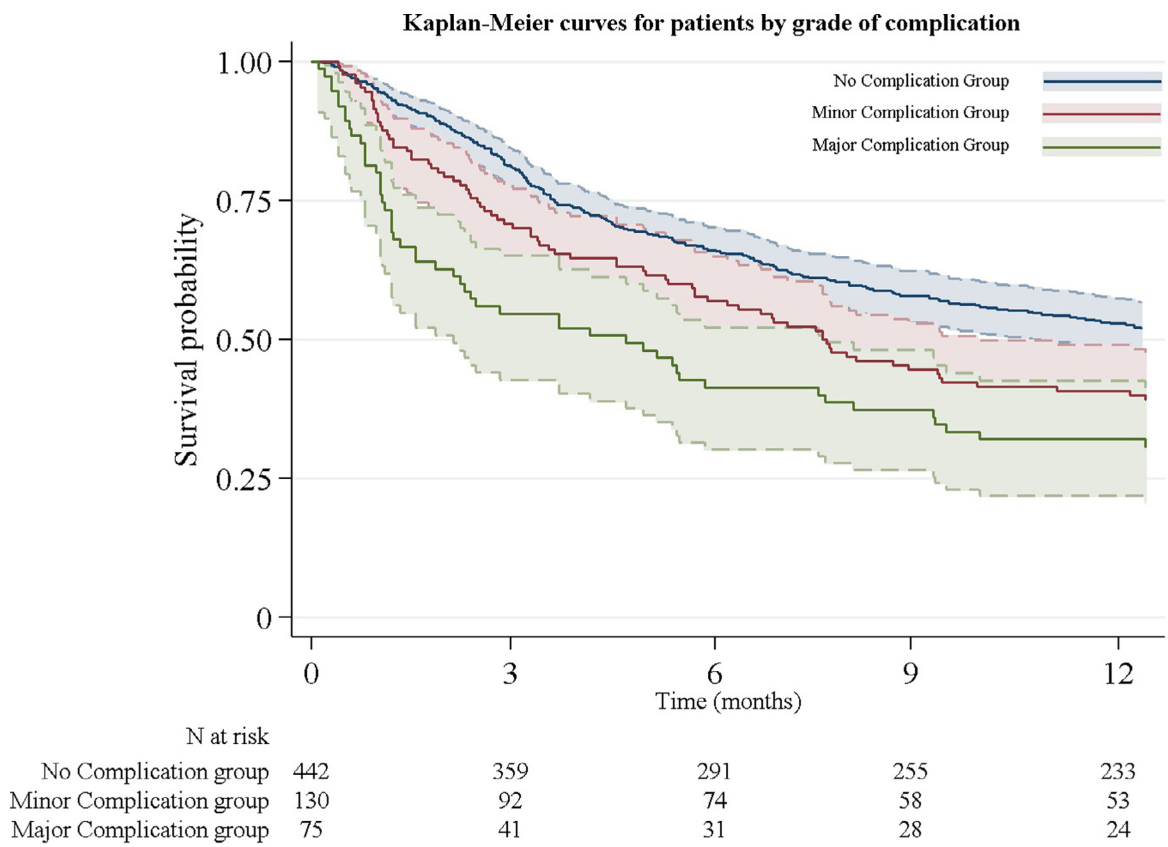

Fig. 3. Kaplan-Meier plot showing the probability of survival with 95% confidence interval for patients without 30-day complications (blue line), patients with minor 30-day complications (red line), and patients with major 30-day complication (green line). Bivariate Cox regression analysis showed a significant difference in survival between no complications and minor complication (HR 1.29; 95% CI=1.04−1.60, p=.019), and between no complications and major complications (HR 1.63; 95% CI=1.25−2.13, p<.001).

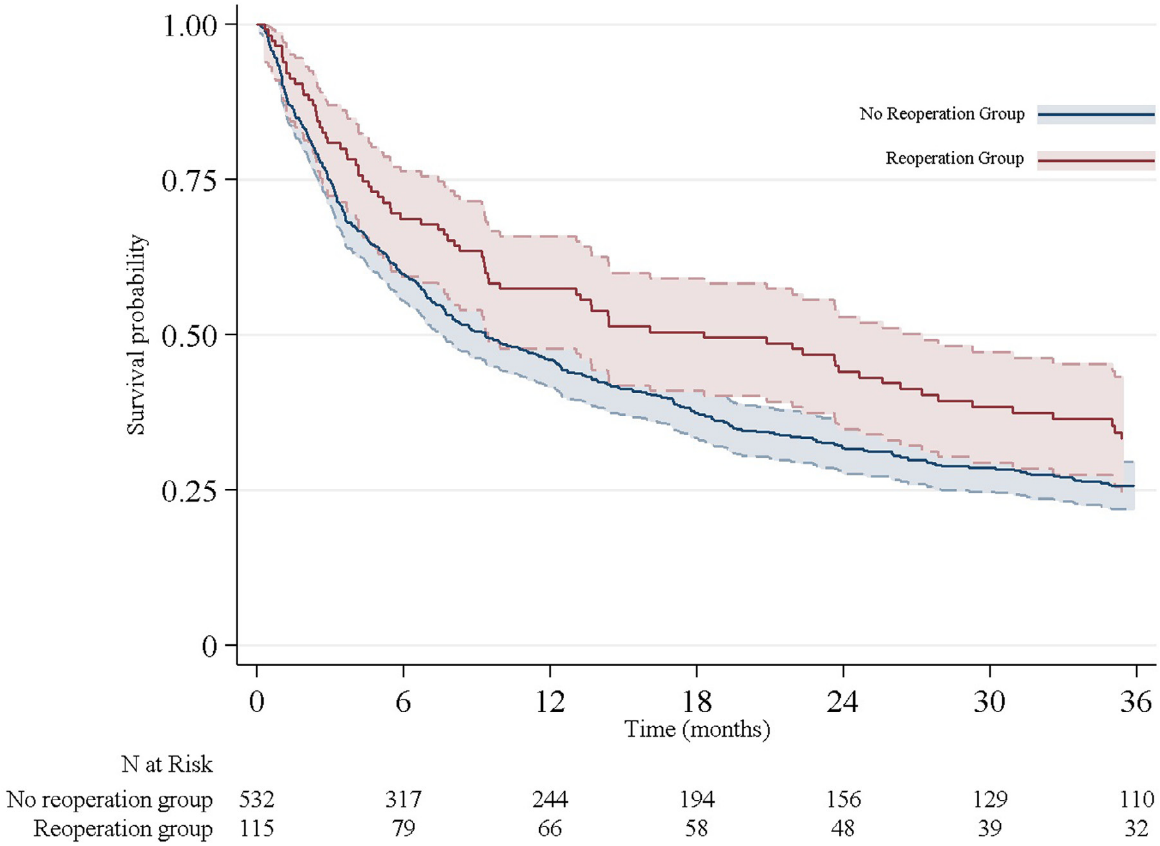

Fig. 4. Kaplan-Meier plot showing the probability of survival with 95% confidence interval for patients without a reoperation (blue line) and patients with reoperation (red line). Bivariate Cox regression analysis showed no significant difference in survival (HR 0.80, 95% CI=0.64−1.00, p=.054)

additional comorbidities, pathologic fracture, more than three spine levels operated on, and combined surgical approach were independent risk factors for 30-day complications; prior radiotherapy was the only risk factor for having a reoperation after the initial surgery. Having a 30-day complication resulted in decreased survival—both for patients with minor and major complications—, and reoperations did not significantly affect postoperative survival rates. The patients' neurologic status remained equal in most patients, and surgery was able to improve the neurologic status in about one of five of all patients.

Table 7
Neurologic status before surgery and at discharge (n=647)

		Discharge status[†]		
		Complete	Incomplete	Normal
Preoperative status*	Complete	2	4	1
	Incomplete	4	151	135
	Normal	0	38	292

Based on ASIA impairment scale: Complete: Grade A, Incomplete: Grade B/C/D, Normal: Grade E.

* Preoperative neurologic status available in 637 cases (98%) and discharge neurologic status in 636 cases (98%).

Our study had several limitations. First, we may have missed complications and reoperations that occurred outside our facilities, which may have led to an underestimation of true complication and reoperation rates. However, only 1.7% of the patients were lost to follow-up within 30 days, and that is why we believe the 30-day time frame to be safe. Second, the retrospective nature of this study may have led to selection bias; choice of surgical treatment was dependent on individual providers and may lack uniformity. Third, there is a large variation in follow-up and survival of patients, inherent to a group of patients with advanced cancer. This may lead to difficulties applying the conclusions of our study to individual patients. We tried to offset this for reoperations by using a Cox regression analysis, which accounts for this variation. Fourth, certain variables in our study suffer from interobserver variability (eg, neurologic status, and performance status). We tried to account for this by categorizing these variables using cutoff point representing meaningful qualitative differences. Fifth, the use of diagnosis codes to identify patients and for constructing the modified Charlson comorbidity index may have led to inaccuracies due to miscoding in clinical practice. Finally, our study population consists of many different cancer types resulting in heterogeneity. However, in bivariate analysis, none of the five most prevalent cancer types was associated with 30-day complications or reoperations (Appendix C).

Despite these limitations, we believe our study represents a large cohort of patients with spine metastatic disease adequately powered to identify risk factors for complications and reoperations. A study by Arrigo et al. [12] (n=200) found similar complication rates in patients who underwent surgery for spine metastatic disease (34% vs 32% in our study). The Charlson comorbidity index was the only independent risk factor for overall complications, although they may have been underpowered to detect other risk factors. Importantly, and contrary to our study, they found a high variation in complication rates per cancer type. A recent study by Schoenfeld et al. [19] assessed the predictive accuracy of the New England Spinal Metastasis Score (NESMS) for 30-day morbidity. The NESMS is a prognostic tool that aims to prognosticate 1-year survival after surgery for spine metastatic disease and is based on ambulatory status, preoperative albumin levels, and the modified Bauer score. They concluded that the NESMS was a significant predictor for 30-day mortality, major systemic complications, and death after major complications. A novel and important finding of their study was that factors associated with worse survival were also predictive for more complications, which is in line with our study. Although our study focused on all 30-day complications, we also found preoperative albumin levels to be associated with complications.

The overall 30-day complication rate (32%) and major complication rate (12%) encountered in our hospitals are comparable with overall (ranging from 20% to 47%) [5−11] and major complication rates in the literature (13.8% to 27%) [6,8,10,11]. An explanation for our relatively low major complication rate may be due to different definitions of major complication. Unfortunately, most articles have unclear definitions for major complications, making it difficult to compare. Another explanation may be that the two high-volume tertiary centers have lower major complication rates due to more experience with this type of complicated surgery and care.

Lower albumin levels have long been associated with increased complication rates after oncologic surgery as well as after other types of orthopedic surgery [20−27]. Although serum albumin is usually seen as a marker for nutritional status, some advocate that hypoalbuminemia is due to systemic inflammation—and not solely by a lowered nutritional status; the increased demand of protein for acute-phase proteins in systemic inflammation results in a fall in serum albumin levels [28−30]. Similarly, the association of additional comorbidities with 30-day complications is likely a reflection of an overall diminished health status. Other studies have found an association between comorbidities and readmission after surgery for spinal tumors [31,32]. Although surgeons will already be wary of patients' comorbidities, it is useful to reaffirm their important role in surgical decision-making.

Pathologic fracture was identified as an independent risk factor for 30-day complications. Although similar studies did not find pathologic fracture to be associated with complications there is recognition that it negatively impacts survival. Bauer and Wedin [33] found pathologic fracture to be an independent marker for worse 1-year survival. Behnk et al. [34] reported that surgical site infection, acute myocard infarction, pneumonia, and pulmonary embolism were independently associated with increased same-admission mortality in patients with pathological fractures. Combined with our findings this suggests the gravity of presenting with pathological fracture by being both associated with complications and with subsequent worsened survival.

Three or more spine levels operated upon was another independent risk factor for 30-day complications. Although similar oncologic studies did not specifically look for or find this association, multilevel surgery has been associated with increased complications after degenerative and traumatic spinal surgery [35−37]. Among the 126 patients with three or more levels operated upon, most common postoperative complications were wound infection (10/126, 7.9%) and wound dehiscence (5/126, 4.0%); we therefore believe that larger incisions (required for multilevel surgery) are most responsible for increased complication rates. Extra attention to wound closure and postoperative wound care is warranted in these patients to prevent (wound) complications [38].

Combined approach was not used frequently in our study (4%) but was independently associated with 30-days complications. Similarly, in an early study on combined approach, Sundaresan et al. [39] reported a high incidence of surgical complications (48%). Furthermore, both Street et al. [8] and Shehadi et al. [11] found higher estimated blood losses compared with other approaches; an association we did not find in our study (p=.095). Because the combined approach is used when a singular approach does not suffice, surgeons need to be aware of the increased risk of complications.

The reoperation rate in our cohort (18%) is comparable with rates in the literature (10.3%−47.5%) [5,7−9]. Although most (72/115, 63%) initial reoperations occurred within 2 months, some reoperations occurred after 2 years (12/115, 10%); this emphasizes the importance of prognosticating life-expectancy in surgical decision-making, because the choice for a surgical treatment is largely based on a patient's life expectancy. Survival algorithms could aid surgeons in this difficult—yet important—task [40].

Prior radiotherapy was the only variable associated with more reoperations. One of the side effects of radiotherapy is delayed wound healing [41]. Fifty-five percent of the reasons for reoperation in the irradiated group were due to wound infections, wound dehiscence, epidural hematoma, or a combination of those compared with 38% in the group without radiotherapy (p=.089; Fisher exact test). Ghogawala et al. [42] found a threefold major wound complication rate in patients who had prior radiotherapy compared with patients without prior radiotherapy. Similarly, Sundaresan et al. [9] found that all wound complications requiring reoperation were in the prior irradiated group. Contradictory, Street et al. [8] did not find an association between prior radiotherapy and wound failure, theorizing this is because none of their patients was operated on within 7 days of radiotherapy. A systemic review by Itshayek et al. [43] aimed to find an optimal interval between radiotherapy and surgery to avoid wound complications, and recommended to wait 1 week after radiotherapy; however, the ideal time will likely vary based on patient characteristics.

Patients with a 30-day complication had significantly worse survival than patients without a complication—28% of the patients with a 30-day complication die within 1 month, 6.2% in the group without complications (Figure 1). Similarly, Jansson et al. [7] found that systemic complications after surgery for spine metastatic disease often led to premature postoperative death. Other articles studied independent predictors of survival, but did not include postoperative complications as possible predictor [6,44]. Several nonorthopedic oncologic surgery studies did find an association between postoperative complications and worse survival [45,46]. Our results indicate that postoperative complications shorten survival; therefore, it is important to carefully select patients for surgery that are less prone to develop postoperative complications.

Our number of patients with a decline in neurologic status after surgery (6.7%) is within the range of previous studies (0%−6.9%) [7−11]; however, the literature on the influence of neurologic status on survival is conflicting. Finkelstein et al. [6] found preoperative neurologic deficit to be an independent risk factor for decreased survival, whereas Jansson et al. [7] did not. Although we did not find a statistically significant effect for neurologic improvement (p=.146) or neurologic worsening (p=.380) on survival, the number of patients in our studies who either retained (71%) or improved neurologic status (22%) proves that decompressive surgery for spine metastatic disease reaches its goals in the vast majority of patients.

Conclusions

Surgery for spine metastatic disease on three or more spine levels and prior radiotherapy should prompt consideration of a preoperative consultation with plastic surgery about soft tissue coverage. Postponing surgery for 1 week after radiotherapy could decrease the risk for wound complications. Furthermore, if time allows, aggressive nutritional supplementation should be considered for patient with low preoperative albumin levels. Although a combined approach may be necessary, surgeons need to acknowledge the possible risk associated with this approach and contemplate its necessity. Additionally, surgeons should be aware of the increase in complications in patients presenting with pathologic fracture, and with any additional preoperative comorbidities. Importantly, our study shows that in patients with spine metastatic disease, 30-day complications were associated with worsened survival.

Appendix A. Bivariate logistic regression assessing risk factors for 30-day complications

Explanatory variables	Odds ratio (95% CI)	Standard error	p value
Preoperative variables			
Age (years)	1.01 (0.99−1.02)	0.01	.145
Modified Charlson comorbidity index	1.06 (0.96−1.16)	0.05	.280
Hemoglobin levels (g/dL)*	0.94 (0.85−1.04)	0.05	.235
White blood cell count ($10^3/\mu L$)*	1.01 (0.98−1.04)	0.01	.492
Creatinine levels (mg/dL)*	1.02 (0.76−1.36)	0.15	.905
Calcium levels (mg/dL)*	0.97 (0.82−1.15)	0.08	.708
Platelet count ($10^3/mm^3$)*	1.00 (1.00−1.00)	0.00	.813
Red blood cell count ($10^6/mm^3$)*	0.85 (0.64−1.13)	0.12	.257
Albumin levels (g/dL)*	0.56 (0.41−0.76)	0.09	**<.001**
Lymphocyte count ($10^9/L$)*	0.82 (0.67−1.00)	0.08	.051
Men	0.89 (0.64−1.25)	0.15	.513
Body mass index (in kg/m^2)*			
< 18.5	1.54 (0.60−3.92)	0.73	.366
18.5−30	*Reference value*		
>30	0.91 (0.60−1.39)	0.20	.674
ECOG performance status*			
0−2	*Reference value*		
3−4	1.24 (0.76−2.02)	0.31	.381
Preoperative back pain	0.82 (0.52−1.29)	0.19	.394
Additional comorbidities†	1.49 (1.07−2.08)	0.25	**.018**
Time between neurologic deficits and surgery for spine metastatic disease			
none	*Reference value*		
<14 days	1.63 (1.11−2.38)	0.32	**.012**
≥14 days	0.98 (0.62−1.54)	0.23	.933
Location of lesion treated for			
Cervical	0.59 (0.34−1.01)	0.16	.053
Thoracic	*Reference value*		
Lumbar	0.94 (0.62−1.42)	0.20	.766
Combined	0.77 (0.37−1.60)	0.29	.483
Prognosis of cancer type‡			
Good prognosis	*Reference value*		
Poor prognosis	1.03 (0.73−1.46)	0.18	.868
Pathologic fracture	1.47 (1.04−2.09)	0.26	**.029**
Visceral/brain metastases			
Visceral—lung or liver	1.10 (0.75−1.61)	0.21	.629
Brain	1.39 (0.64−3.03)	0.55	.406
Visceral and brain	1.22 (0.63−2.36)	0.41	.557
Number of spine metastatic lesions (excluding sacrum)			
1	*Reference value*		
2	0.84 (0.48−1.44)	0.23	.522
≥3	1.08 (0.74−1.59)	0.21	0.687
Bone metastases outside the spine	1.06 (0.76−1.47)	0.18	.741
Prior radiotherapy to the spinal tumor	1.17 (0.83−1.65)	0.21	.375
Prior systemic therapy for the cancer diagnosis	0.99 (0.71−1.39)	0.17	.962
Operative variables			
Type of surgery			
Corpectomy with stabilization	*Reference value*		

(Continued)

Explanatory variables	Odds ratio (95% CI)	Standard error	p value
Decompression with stabilization	1.04 (0.72−1.50)	0.19	.831
Decompression alone	0.98 (0.58−1.66)	0.26	.950
Stabilization alone	1.18 (0.46−3.05)	0.57	.731
Surgical approach			
Posterior	*Reference value*		
Anterior	0.54 (0.29−1.00)	0.17	**.048**
Combined	1.56 (0.72−3.36)	0.61	.258
Number of spine levels operated upon			
1	*Reference value*		
2	1.22 (0.79−1.90)	0.27	.373
≥3	1.63 (1.07−2.47)	0.35	**.022**

Bold indicates significance (p value less than 0.05). CI, confidence interval; g/dL, gram per deciliter; μL, microliter; mg/dL, milligram per deciliter; mm^3, cubic millimeter; kg/m^2, kilogram per square meter; L, liter; ECOG, Eastern Cooperative Oncology Group.

* Hemoglobin levels was available in 441 cases (98%) of the no complication group and in 196 cases (99%) of the complication group, white blood cell count in 441 cases (98%) of the no complication group and in 195 cases (99%) of the complication group, creatinine levels in 433 cases (96%) of the no complication group and in 193 cases (98%) of the complication group, calcium levels in 409 cases (91%) of the no complication group and in 183 cases (93%) of the complication group, platelet count in 440 cases (98%) of the no complication group and in 195 cases (99%) of the complication group, red blood cell count in 440 cases (98%) of the no complication group and in 195 cases (99%) of the complication group, albumin levels in 384 cases (85%) of the no complication group and in 175 cases (89%) of the complication group, lymphocyte count in 385 cases (86%) of the no complication group and in 173 cases (88%) of the complication group, body mass index in 386 cases (86%) of the no complication group and in 171 cases (87%) of the complication group, and ECOG in cases 308 (69%) of the no complication group and in 132 cases (66%) of the complication group.

† Based on comorbid conditions in Charlson comorbidity index.

‡ The good prognosis group includes lymphoma, breast cancer, multiple myeloma, kidney cancer, prostate cancer, and thyroid cancer. The poor prognosis group includes lung cancer, colon cancer, rectal cancer, bladder cancer, esophageal cancer, liver cancer, melanoma, gastric cancer, and other cancers.

Appendix B. Bivariate cox regression analysis assessing risk factors for reoperation (n=647)

Explanatory variables	Hazard ratio (95% CI)	Standard error	p value
Preoperative variables			
Age (years)	0.99 (0.98−1.01)	0.01	*.288*
Modified Charlson comorbidity index	1.02 (0.91−1.13)	0.06	*.781*
Hemoglobin levels (g/dL)*	0.93 (0.83−1.04)	0.05	*.194*
White blood cell count ($10^3/\mu$L)*	0.98 (0.94−1.02)	0.02	*.273*
Creatinine levels (mg/dL)*	1.01 (0.74−1.38)	0.16	*.936*
Calcium levels (mg/dL)*	1.04 (0.85−1.26)	0.10	*.717*
Platelet count ($10^3/mm^3$)*	1.00 (1.00−1.00)	0.00	*0.319*
Red blood cell count ($10^6/mm^3$)*	0.75 (0.54−1.02)	0.12	*.074*
Albumin levels (g/dL)*	1.19 (0.83−1.73)	0.22	*.343*
Lymphocyte count (10^9/L)*	0.98 (0.82−1.18)	0.09	*.855*

(Continued)

Explanatory variables	Hazard ratio (95% CI)	Standard error	p value
Men	1.03 (0.71−1.49)	0.19	*.881*
Body mass index (in kg/m^2)*			
<18.5	1.01 (0.32−3.21)	*0.6*	.986
18.5−30	*Reference value*		
>30	1.26 (0.82−1.92)	0.27	*.288*
ECOG performance status*			
0−2	*Reference value*		
3−4	1.09 (0.60−2.00)	0.29	*.774*
Preoperative back pain	0.86 (0.53−1.39)	0.21	*.543*
Additional comorbidities†	0.94 (0.65−1.36)	0.18	*.744*
Time between neurologic deficits and surgery for spine metastatic disease			
none	*Reference value*		
<14 days	1.11 (0.71−1.74)	0.25	*.635*
≥14 days	1.41(0.90−2.21)	0.32	*.138*
Location of lesion treated for			
Cervical	0.88 (0.50−1.57)	0.26	*.675*
Thoracic	*Reference value*		
Lumbar	0.98 (0.63−1.54)	0.23	*.940*
Combined	1.32 (0.63−2.76)	0.50	*.455*
Prognosis of cancer type‡			
Good prognosis	*Reference value*		
Poor prognosis	0.95 (0.63−1.44)	0.20	*.817*
Pathologic fracture	1.17 (0.80−1.71)	0.23	*.419*
Visceral/brain metastases			
Visceral—lung or liver	1.35 (0.89−2.05)	0.29	*.156*
Brain	1.58 (0.69−3.65)	0.68	*.281*
Visceral and brain	1.30 (0.59−2.83)	0.52	*.512*
Number of spine metastatic lesions (excluding sacrum)			
1	*Reference value*		
2	0.94 (0.53−1.68)	0.28	*.838*
≥3	1.01 (0.67−1.54)	0.22	*.949*
Bone metastases outside the spine	1.07 (0.74−1.55)	0.2	*.701*
Prior radiotherapy to the spinal tumor	1.68 (1.16−2.43)	0.32	***.006***
Prior systemic therapy for the cancer diagnosis	1.39 (0.96−2.03)	0.27	*.083*
Operative variables			
Type of surgery			
Corpectomy with stabilization	*Reference value*		
Decompression with stabilization	1.13 (0.76−1.68)	0.23	*.560*
Decompression alone	1.15 (0.65−2.04)	0.34	*.631*
Stabilization alone	0.56 (0.14−2.30)	0.40	*.422*
Surgical approach			
Posterior	*Reference value*		
Anterior	0.80 (0.43−1.50)	0.26	*.488*
Combined	1.30 (0.60−2.81)	0.51	*.501*
Number of spine levels operated upon			
1	*Reference value*		
2	1.33 (0.84−2.10)	0.31	*.225*
≥3	1.09 (0.66−1.79)	0.28	*.735*

Bold indicates significance (p value less than 0.05). CI, confidence interval; g/dL, gram per deciliter; μL, microliter; mg/dL, milligram per deciliter; mm^3, cubic millimeter; kg/m^2, kilogram per square meter; L, liter; ECOG, Eastern Cooperative Oncology Group.

* Hemoglobin levels were available in 637 cases (98%), white blood cell count in 636 cases (98%), creatinine levels in 626 cases (96%),

calcium levels in 592 cases (91%), platelet count in 635 cases (98%), red blood cell count in 635 cases (98%), albumin levels in 559 (86%), lymphocyte count in 558 cases (86%), body mass index in 557 cases (86%), and ECOG in 440 cases (68%).

† Based on comorbid conditions in Charlson Comorbidity Index.

‡ The good prognosis group includes lymphoma, breast cancer, multiple myeloma, kidney cancer, prostate cancer, and thyroid cancer. The poor prognosis group includes lung cancer, colon cancer, rectal cancer, bladder cancer, esophageal cancer, liver cancer, melanoma, gastric cancer, and other cancers.

Appendix C. Complications and reoperations for the five most prevalent cancer types

Cancer type	Number	Complications number (%)	p value	Reoperations number (%)	p value
Lung	115	32 (27.8)	*Reference value*	15 (13.0)	*Reference value*
Kidney	81	24 (29.6)	*0.783*	15 (18.5)	*.279*
Breast	77	19 (24.7)	*0.628*	16 (20.8)	*.157*
Myeloma	71	28 (39.4)	*0.101*	11 (15.5)	*.640*
Prostate	57	17 (29.8)	*0.785*	10 (17.5)	*.432*

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