

Original Article

## Evaluation of prognostic preoperative factors in patients undergoing surgery for spinal metastases: Results in a consecutive series of 81 cases

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### ABSTRACT

**Background:** Surgical treatment of spinal metastases should be tailored to provide pain control, neurological deficit improvement, and vertebral stability with low operative morbidity and mortality. The aim of this study was to analyze the predictive value of some preoperative factors on overall survival in patients undergoing surgery for spinal metastases.

**Methods:** We retrospectively analyzed a consecutive series of 81 patients who underwent surgery for spinal metastases from 2015 and 2021 in the Clinic of Neurosurgery of Ancona (Italy). Data regarding patients' baseline characteristics, preoperative Karnofsky Performance Status Score (KPS), and Frankel classification grading system, histology of primary tumor, Tokuhashi revised and Tomita scores, Spine Instability Neoplastic Score, and Epidural Spinal Cord Compression Classification were collected. We also evaluated the interval time between the diagnosis of the primary tumor and the onset of spinal metastasis, the type of surgery, the administration of adjuvant therapy, postoperative pain and Frankel grade, and complications after surgery. The relationship between patients' overall survival and predictive preoperative factors was analyzed by the Kaplan–Meier method. For the univariate and multivariate analysis, the log-rank test and Cox regression model were used.  $P \leq 0.05$  was considered as statistically significant.

**Results:** After surgery, the median survival time was 13 months. In our series, the histology of the primary tumor ( $P < 0.001$ ), the Tomita ( $P < 0.001$ ) and the Tokuhashi revised scores ( $P < 0.001$ ), the preoperative KPS ( $P < 0.001$ ), the adjuvant therapy ( $P < 0.001$ ), the postoperative Frankel grade ( $P < 0.001$ ), and the postoperative pain improvement ( $P < 0.001$ ) were significantly related to overall survival in the univariate analysis. In the multivariate analysis, the Tomita ( $P < 0.001$ ), Tokuhashi revised scores ( $P < 0.001$ ), and the adjuvant therapy were confirmed as independent prognostic factors.

**Conclusion:** These data suggest that patients with limited extension of primitive tumor and responsive to the adjuvant therapy are the best candidates for surgery with better outcome.

**Keywords:** Neurosurgery, Overall survival, Spinal cord compression, Spinal metastases, Spinal tumors

### INTRODUCTION

Nowadays, advances in cancer treatment have prolonged patients' life expectancy. Spinal metastases are a common occurrence in cancer patients. The most common sites for metastases

in cancer patients are the liver and the lungs, followed by the spine.<sup>[27]</sup>

Breast, prostate, and lung cancer are the most frequent histologic type for spinal metastases. Spinal metastases are casually the first manifestation of an unknown primary tumor in about 10% of the patients.<sup>[8]</sup> The most frequently involved areas are the thoracic spine (70%) followed by the lumbar spine (20%) and last the cervical spine (10%).<sup>[21]</sup> Approximately 95% of affected patients will develop epidural metastases, mainly involving the vertebral body and the pedicle regions, while 5% will present with intradural and <1% with intramedullary metastases.<sup>[23]</sup> Symptomatic spinal cord compression occurs more frequently in the thoracic spine, related to the higher number of vertebrae and the small canal diameter.<sup>[10]</sup>

Since the therapy for primary tumors is continuously improving, the treatment of metastases is becoming one of the major challenges to prevent cancer-related disability and death. Surgical treatment should be chosen to provide the maximum palliative effect with a minimum operative morbidity and mortality for each patient.<sup>[28]</sup> Surgery for spine metastases is essentially palliative with five goals: pain control, maintenance or improvement of neurological status, spine stabilization, local disease control, and finally improvement in quality of life.<sup>[18]</sup> The knowledge of preoperative factors predicting survival is the key to select the best candidates for surgery with better outcome.

The purpose of the present study was to evaluate which preoperative factors predicted survival in patients with spinal metastasis undergoing surgery.

## MATERIALS AND METHODS

We retrospectively analyzed the outcomes of a consecutive series of 81 patients who underwent surgical treatment for spinal metastases between January 2015 and January 2021 at the Clinic of Neurosurgery-Ancona (Italy). The follow-up ranged from 6 to 72 months.

Candidates for surgery were selected on the basis of three factors: (1) more than 6 months of life expectancy; (2) untreatable severe pain and/or presence of neurological deficits; and (3) need to collect tissue for diagnosis. Patients with previous surgery, aged <18 years old, and patients with diagnosis of multiple myeloma or lymphoma were excluded from this study.

All patients were preoperatively evaluated with computed tomography (CT) scan and magnetic resonance (MR) imaging of the spine. Chest, abdomen, and brain CT scan were also performed to detect systemic metastases. For each patient, we evaluated the following data: (1) demographics, (2) histology of primary tumor and systemic disease burden according to Tokuhashi revised and Tomita scores,<sup>[25,26]</sup> (3) the

preoperative Karnofsky Performance Status Score (KPS) (range 0–100),<sup>[16]</sup> (4) the preoperative Frankel classification grading system (range A–E),<sup>[12]</sup> (5) the presence or absence of preoperative pain, (6) the Spine Instability Neoplastic Score (SINS) (range 0–18),<sup>[4,11]</sup> and (7) the Epidural Spinal Cord Compression Classification (ESCC) (range 0–3).<sup>[3]</sup> We also evaluated the interval time between the diagnosis of the primary tumor and spinal metastases onset and we classified the patients into three groups: (1) metastasis already present at the time of the primary diagnosis; (2) early metastasis (within 1 year); and (3) late metastasis (after 1 year). The operative procedures included tumor removal or biopsy plus laminectomy with or without stabilization. Moreover, we analyzed the administration of adjuvant therapy (chemo- and/or radiotherapy), the postoperative Frankel grade, the postoperative improvement or worsening of pain, and complications after surgery.

The statistical analysis was performed by the software package SPSS, version 25.0 (Chicago, IL). We analyzed the relationship between patients' overall survival and preoperative factors by the Kaplan–Meier method. For the univariate and multivariate analysis, the log-rank test and Cox regression model were used.  $P \leq 0.05$  was considered as statistically significant.

## RESULTS

The outcomes of 81 consecutive patients (42 men and 39 women) with a median age of  $67.0 \pm 10.7$  years ( $68.0 \pm 8.2$  in men and  $65.0 \pm 12.7$  in women) were retrospectively reviewed. The preoperative characteristics of the study population are summarized in Table 1.

Breast, prostate, and lung cancers were the most common types of primary tumors. At admission, 78 patients out of 81 (96.3%) had pain and/or neurological deficits; in 26 patients out of 81 (32.01%), we documented a complete loss of motor and sensory function (Frankel Grade A). Most frequently spinal metastases were detected at the thoracic level (49.38%). According to the KPS score, patients were assigned to the following three groups: (1) scores 80–100% (45, 55.55%); (2) scores 50–70% (29, 35.8%); and (3) scores 10–40% (7, 8.65%). About 46.91% of all patients were included in Class III of Tokuhashi revised score; while 64.19% had been classified into Classes I and II of Tomita score [Table 1]. Spinal metastases were already present at the time of the primary tumor diagnosis in 40 patients out of 81 (49.38%). These tumors were breast 17%, lung 39%, prostate 7%, kidney 17%, colon 10%, and others 10%. Metastases detected later after primary tumor management were diagnosed in 41 patients out of 81 (51.62%) subdivided into breast 17%, lung 10%, prostate 23%, kidney 4%, colon 30%, and others 16%. We performed immediate surgery after diagnosis in 66 patients out of 81 (81.5%). In our series, 36 patients out

**Table 1:** Preoperative characteristics of 81 patients.

Characteristics	Number of patients (%)
Age	
<65 years	34 (41.98)
≥65 years	47 (58.02)
Sex	
Men	42 (51.85)
Women	39 (48.15)
Primary tumor	
Breast	15 (18.51)
Prostate	14 (17.28)
Lung	20 (24.70)
Kidney	13 (16.04)
Colon	11 (13.60)
Others	8 (9.87)
Tomita score	
Class I (2–3 patients)	30 (37.03)
Class II (4–5 patients)	22 (27.16)
Class III (6–7 patients)	10 (12.35)
Class IV (8–10 patients)	19 (23.46)
Tokuhashi revised score	
Class I (0–8 patients)	21 (25.93)
Class II (9–11 patients)	22 (27.16)
Class III (12–15 patients)	38 (46.91)
Karnofsky Performance Status Score (KPS)	
80–100%	45 (55.55)
50–70%	29 (35.80)
10–40%	7 (8.65)
Vertebral level	
Cervical	8 (9.88)
Cervicothoracic junction	8 (9.88)
Thoracic	40 (49.38)
Thoracolumbar junction	7 (8.64)
Lumbar	12 (14.81)
Sacral	0 (0)
Multiple	6 (7.41)
Symptoms	
Pain	38 (46.92)
Neurological deficit	22 (27.16)
Pain and neurological deficit	18 (22.22)
None	3 (3.70)
Frankel grading system	
A	26 (32.01)
B	7 (8.64)
C	7 (8.64)
D	2 (2.50)
E	39 (48.16)

(Contd...)

**Table 1:** (Continued).

Characteristics	Number of patients (%)
Surgical approach	
Stabilization+laminectomy+tumor removal	45 (55.55)
Laminectomy+tumor removal or biopsy	36 (44.44)
Adjuvant therapy	
Yes	69 (85.18)
No	12 (14.82)
Interval between the diagnosis of primary tumor and that of spinal metastasis	
No time interval	40 (49.38)
<1 year	17 (21.00)
>1 year	24 (29.62)
Spine Instability Neoplastic Score (SINS)	
Spine stability (0–6 pt)	25 (30.86)
Imminent spine instability (7–12)	20 (24.70)
Spine instability (13–18)	36 (44.44)
Epidural Spinal Cord Compression Classification (ESCC)	
Grade 0	1 (1.23)
Grade 1	7 (8.64)
Grade 2	26 (32.11)
Grade 3	47 (58.02)

of 81 (44.44%) had preoperative spine instability according to SINS score. Based on ESCC scale, 47 patients out of 81 presented a severe compression [Table 1]. In 45 patients out of 81 (55.55%), the surgical treatment consisted of laminectomy, tumor removal, and posterior stabilization, while in the remaining sample (44.44%), the surgical treatment was decompressive laminectomy and partial debulking of tumor or biopsy. After surgery, 69 patients out of 81 (85.18%) were additionally treated with adjuvant therapy (chemotherapy and/or radiotherapy) according to the tumor histology. The median survival time after surgical treatment was 13 months (minimum 4 months; maximum 65 months; SD: 18. 2). Clinical and surgical results are summarized in Table 2. We observed pain improvement in 33 patients out of 56 (40.76%) and neurological improvement in 34 patients out of 40 (85%) with an overall improvement of symptoms (pain and/or neurological improvement) in 83% of study population. Postoperative complications were present in 7 patients out of 81 (8.6%) as summarized in Table 2 and managed as following: cerebrospinal fluid (CSF) leakage reoperation, epidural hematoma reoperation, wound infection antibiotic therapy, wound dehiscence reoperation, and respiratory failure mechanical ventilation.

At univariate survival analysis, the histology of the primary tumor ( $P < 0.001$ ), the preoperative KPS score ( $P < 0.001$ ), the Tomita score ( $P < 0.001$ ) and Tokuhashi revised score ( $P < 0.001$ ), the administration of the adjuvant therapy

( $P < 0.001$ ), the postoperative Frankel grade ( $P < 0.001$ ), and the postoperative pain improvement ( $P < 0.001$ ) were significantly related to overall survival [Table 3]. Figures 1 and 2 show Kaplan–Meier curves for primary tumor, preoperative KPS score, Tomita score, Tokuhashi revised

score, adjuvant therapy, postoperative Frankel grade, and postoperative pain. In the multivariate analysis, only the Tomita score ( $P < 0.001$ ), the Tokuhashi revised score ( $P < 0.001$ ), and the administration of adjuvant therapy ( $P = 0.019$ ) were confirmed as independent prognostic factors [Table 4].

**Table 2:** Clinical and surgical results of 81 patients.

Parameter	Number of patients (%)
Postoperative pain	
No preoperative pain	25 (30.82)
Improvement	33 (40.76)
Unchanged	8 (9.88)
Worsening	15 (18.54)
Postoperative Frankel grading system	
A	7 (8.64)
B	14 (17.28)
C	12 (14.81)
D	8 (9.88)
E	40 (49.39)
Postoperative Frankel grading system changing	
Improvement	34 (42.05)
Unchanged	45 (55.55)
Worsening	2 (2.47)
Complications	
CSF leakage	1 (1.23)
Epidural hematoma	2 (2.47)
Wound infection	1 (1.23)
Wound dehiscence	2 (2.47)
Respiratory failure	1 (1.23)

**Table 3:** Univariate survival analysis (survival curves of different prognostic variable were made by Kaplan–Meier analysis and the variables entered in a Cox proportional hazards model to determinate their significance on survival).

Factors	P-value*
Age (</>65 years)	0.926
Sex	0.324
Primary tumor	<0.001
Tomita score	<0.001
Tokuhashi revised score	<0.001
KPS score	<0.001
Preoperative Frankel grading system	0.009
Symptoms	0.18
Vertebral level	0.793
Surgical approach	0.494
Adjuvant therapy	<0.001
Postoperative Frankel grading system	<0.001
Interval between the diagnosis of primary tumor and that of spinal metastasis	0.057
SINS score	0.325
ESCC grade	0.892
Postoperative pain	<0.001

\* $P \leq 0.05$  is statistically significant

## DISCUSSION

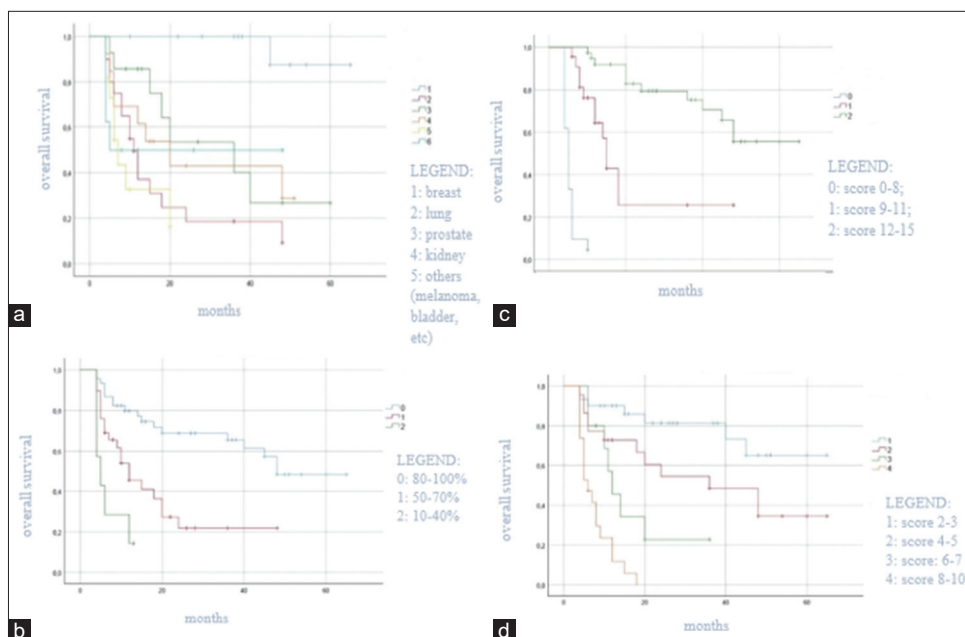
The best treatment of spinal metastases requires an integrated approach with input from a multidisciplinary team comprised medical and radiation oncologists and neurosurgeons. In this regard, a new decision framework NOMS has been developed to tailor the treatment to each patient.<sup>[6]</sup>

In this study, we examined several preoperative factors to identify their prognostic value in patients operated for spinal metastases with the traditional decompression and maximal cytoreduction of the metastatic mass. Recently, a new technique of less aggressive surgery in vertebral metastases is performed by many authors with the name of separation surgery. This technique achieves the circumferential separation of the spinal cord from the tumor mass entrusting the control of the tumor growth to adjuvant therapy.<sup>[9]</sup> This concept shows promising results but further studies are needed cause the greater heterogeneity of RT and chemotherapy protocols adopted by the various oncologic departments. According to the literature and our results, gender and age have no significant relationship with overall survival. Preoperative KPS score was significantly associated with survival in the univariate analysis, in line with several studies that have identified performance status as one of the strongest prognostic factors for overall survival in patients with cancer.<sup>[2,24]</sup> In our study, the primary tumor histology is related to overall survival, as reported in the literature<sup>[5,22]</sup> Particularly, in our study population, breast and prostate cancers had the best survival, whereas colon cancer had the worst one [Figure 1a]. Preoperative KPS score higher than 70% was associated with higher overall survival as shown in

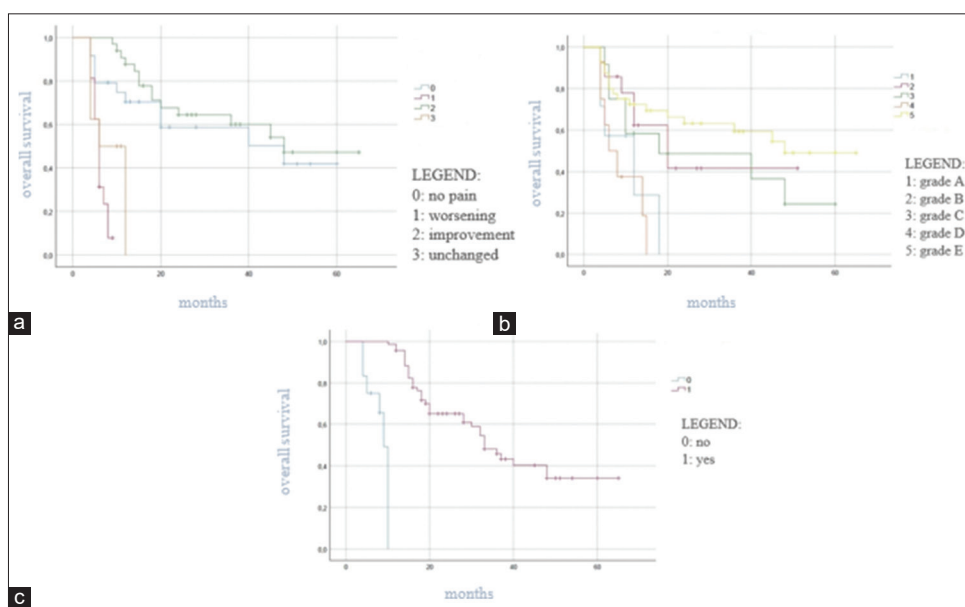
**Table 4:** Multivariate survival analysis (for the multivariate analysis the Cox proportional hazards model was used).

Covariate	SE <sup>§</sup>	95% CI	P-value*
Primary tumor	0.097	0.966–1.413	0.110
Tomita score	0.168	1.559–3.014	<0.001
Tokuhashi revised score	0.285	0.270–0.133	<0.001
KPS score	0.288	1.140–3.522	0.16
Adjuvant therapy	0.397	0.162–0.771	0.019
Postoperative Frankel grading system	0.113	0.861–3.522	0.16
Postoperative pain	0.158	0.778–1.448	0.706

\* $P \leq 0.05$  is statistically significant, <sup>§</sup>SE: Standard error, 95% CI: 95% confidence interval



**Figure 1:** The relationship between patients' overall survival and predictive factors by the Kaplan–Meier.



**Figure 2:** The relationship between patients' overall survival and predictive preoperative factors by the Kaplan–Meier.

Figure 1b. For the prediction of the overall survival in cancer patients, the Tokuhashi revised score and the Tomita score had the most robust validation data in the literature<sup>[14]</sup> but still today, there is a debate regarding the best score to predict survival.<sup>[1,30]</sup> In our study, we found that the Tokuhashi revised and Tomita scores are statistically significant independent prognostic factors in both the univariate and the multivariate analyses for overall survival. Our data confirm that patients

with favorable primary cancers and limited general body extension of disease are the best candidates for surgery with favorable outcome; in fact in our study, the population patients with Tomita score  $\leq 6$  and Tokuhashi revised score  $\geq 8$  had higher overall survival [Figures 1c and d], according to the literature.<sup>[13,17,20]</sup>

Neither the epidural spinal cord compression based on ESCC scale nor the spinal instability defined by SINS score was

statistically correlated with the overall survival in this study. However, the ESCC scale may play a role in early and proper diagnosis of spinal metastases and the SINS score may predict pathological fractures and radiotherapy failure.<sup>[15]</sup> In our results, the interval time between the diagnosis of the primary cancer and the onset of spinal metastases is not related to overall survival, although it was identified as independent prognostic factors in the previous studies.<sup>[5,8]</sup> In fact, other factors such as the burden of the systemic disease and patients' general conditions may be better determinants for overall survival in cancer patients. The postoperative pain improvement and postoperative Frankel Grade E-D-C were statistically associated with the overall survival in the univariate analysis [Figures 2a and b]. These data may be due to the greater chances of access to adjuvant therapy (RT and chemotherapy) and neurorehabilitation program for patients with less pain and better neurological status.<sup>[19]</sup> In our sample, in accordance with the literature that documents the important role of RT to relieve pain, control the metastases bone growth, and prevent pathological fractures,<sup>[7]</sup> patients who received adjuvant therapy (RT and chemotherapy) (85.18%) had longer overall survival when compared with patients who did not [Figure 2]; this finding resulted significant both in the univariate and in the multivariate analyses. As reported in the literature and clinical practice, the type of chemotherapy depends on histology and other tumor characteristics.<sup>[29]</sup> Finally, postoperative complications were treated with good results: CSF leakage with spinal drainage or reoperation; wound infection with the use of antibiotics; and in some cases with the negative wound pressure as reported in the literature.<sup>[9]</sup>

The limits of this study are the retrospective nature design and the single-center cohort with a relatively small population sample size.

## CONCLUSION

The Tomita score, the Tokuhashi revised score, and the adjuvant therapy were statistically significant predictive factors for overall survival. The treatment of spinal metastases should be multifactorial and multidisciplinary, to obtain less operative morbidity and mortality with the maximum effectiveness.

## Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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