Survival Rates, Risk Factors and Complications of Surgically Treated Metastatic Disease of the Spine: A Retrospective Study of a Single Center Experience from Southern Malaysia

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Abstract: ***Background**: Surgical intervention is the recommended treatment for mechanical and neurological instability in spine metastasis, but there are no published data on our population. **Objectives:** This study aims to investigate the survival of our local patients with spine metastasis who have undergone surgery, in addition to the associated risk factors and complications. **Methods**: A retrospective analysis (n=23) of surgically treated metastatic spine disease at a single center in southern Malaysia from 2017 to 2022. Patients' demographics, comorbidities, primary cancer type, complications, pre- and postoperative pain scores, and neurological status were among the data collected. The use of Tokuhashi score, Karnofsky performance scale, and the SINS score was examined. **Results**: The mean age at surgery was 58.2 (10.09) years and the mean survival time was 25.37 (95%CI= 16.17 - 34.56) months. Serum albumin of over 3.5g/dL was statistically significant in survival with a p-value of 0.022, whereas serum protein was not. Six (26.1%) showed no improvement whereas seventeen (73.9%) had pain relief. Three (13%) showed neurologic improvement, while twenty (87.0%) did not. Preoperative good neurological function significantly improved survival relative to worse Frankel grades (p-value 0.033). Mantel-Cox indicated no statistical significance for the other factors. Five (21.74%) had postoperative complications. **Conclusions**: Our surgically treated spine metastases patients' survival rates vary. Postoperative survival was statistically significant with preoperative albumin levels >3.5g/dL and good Frankel grade. Tokuhashi scoring and Karnofsky scale helped determine surgery candidates.*

Keywords: spine metastasis, survival rate, serum albumin, surgical complications

1. Introduction

The mortality rate of patients with malignancy increases by nearly 70% with metastatic disease, and the skeletal system, along with the axial spine, is the third most common site [1-4]. Mechanical and neurological instability caused by spinal metastases may necessitate surgical intervention, such as pathologic vertebral compression fractures (pVCF) and/or metastatic epidural spinal cord compression (MESCC). Approximately 10% of those with spinal metastases will develop MESCC, and another 12.6% will develop pVCF [5]. Even in the absence of major spinal consequences, symptomatic spinal metastases may prevent patients from actively participating in society and doing their daily tasks as usual, lowering performance status, worsening symptoms, and consequently life expectancy in a vicious circle.

Surgical intervention is the preferred course of action for alleviating pain associated with spinal segment stabilization, enhancing patients' quality of life, and aiming to restore or, at the very least, maintain neurological function [6-8]. Nevertheless, it is crucial to acknowledge that there are inherent risks associated with the procedure, thus emphasizing the significance of carefully selecting patients who are likely to derive benefits from the surgery. Patients who are at a high risk of developing severe complications, as well as those with a poor prognosis or low chances of survival, may not be suitable candidates for surgical intervention. Numerous prognostic scoring systems have been developed to aid in decision-making; however, their applicability across diverse populations and healthcare settings worldwide remains uncertain.

Several scoring systems have been utilized for decision-making purposes; however, there is a lack of published data about spine metastases and the survival rates of surgically treated patients in Malaysia. Therefore, we are undertaking a retrospective analysis of our patient cohort from Southern Malaysia in order to examine the rates of survival, identify risk variables, and assess the occurrence of complications.

2. Materials and Methods

This study presents a retrospective analysis of surgically treated cases of metastatic spine disease at Hospital Sultan Ismail Johor Bahru, a tertiary referral center located in Southern Malaysia. The data collected spans from 2017 to 2022. The data was acquired from the electronic medical records database of the Hospital Information System (HIS). The purpose of this study is to examine the survival of our local patients with spine metastasis who have undergone surgery, the associated risk factors and complications.

All spinal metastatic cases that had surgery during the specified time frame were included in the study, except for those with primary spine cancer, without histological primary biopsy, lacking CT staging and MRI spine, and those with insufficient data in their medical records.

The collected data encompassed several aspects, such as patient demographics (including gender, ethnicity, and age at presentation) and clinical data (such as pain levels, neurological state, type of cancer, site of metastasis, total protein and albumin levels, functional status, complications, and survival duration). The study gathered data on perioperative and postoperative problems, which encompassed many factors such as the length of the surgical procedure, amount of blood loss, occurrence of dural tear, infection, implant failure, neurological deficit as measured by the Frankel grade, and pain intensity as assessed by the Visual Analog Scale (VAS score) [9,10].

A comprehensive analysis was conducted on a cohort of 28 individuals who underwent surgical intervention for metastatic spinal illness. After applying rigorous inclusion and exclusion criteria, a total of 23 patients were deemed eligible for inclusion in the study. The surgical indications encompass the presence of growing neurologic impairment accompanied by signs of cord compression, an indeterminate and unstable spine as determined by the Spinal Instability Neoplastic Score (SINS), and the patient's suitability for surgery, together with a prognosis of more than 6 months as determined by the Tokuhashi score [11,12]. All patients who underwent procedures including anterior, posterior, or combination decompression and stabilization were included in the study.

The study employed the Kaplan-Meier method and Log Rank (Mantel-Cox) test to assess survivorship and identify characteristics that influence survival. The criterion employed to ascertain the survival rate was mortality. The significance level was set at a p-value of < 0.05 and the statistical analyses were conducted using SPSS version 27.0.

3. Results

There were 8 male (34.8%) and 15 female (65.2%) with the mean age at time of surgery was 58.2 (10.09) years. Majority of them are Malay ethnicity (n=11, 47.8%) followed by Chinese (n=9, 38.9%), Indian (n=2, 8.7%) and others (n=1, 4.3%). 16 (69.6%) of them had comorbidities such as Diabetes mellitus, hypertension, and heart problems while the rest of them (n=7, 30.4%) were free from other illnesses.

We found 10 different primary tumors in our cohort in which breast cancer (n=9, 39.1%) contribute the most cases followed by prostate cancer (n=5, 21.7%), thyroid cancer (n=2, 8.7%) and one patient each for angiosarcoma, bladder cancer, cervix cancer, colon cancer, lung cancer, multiple myeloma and plasmacytoma (Table 1). Out of 23 patients, 10 of them still alive and 13 died with the mean survival time after the surgery was 25.37 (95%CI= 16.17 - 34.56) months. The survival probability is around 65% at 6 months, 60% at 1 year and around 40% at 3 years (Figure 1).

Table 1: Types of primary cancer with the distribution (n=23), survival status and the mean survival time (months)

		Status		Mean survival time (months)
	No. of patient (%)	Alive (n=10) n (%)	Death (n=13) n (%)	
Primary tumor				
Angiosarcoma	1 (4.3)	1 (100.0)	0 (0.0)	50.2
Bladder	1 (4.3)	0 (0.0)	1 (100.0)	3.5
Breast	9 (39.1)	4 (44.4)	5 (55.6)	28.5
Cervix	1 (4.3)	1 (100.0)	0 (0.0)	7.9
Colon	1 (4.3)	0 (0.0)	1 (100.0)	5.0
Lung	1 (4.3)	1 (100.0)	0 (0.0)	15.6
M. myeloma	1 (4.3)	0 (0.0)	1 (100.0)	3.0
Plasmacytoma	1 (4.3)	0 (0.0)	1 (100.0)	0.6
Prostate	5 (21.7)	2 (40.0)	3 (60.0)	13.2
Thyroid	2 (8.7)	1 (50.0)	1 (50.0)	14.2

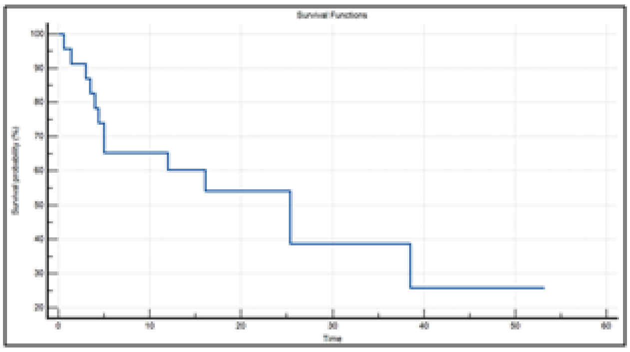

Figure 1: Kaplan–Meier curve for overall survival analysis (n=23). Survival probability is based on the time from date of surgery to date of death or last follow-up

This study incorporates blood markers, namely albumin and protein, due to their inclusion in a novel prognostication method for spinal metastasis developed by the Budapest group. Additionally, albumin is a component of the New England Spinal Metastasis Score (NESMS)[13,14]. Albumin of more than 3.5g/dL was found to have a significant impact on the survival as compared to level less than 3.5g/dL with p-value of 0.022 based on Log Rank (Mantel-Cox) test. In the other hand, the protein level of less or more than 6.5g/dL showed no significant difference (p=0.114) but the mean survival time was longer for higher protein level (14.6 months) as compared to lower protein level (3.5 months) (Table 2).

Various scoring and classification systems were used for patient selection for surgery which includes Tokuhashi scoring, Karnofsky performance scale and SINS score. We did include Budapest's novel prognostication system in this study to see its usability, but it was not clinically significant (p=0.548). The good prognosis group for Tokuhashi score showed 38 months mean survival time as compared to poor group with 7.9 months (p=0.193). Karnofsky performance scale also showed better survival in good functional group as compared to poor group with 31.5 months and 3.3 months respectively (p=0.072). The preoperative spine stability based on SINS score also showed statistically not significant to the survival with p-value of 0.077.

ISSN: 2319-7064
SJIF (2022): 7.942

Table 2: Difference in survival time between several independent variables (blood parameters, clinical symptoms, perioperative blood loss and survival scoring systems)

Variables	Status		Mean survival time	95% CI	p-value*
	Alive (n=10) n(%)	Death (n=13) n(%)			
Albumin					
<3.5	0 (0.0)	2 (100.0)	2.0	(0.04, 3.96)	0.022
>3.5	10 (47.6)	11 (52.4)	12.7	(4.86, 20.54)	
Protein					
<6.5	2 (33.3)	4 (66.7)	3.5	(1.46, 5.54)	0.114
>6.5	8 (47.1)	9 (52.9)	14.6	(5.22, 24.03)	
EBL					
Mild	2 (66.7)	1 (33.3)	6.0	(6.00, 6.00)	0.880
Moderate	4 (40.0)	6 (60.0)	9.8	(0.75, 18.85)	
Severe	4 (40.0)	6 (60.0)	12.7	(0.49, 24.84)	
Tokuhashi					
Good	4 (80.0)	1 (20.0)	38.0	(38.00, 38.00)	0.193
Intermediate	2 (28.6)	5 (71.4)	9.5	(0.00, 19.64)	
Poor	4 (36.4)	7 (63.6)	7.9	(1.06, 14.65)	
Novel system					
Good	4 (50.0)	4 (50.0)	8.3	(0.00, 19.26)	0.548
Moderate	4 (36.4)	7 (63.6)	14.8	(3.26, 26.41)	
Poor	2 (50.0)	2 (50.0)	4.5	(1.56, 7.44)	
SINS					
Stable	0 (0.0)	1 (100.0)	1.0	(1.00, 1.00)	0.077
Indeterminate	3 (37.5)	5 (62.5)	13.2	(0.21, 26.19)	
Unstable	7 (50.0)	7 (50.0)	10.7	(1.69, 19.64)	
Karnofsky					
Good	6 (75.0)	2 (25.0)	31.5	(18.76, 44.24)	0.072
Moderate	2 (20.0)	8 (80.0)	8.3	(1.75, 14.82)	
Poor	2 (40.0)	3 (60.0)	3.3	(0.49, 6.18)	
Preop Frankel					
A	1 (33.3)	2 (66.7)	2.0	(0.04, 3.96)	0.033
C	1 (33.3)	2 (66.7)	9.5	(0.00, 22.24)	
D	3 (30.0)	7 (70.0)	7.5	(0.51, 14.49)	
E	5 (71.4)	2 (28.6)	31.5	(18.76, 44.24)	
Preop pain					
Mild	5 (33.3)	10 (66.7)	7.1	(1.83, 12.39)	0.148
Moderate	4 (66.7)	2 (33.3)	14.5	(0.00, 35.08)	
Severe	1 (50.0)	1 (50.0)	38.0	(38.00, 38.00)	

*Log Rank (Mantel-Cox) test

The perioperative complication observed was fast AF (HR 160-180) in one patient and another patient had flat motor evoked potentials (MEPs) for all four limbs with labile blood pressure, thus abandoning the cage insertion. The main complication monitored was estimated blood loss (EBL) and we grouped into mild (<500ml), moderate (500ml-1000ml) and severe (>1000ml) [15]. The mean blood loss was 1365ml, ranging from 200ml to as much as 5500ml. Three patients fall into mild EBL group (13%), ten patients each in moderate (43.5%) and severe EBL (43.5%) group. However, there was no significant difference in the survival between the groups with the Log Rank (Mantel-Cox) test (p=0.880).

Clinical outcomes evaluated in this study include VAS pain score and neurological status based on Frankel grade prior to and following surgery. In terms of pain, Table 3 shows that five patients (21.7%) had no pain, seventeen (73.9%) had minimal symptoms, and only one had moderate pain after surgery. In terms of improvement, six patients (26.1%) exhibited no change in their symptoms, whereas the remaining seventeen (73.9%) had reduced discomfort. With a p-value of 0.148, there was no statistical significance between preoperative pain score and survival (Table 2).

Table 3: Preoperative and postoperative VAS score (N=23)

	Preoperative		Postoperative	
	N	%	N	%
Pain score (VAS)				
None (0)	0	0	5	21.7
Mild (1-3)	15	65.2	17	73.9
Moderate (4-6)	6	26.1	1	4.3
Severe (7-10)	2	8.7	0	0

The preoperative neurological status showed three patients with complete spinal cord injury (Frankel A), none in sensory only preserved group (Frankel B), thirteen with incomplete motor function (Frankel C and D) and seven had no neurological deficit (Frankel E). Postoperatively, three patients in Frankel A, one with Frankel C, eleven with Frankel D and eight with Frankel E (Table 4). Overall, 20 (87.0%) patients had no neurological improvement after the surgery and only 3 (13.0%) had improvement. The mean survival time was 31.5 months for Frankel E, followed by Frankel C, D and A with mean survival of 9.5, 7.5 and 2 months respectively. Based on the Log rank test, preoperative Frankel showed statistically significant difference in survival between the Frankel grades with p-value of 0.033. (Table 2). A comparison of survival between the Frankel grades was performed using the Kaplan-Meier survivorship curve with a significance level of p<0.05 (Figure 2).

Table 4: Preoperative and postoperative Frankel cross tabulation

		Postop Frankel				Total
		A	C	D	E	
Preop Frankel	A	3	0	0	0	3
	C	0	1	2	0	3
	D	0	0	9	1	10
	E	0	0	0	7	7
Total		3	1	11	8	23

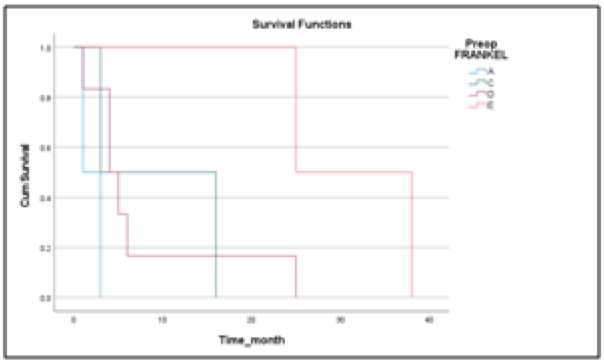

Figure 2: Kaplan-Meier survivorship curve illustrating the comparison betweenthe preoperative Frankel grades

Five patients (21.74%) suffered postoperative complications. Twohad surgical site infection (SSI), one with wound breakdown, one with perianal abscess and UTI. One patient experienced pulmonary embolism, hematuria, lower GI bleed (LGIB), and klebsiella and proteus bacteremia (Table 5).

Table 5: Postoperative complications

	No. of patients	
	N	%
Perianal abscess, UTI	1	4.3%
Pulmonary embolism, hematuria, LGIB, klebsiella and proteus bacteremia	1	4.3%
SSI after 2 months with covid positive	1	4.3%
SSI with wound breakdown after 1 week	1	4.3%
Wound breakdown	1	4.3%
Total	5	21.74%

4. Discussion

In the realm of medical advancements, the treatment of metastatic disease of the spine has seen significant progress over the years. This piece delves into the crucial aspects of survival rates, risk factors, and the intricate web of complications associated with surgically treating this complex condition. This study included 23 patients who were surgically treated after confirming diagnosis of spinal metastasis from histopathological report and fulfill the inclusion and exclusion criteria. All patients operated were decided based on mechanical and neurological instability as well as multiple prognostic scoring systems to help in deciding patients' suitability to undergo surgery.

There were mostly female, with 15 (65.2%) patients and the other 8 (34.8%) were male. The mean age at the time of surgery was 58.2 (10.09) years. In Johor, 60.1% of the population is Malay, 32.8% is Chinese, and 6.6% is Indian [16]. According to our findings, Malay (n=11, 47.8%) is the predominant ethnic group, with Chinese (n=9, 38.9%), Indians (n=2, 8.7%), and other (n=1, 4.3%) following. 16 (69.6%) of them had comorbidities such as Diabetes mellitus, hypertension, and heart problems, while the rest of them (n=7, 30.4%) were free from other illnesses.

Numerous primary tumor types are linked to spinal metastasis. According to reports, the proportions of some common primary sites for spinal metastases are as follows: 13.9–37.0% lung cancer, 16.2–16.5% cancer of unknown origin, 6.4–16.9% breast cancer, 4.4–14.8% prostate cancer%, 6.1–12.0% kidney cancer, and 2.5–3.1% thyroid cancer [17-20]. In some published prognostic scoring systems (Tokuhashi, Tomita, van der Linden, and Bauer) for spinal metastases , the primary tumor site of endocrine origin such as breast, thyroid and prostate is one of the most influential factors on good survival [21,22]. Therefore, differential diagnosis of the primary tumor site of spinal metastases is essential for prognosis prediction and treatment decision-making. We found 10 different primary tumors in our group. Breast cancer was the most prevalent type (n=9, 39.1%), then prostate cancer (n=5, 21.7%),thyroid cancer (n=2, 8.7%), angiosarcoma, bladder cancer, cervix cancer, colon cancer, lung cancer, multiple myeloma, and plasmacytoma (n=1 each). The survival rate after surgery varied among the different types of primary tumors and we found almost similar finding in which the mean survival time for the breast, thyroid and prostate cancer's patients were more than 12 months with 28.5 months, 14.2 months, and 13.2 months respectively. However, it is difficult to conclude in this study due to the small sample size. Surprisingly, our Lung cancer patient is still alive after more than 15 months despite poor survival in literature and this maybe be due to early detection and treatment advancement.

We only include albumin and protein level in this study because protein is included in a novel prognostication system for spinal metastasis by the Budapest group and albumin is part of the New England Spinal Metastasis Score (NESMS) [13,14]. Hirase et al. (2023) reported that patients with low blood albumin levels (< 3.25 g/dL) exhibited a significantly increased incidence of perioperative adverse events (p= .041), longer post-operative length of stay (p < .001), higher 30-day reoperation rate (p=.014), and elevated in-hospital death rate (p=.046) [23]. We use a serum albumin of 3.5g/dL as a cut of point following NESMS and found that Albumin level of more than 3.5g/dL was statistically significant with better survival rate as compared to low serum albumin with p-value of 0.022 based on Log Rank (Mantel-Cox) test. In the other hand, the protein level of less or more than 6.5g/dL showed no significant difference (p=0.114) but the mean survival time was longer for higher protein level (14.6 months) as compared to lower protein level. The study conducted by Mezei et al. revealed that those with hypoproteinemia experienced a 1.321-fold higher risk of mortality whencompared to those within the normal range [13].

In terms of survival or prognostic scoring, we incorporate Tokuhashi, Karnofsky, and SINS scores into our decision-making. In addition, the novel prognostication system of Budapest is included in this study to determine its applicability in our context, but it was not clinically significant (p=0.548). For the Tokuhashi score, it was intriguing that the excellent prognosis group had a mean survival time of 38 months compared to 7.9 months for the poor prognosis group (p=0.193). The Karnofsky performance scale also revealed that the excellent functional group had a higher survival rate than the poor functional group, 31.5 months versus 3.3 months, respectively (p=0.072). It demonstrates that these two scoring systems can guide us to the finest surgical candidate, even though they cannot be used independently. The new Budapest prognostic system, however, showed no statistically significant difference between the three groups (p=0.548), which may be due to the fact that their study was based on their local population and health care technology. In addition, the preoperative spine stability based on the SINS score was not statistically significant in relation to survival (p=0.077), but it is valuable for identifying mechanically unstable spines that will benefit from surgery.

All our cases were performed using open surgery techniques, which carry a significant risk of bleeding. Therefore, the focus of our study was to observe perioperative complications, namely the estimation of blood loss (EBL). This parameter was divided into three distinct categories [15]. Mohme et al. discovered that the mean intraoperative blood loss during oncological spine surgery in their cohort was 1176 ± 1209 ml, and that 33.8% of the patients required blood transfusions. In addition, theydiscovered that myeloma, operative procedure length, epidural spinal cord compression (ESCC) score, tumor localization, BMI, and surgical strategy were substantially related to increased intraoperative blood loss or risk of requiring allogeneic blood transfusions [24]. The range of blood loss in our cohort was 200 ml to 5500 ml, with an average of 1365 ml. Three patients, or 13% of the total, were assigned to the mild estimated blood loss (EBL) group. Ten patients were assigned to both the moderate and severe EBL categories, accounting for 43.5% of the total population. The Log Rank (Mantel-Cox) test, however, revealed no statistically significant difference in survival rates between the groups (p=0.880).

In a study on survival prognostic factors and clinical outcomes in patients with spinal metastases, Pointillart et al. discovered that the majority of patients who underwent operative intervention experienced an immediate and prolonged improvement in pain, neurological deficit, function, and quality of life [25]. Therefore, it is postulated that pain potentially assumes a significant function in this context. Our investigation revealed that a total of five individuals (constituting 21.7% of the sample) reported an absence of pain, whereas seventeen patients (73.9%) experienced mild symptoms subsequent to the surgical procedure. Conversely, only one participant reported moderate pain in the postoperative period. In total, a majority of seventeen patients (73.9%) saw a notable improvement in pain, whereas the remaining six patients (26.1%) did not exhibit any change in symptoms.

In a prior investigation conducted by Wise et al., it was shown that 81.3% of the participants exhibited no alteration in their Frankel grade, 23.8% saw an improvement of one Frankel grade, while 1% of theparticipants demonstrated a decline of one Frankel grade [26]. In a recent study of surgically treated cases of metastatic spinal differentiated thyroid carcinoma, preoperative and postoperative Frankel grades and radioactive iodine (RAI) therapy were found to be associated with patient survival (p 0.05) [27]. Twenty patients (87.0%) in our study showed no neurological improvement following surgery, while three patients (13.1%) did. Preoperative Frankel E had the longest mean survival time of 31.5 months, followed by Frankel C, D, and A with mean survival times of 9.5, 7.5, and 2 months, respectively. The Log rank test and Kaplan-Meier survival curve revealed a statistically significant difference in survival between the preoperative Frankel grades with a p-value of 0.033. Those with intact neurology or improved neurological function prior to surgery will have a longer survival rate than those with poor neurological function because they are able to care for themselves and mobilize, thereby minimizing the other complications of being bedridden.

In a systematic review by Tarawneh et al., surgical site infection (SSI) was found to be the most common complication following spinal metastasis surgery, occurring in 6.5% of cases, followed by neurological deterioration in 3.3% of cases and instrumentation failure in 2.0% of cases. The re-operation rate was 8.3% (54 out of 651), with surgical site infection (SSI) identified as the primary cause in 27.8% of these cases [28]. Five (21.74%) of our patients experienced postoperative complications, with two developing surgical site infections (SSI). One case of SSI occurred one week after surgery and was treated with antibiotics and a dressing, while the other was diagnosed two months later and wound debridement was performed. One (4.3% of patients) presented with perianal abscess and urinary tract infection (UTI), both of which were associated with primary prostate cancer. One patient experienced wound breakdown without infection. One patient with primary plasmacytoma scored poorly on the Tokuhashi and clinically paraplegia (Frankel A) had the most severe complications, including pulmonary embolism, hematuria, lower gastrointestinal bleeding (LGIB), and klebsiella and proteus bacteremia. After the operation, he only lived for 18 days. Therefore, it is crucial to carefully consider patient selection in order to identify those who may derive potential benefits from the surgical procedure, taking into account several aspects that influence survival outcomes.

5. Conclusion

Our community's spine metastasis survivors had an average survival time of 25.37 months after surgery. However, several factors affect this outcome. Despite the small sample size, endocrine primary tumor patients had better survival rates. Preoperative blood albumin levels exceeding 3.5g/dL and good neurological function predict survival ($p<0.05$). Patients with good Tokuhashi scores, functional skills, nutritional statuses, and mobility reduce surgical complications. Spinal metastases require interdisciplinary treatment. Many survival and prognostic scoring systems, along with a thorough assessment of patients' comorbidities, primary tumor characteristics, preoperative neurological status, and blood parameters, can help identify the best candidates for surgery and improved survival. Thus, optimizing patient nutrition before surgery and discussing the surgical procedure's expected outcomes and goals are essential.

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