Prognostic factors of surgical complications and overall survival of patients with metastatic spinal tumor

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Abstract

OBJECTIVE: Oncologic treatments increase the incidence of spinal metastases. Surgical treatment of spinal metastases results in a high complication rate, which must set against the expected benefits. The aim of this article was to study the effect of several prognostic factors on surgical complications and survival time using an extended database of patients with spinal metastases.

METHODS: This retrospective study comprised 337 patients with spinal metastases who were surgically treated between 2008 and 2015. Demographic and clinical features, oncologic histories, surgical interventions, and end results were collected. Descriptive statistical methods were used to analyze the cohort of patients. Kaplan-Meier formula and log-rank test were used to examine overall survival times.

RESULTS: Median overall survival time was 222 days (range, 175-274 days). Age, preoperative motor disorders, preoperative Frankel grade categories, Karnofsky performance scale, type of primary tumor, and presence of internal metastasis had a significant negative effect on overall survival. Complications such as bleeding or need for intensive care could be predicted preoperatively based on preoperative performance status, type of primary tumor, affected vertebral levels, and type of surgical interventions.

CONCLUSION: Spinal metastatic disease is a challenging surgical problem. If the exact prognostic factors are known preoperatively, surgical outcome and overall survival can be predicted more precisely. Our results could provide a basis for a future multicenter prospective study to determine the best treatment protocol for patients with spinal metastases.

Introduction

Longer life expectancy of patients with cancer and successful oncologic treatments have resulted in an increased incidence of spinal metastases [1-4]. Spinal metastases can be expected in 70% of patients with a cancer diagnosis, and neurologic symptoms related to spinal cord compression may develop in 10% [5]. The main goals of surgical treatment should be to improve mechanical stability, decompress neural structures, relieve neurological symptoms, and improve quality of life; however, most of the underlying cancer types and stages carry dismal prognoses [2, 6]. Surgical treatment of spinal metastases results in a complication rate of 20-30% which must be considered against the expected benefits [2, 7]. If the exact risk and complication factors are known preoperatively, surgical outcome can be predicted more precisely. Scoring systems such as Tokuhashi [8-10], Tomita [11], Bauer [12, 13] and Linden [14] systems are widely used in clinical practice to offer the best surgical strategy based on the patient's prognostic factors. Using an extended database of patients who underwent surgical interventions because of spinal metastases, the aim of this article was to study the effect of the risk factors of 4 prognosis scoring systems on the survival time of patients with metastatic spinal tumors. Furthermore, we aimed to investigate the prediction ability of scoring systems for prognosis and to possibly evaluate new risk factors to extend the prediction ability of various prognostic systems in the future. Correlating risk factors with the main surgical complications were also examined.

Methods

Patient database

We created a retrospective database of 337 patients who underwent spinal surgery for spinal metastases at the National Institute of Clinical Neuroscience, Department of Neurosurgery, Semmelweis University, Budapest, Hungary, between 2008 and 2015. Surgical intervention was the only criterion of admission for the study. Of the 382 interventions identified in the inquiry, 337 patient histories were compiled; 38 patients had records with multiple surgical interventions (31 patients with 2 interventions and 7 patients with 3 interventions; none of the patients had >3 interventions).

Most of the examined risk factors are presented in prognosis prediction systems (revised Tokuhashi, Tomita, modified Bauer, and van der Linden scores) **(Tables 1-4.)**. Several other factors from the patients' history were also collected. Demographic and baseline clinical variables of interest included sex and age at time of surgery. Baseline functional status was measured with the Karnofsky performance scale (KPS). Further data recorded about the status of the patient included main clinical symptoms, presence of motor or sensory deficit, Frankel scores, extraspinal bony metastases, and metastases in the internal organs. Regarding the surgical intervention, we have extracted the following factors: affected vertebral levels, steps of intervention, postoperative condition, and period of hospital stay. Each patient history consisted of data about the metastasis (categorized by primary site of origin), histologic diagnoses, and other comorbidities. Finally, 2 main types of complications were examined. A bleeding complication was defined as an intraoperative or postoperative hemorrhage that necessitated blood transfusion. Other complications were defined as the need for postoperative intensive care related to difficulties because of the surgery in at least 1 of the 7 main organ systems (cardiovascular, respiratory, central nervous system, gastrointestinal tract, renal, hematologic, or metabolic).

Statistical analysis

Descriptive statistics were used to describe the cohort of patients. The selected factors and their clustering were not modified after the first statistical evaluation to avoid distortion of retrospective results. Fisher exact tests were employed to identify significant associations between covariants of interest and categorical outcomes (complications). Kaplan-Meier formula and log-rank test were used to examine overall survival (OS). Results with P values

<0.05 were considered statistically significant in the final analysis. In the post hoc analysis, we applied statistical corrections (Bonferroni correction) where combinatorial selection was used. R software (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.[32]

Results

Survival data and rate of complications

We identified 337 patients, 199 (59.1%) men and 138 (40.9%) women, with a mean age of 63 ± 12 years (range, 15–88 years). OS was calculated by the Kaplan-Meier formula **(Table 5)**. Median OS (amount of time when 50% of the patients have died) was 222 days; the 95% confidence interval ranged from 175 to 274 days. Because some patients were alive at the time of data taking, we provide the restricted mean (upper limit = 2739 days) for the OS time as 660.3 days (with SE 56.7 days). The Kaplan-Meier curve with censored data and with pointwise 95% confidence intervals is presented in **Figure 1.** Of the 337 patients, 135 (40.06%) had some complication during or right after the surgery (11 patients needed intensive care only, 102 had bleeding only, and 22 had both bleeding and need for postoperative intensive care). Some patients with >1 intervention may have had both complications during their history without having any intervention with 2 complications.

Predictors of OS

Evaluating the predictors of OS, we calculated the OS value with the Kaplan-Meier formula for each category, and we examined several risk factors. The significance of the difference between subgroups was tested with the log-rank test.

The subpopulations with specific values of the following factors differ significantly from each other in OS according to the log-rank test:

Age. (subgroups: <40, 40-50, 50-60, 60-70, >70). The subgroups of age were significantly different from each other (P=0.021). The subgroup <40 (P=0.028) was associated with longer survival time **(Figure 2)**.

Preoperative motor deficits (subgroups: paresis, paralysis, none; P=0.014). The paralysis subgroup (P=0.0068) was associated with a shorter survival **(Figure 3.)**.

Frankel grade (subgroups: A, B, C, D, E; P=0.0223). Frankel A and B categories (P=0.00293) were associated with shorter survival **(Figure 4)**.

KPS (subgroups: 10%-40%, 50%-70%, 80%-100%; P=0.0001). For KPS, we found 2 subgroups that are different from the rest of the population. The poor condition group (10%-

40%; P=0.00039) had a shorter survival, and the good condition group (80%-100%; P=0.0004) had a longer survival **(Figure 5)**.

The type of the primary tumor significantly affected patient survival (P<1e^{-6}). From the tested tumor categories, the most common primary tumor types in the population were lung malignancies (24.9%), multiple myeloma (11.3%), breast cancers (8.9%), renal cell carcinomas (7.7%), and prostate malignancies (6.5%) **(Table 6)**. From the solid types, lung (P<1e^{-6}) **(Figure 6a)** and the cervical P=5e^{-6}) carcinomas **(Figure 6b)** had a significantly poorer prognosis compared with the other tumors. Among the hematologic malignancies, multiple myeloma had a much better OS than the other types (p<1e^{-6}) **(Figure 6c).**

Internal metastasis (subgroups: no metastasis, surgically removable, surgically unremovable; P=0.0262). The surgically unremovable metastasis category has shorter survival than the other subgroups (P=0.0074) **(Figure 7)**.

Number of metastasis in the vertebral body (subgroups: 1-2, 3-10) significantly affected patient survival (P=0.0139). Dissemination of the disease was associated with a worse prognosis **(Figure 8).**

For the following factors, OS was not significantly different in the subgroups with given values of the factors:

1. *sex* (subgroups: female, male)

2. *operation type* (subgroups: palliative, excisional)

3. *preoperative sensory deficits* (subgroups: no deficit, hypoesthesia, hyperesthesia, paresthesia, multiple sensory deficits)

4. *symptoms at clinical presentation* (subgroups: sensorial deficits, vegetative disorder, motor deficits, pain, other symptoms)

5. *affected vertebral levels* (subgroups: sacral, lumbal, thoracic, cervical, multiplex),

6. *extraspinal bone metastasis* (subgroups by number of metastases: 0, 1, 2, more)

Predictors of complications

Correlations between preoperative factors and complications (bleeding and need for postoperative intensive care) were also tested. **Table 7** lists all factors that have at least 1 subcategory in which the odds ratio of a complication is either significantly high or significantly low. The associations between the complications and factor values were

identified with a 3-step procedure. First, we calculated the Fischer exact test to find significant co-occurrence of factors and complication types (bleeding or need for postoperative intensive care). Second, with a post hoc analysis, we selected the subcategory of the factor type and the complication type that were significantly associated. Finally, associations with high P values were tested with Bonferroni correction.

Discussion

Modern oncologic treatment and developing surgical techniques extend the life expectancy of patients with cancer, allowing malignant mutations to eventually grow and metastasize [2, 11, 15]. The spinal column is the most frequently affected part of the skeletal system in terms of metastasis [15-17]. Owing to the oncologic nature of the disease, surgery alone is not sufficient to determine the most effective treatment method. A more personalized, multifactorial approach is necessary to provide a better outcome for the patients by extending survival time or improving the quality of life. Our research focused on surgery for metastatic spinal tumors. We evaluated several preoperative factors that could affect the OS of patients or predict intraoperative and postoperative complications. The factors were classified into subgroups to examine connections between variations in details.

Age, preoperative motor disorders, Frankel grade categories, KPS, type of the primary tumor, presence of internal metastasis, and number of metastases in the vertebral body were found to have a significant negative effect on OS. Eap et al [18] found increased *age* to be a bad prognostic factor for survival, which our results also confirm. *Preoperative motor disorders* were previously reported to be a bad prognostic factor for survival [19, 20]. Another important factor for survival is the speed of neurologic deficit. Rades et al. [21, 22] showed that slower development of the motor deficit (>14 days) before radiotherapy predicts better functional outcome, and the length of development is a relevant prognostic factor. Fan et al. [23] found the timing of surgical intervention is key to predicting the postoperative outcome. They argued that the best surgical and functional outcome was observed for patients with Frankel A functional status if the patients received treatment within 24 hours. In our cohort, nearly half of the patients already had motor deficits at the time of presentation, but only paralysis was an indicator of significantly shorter survival. Poor *preoperative functional status* (Frankel grade system groups A and B, KPS 10%-40%) had a negative impact on survival, and these results correlate with clinical experiences and expectations. Considering the features of malignancies, expanded disease (if the *number of metastases* in the vertebral column are >=2) or the presence of an inoperative *internal organ metastasis* shortened the expected survival time, which is in conjunction with the findings in the literature [20]. Solitary metastases allow radical treatment resulting in better tumor control and increased OS. Furthermore, neurologic symptoms and pain could be treated more effectively, leading to increased quality of life [24]. Our results support these findings, as significant change in OS was observed if the number of vertebral metastases was >2 (Figure 8). From the group of

primary tumors types, lung and cervical carcinoma had significantly shortened the expected survival; however, according to our observations, lung tumors should be examined in subgroups later because prognosis may vary greatly in the different pathologic subtypes of lung cancers.

Our analysis revealed that sex, surgical complications, preoperative sensory deficits, symptoms at clinical presentation, affected vertebral levels, and extraspinal bone metastases did not have an effect on OS of patients. However, we emphasize that nearly one fourth of our patients (25.6%) had pain only as the presenting symptom of their diseases, and many patients were treated by ineffectual rheumatologic methods for months before a proper imaging examination was performed. Hosono et al. [25] found that intense pain is also a bad prognostic factor in a patient with cancer, but our results do not confirm these findings statistically.

Surgical complications occur in 25%-34% of operations for metastatic spinal diseases [26]. Our investigation focused on 2 main types of complications: bleeding and need for postoperative intensive care because of the poor postoperative status. Several articles studied the typical volume of bleeding during surgery [27, 28]; however, the number of studies that report blood losses by type of surgical interventions [29, 30] and tumor types is limited [28, 31]. Furthermore, only a few studies investigated a relatively larger series of patients [28, 29]. Kumar et al. [28] proved that the type of primary tumor is a key factor for estimating the amount of intraoperative blood loss, and an extended surgery is likely to increase the bleeding complications. If risk factors for increased intraoperative bleeding are known preoperatively, appropriate preoperative planning allows sufficient intraoperative and postoperative management of homeostasis and fluid balance and may reduce the prevalence of perioperative morbidities [28]. Our results are in agreement with previous reports [28, 29] and support mainly the clinical experiences and observations. We found the following factors to be associated with higher risk of bleeding: *preoperative poor performance status*, *primary renal tumor,* and *corpectomy*. Renal tumors by an intense vascular endothelial growth factor secretion and invasive marginal or en bloc tumor resections are known to be associated with bleeding [28]. The relationship between poor preoperative performance status and bleeding can be explained by the poor general condition and homeostatic features of the patients. For the prediction of need for postoperative intensive care, a very significant factor is *cervical segment involvement* with a nearly 7-fold increased risk because of respiratory system complications, which is also in agreement with clinical experiences.

We examined the effect of several risk factors of prognosis scoring systems on OS time of patients with spinal metastases, and we examined the prognostic factors of surgical complications. However, this study is limited by the general drawback of retrospective statistical evaluation of human data. Usually, there are large variations in intervention responses if only a few factors or observations are fixed. In our retrospective analysis, we were restricted to consider only available data, and hence further investigations could not be made to distinguish between cases with similar input but different output values. The single site cohort may introduce some bias in the data, where unrecorded genetic or habitual similarities between the cases could affect the results.

Conclusions

The aim of the study was to analyze an extended database of patients with spinal metastases who underwent surgical interventions. Our investigation mainly focused on risk factors for surgical complications and prognostic factors of OS time. Age, preoperative motor disorders, preoperative Frankel grade categories, KPS, type of primary tumor, and presence of internal metastasis have a significant negative effect on OS. Complications such as bleeding or need for intensive care could be predicted preoperatively based on preoperative performance status, type of primary tumor, affected vertebral levels, and type of surgical interventions. Spinal metastatic disease still remains a serious and challenging surgical problem, but early diagnosis and sufficient treatment may prevent serious complications and result in longer survival. If the exact risk and prognostic factors are known preoperatively, surgical outcome can be predicted more precisely. We believe our results could provide a basis for a future multicenter prospective study to determine the best treatment protocol for patients with spinal metastases.

Abbreviations

CI: Confidence Interval

KPS: Karnofsky Performance Scale

OR: Odds Ratio

OS: Overall Survival

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Fig. 6a. Kaplan-Meier curve of the primary tumor categories

Fig. 6b. Kaplan-Meier curve of the primary tumor categories

Fig. 6c. Kaplan-Meier curve of the primary tumor categories

Fig. 7. Kaplan-Meier curve of the internal metastases categories

Fig. 8. Kaplan-Meier curve of the vertebral metastases categories

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Table list

Table 1. Revised Tokuhashi score

Predictive Factors	Points
General condition (KPS)	
Poor (KPS 10%-40%)	0
Moderate (KPS 50%-70%)	1
Good (KPS 80%-100%)	2
Number of extraspinal bone foci	
>=3	0
1-2	1
0	2
Number of metastases in vertebral body	
>=3	0
2	1
1	2
Metastases to major internal organs	
Nonremovable	0
Removable	1
No metastasis	2
Primary site of cancer	
Lung, osteosarcoma, stomach, bladder, esophagus, pancreas	0
Liver, gallbladder, unidentified	1
Others	2
Kidney, uterus	3
Rectum	4
Thyroid, breast, prostate, carcinoid	5
Palsy	
Frankel A, B (complete)	0

Predictive Factors	Points
Frankel C, D (incomplete)	1
Frankel E (none)	2
<mark>Prognostic Categories</mark>	<mark>Interpretation</mark>
0-8 points	85% live <6 months --> conservative treatment or palliative surgery
9-11 points	73% live >6 months (and 30% live >1 year) --> palliative surgery or (exceptionally) excisional surgery
12-15	points 95% live >1 year --> excisional surgery
KPS, Karnofsky performance scale.	

Table 2. Tomita score

Predictive Factors	Point(s)
Primary tumor	
Slow growth (e.g., breast, prostate, thyroid)	1
Moderate growth (e.g., kidney, uterus)	2
Rapid growth (e.g., lung, liver, stomach, colon, primary unknown)	4
Primary tumor	
No visceral metastasis	0
Treatable	2
Untreatable	4
Bone metastasis (including spine)	
Solitary/isolated	1
Multiple	2
Prognostic Categories (Points)	Interpretation
2-3	Long-term local control (mean survival 50 months) --> wide or marginal excision
4-5	Mid-term local control (mean survival 23.5 months) --> marginal or intralesional excision
6-7	Short-term palliation (mean survival 15 months) --> palliative surgery
8-10	Terminal care (mean survival 6 months) --> supportive care, no surgery

Table 3. The modified Bauer score

Predictive Factors	Point(s)
No visceral metastasis	1
No lung cancer	1
Primary tumor = breast, kidney, lymphoma, multiple myeloma	1
1 solitary skeletal metastasis	1
Prognostic Categories (Points)	Interpretation
0-1	4.8 monthsesupportive care, no surgery
2	18.2 monthseshort-term palliation, dorsal surgery
3-4	28.4 monthsemid-term local control, dorsoventral surgery

Table 4. van der Linden score

Predictive Factors	Point(s)
Karnofsky Performance Status	
80-100	2
50-70	1
20-40	0
Primary tumor	
Breast	3
Prostate	2
Lung	1
Other	0
Visceral metastasis	
No	1
Yes	0
Prognostic Categories (Points)	Interpretation
0-3	4.8 monthseconservative therapy
4-5	13.1 monthsepalliative surgery
6	18.3 monthseexcisional surgery

Table 5. Overall survival data

Time	Survival	SE	Lower 95% CI	Upper 95% CI
30 days	0.924	0.0146	0.896	0.953
60 days	0.827	0.0209	0.787	0.869
90 days	0.748	0.0239	0.702	0.796
180 days	0.543	0.0276	0.492	0.6
1 year	0.389	0.0277	0.338	0.447
3 years	0.191	0.0249	0.148	0.247
5 years	0.145	0.0253	0.103	0.205
CI, confidence interval.				

Table 6. Data of patients categorized by the type of primary tumors

Tumor Type	Number of Patients (%)
All	337 (100)
Bladder cancer	7 (2.1)
Breast cancer	30 (8.9)
Cervical carcinoma	4 (1.2)
Colorectal carcinoma	22 (6.5)
Hematologic malignancies	11 (3.3)
Hepatic cancer	6 (1.8)
Renal cell carcinoma	26 (7.7)
Lung cancer	84 (24.9)
Malignant bone tumor	2 (0.6)
Melanoma	6 (1.8)
Multiple myeloma	38 (11.3)
Neuroendocrine carcinoma	6 (1.8)
Others	24 (7.1)
Other squamous cell carcinoma	4 (1.2)
Ovarian carcinoma	3 (0.9)
Prostate carcinoma	22 (6.5)
Gastric cancer	2 (0.6)
Thyroid cancer	7 (2.1)
Cancer of unknown primary site	30 (8.9)
Uterine carcinoma	3 (0.9)

Table 7. Predictive factors that affected the odds of complications

Tested Factors for Complications	Subcategory	Type of Complication	P Value	OR	95% CI
Age	50-60 years	Bleeding	0.014	0.53	0.30-0.89
KPS	10%-40%	Bleeding	0.042	1.69	1.00-2.84
Affected vertebral level	Cervical	Need for postoperative intensive care	<1e-6	6.62	2.82-15.92
Affected vertebral level	Thoracic	Need for postoperative intensive care	0.005	0.33	0.14-0.76
Affected vertebral level	Lumbal	Need for postoperative intensive care	0.027	0.32	0.09-0.89
Type of primary tumor	Renal	Bleeding	0.009	3.11	1.27-7.96
Type of primary tumor	Prostate	Bleeding	0.047	0.33	0.08-1.03
Main operative step	Corpectomy	Bleeding	<1e -6	3.25	2.03-5.25
OR, odds ratio; CI, confidence interval; KPS, Karnofsky performance scale.					