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Survival days of patients with metastatic spinal tumors of lung cancer requiring surgery: a prospective multicenter study

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Surgery for metastatic spinal tumors has improved postoperative activities of daily living. A few studies reported on prognostic factors assessed in large multicenter prospective studies for metastatic spinal tumors of lung cancer origin. This study aimed to determine preoperative prognostic factors in patients undergoing surgery for metastatic spinal tumors associated with lung cancer. This prospective registry study included 74 patients diagnosed and operated with metastatic spine tumors derived from lung cancer in 39 high-volume cancer centers. We examined the postoperative survival period and the preoperative factors related to postoperative survival time. We conducted univariate and multivariate Cox regression analyses to determine preoperative prognostic factors. The mean postoperative survival period was 343 days. Multivariate Cox regression analysis revealed a higher feeding score of vitality index, indications for molecularly targeted therapy, and a higher mobility score of Barthel index as independent factors associated with postoperative survival time in metastatic spinal tumors derived from lung cancer. Patients with indications for molecular-targeted therapy and good vitality exhibited longer survival. These results may help in surgical selection for patients with metastatic spinal tumors derived from lung cancer.

Keywords Metastatic spinal tumor, Lung cancer, Postoperative survival period, Barthel index, Vitality index, Molecularly targeted therapy

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Lung cancer is one of the most prevalent cancers globally and is the leading cause of cancer-related death[1]. The spine is the most predominant location of bone metastases, as evidenced in 70% of patients with terminal cancer[2]and is the most prevalent lung cancer site[3]. Metastatic spine tumors derived from lung cancer demonstrate rapid progression, causing an unfavorable prognosis. These patients demonstrated poor prognosis, and the average survival time is less than one year [4,5] with a 2-year survival rate of 3% [6]. However, molecularly targeted and bone-modifying agents have improved the treatment outcomes of lung cancer and lung cancer-derived spinal metastasis[5,7]and survival rates in patients with spinal metastases have increased in the past decade, including lung cancer [8–10]. In surgery, spinal decompression and stabilization are the standard of treatment for patients with unstable spines and neurological disorders[11]. These treatments have improved postoperative ambulation[12]. Therefore, evaluating prognostic factors for the long-term survival of patients with metastatic spinal tumors derived from lung cancer and predicting them preoperatively is important. However, to the best of our knowledge, very few reports focused on the prognostic factors assessed in large, multicenter, and prospective studies. We aimed to determine preoperative prognostic factors in patients undergoing surgery for lung cancer-related metastatic spinal tumors. We hypothesized that once identified, these factors would help plan surgery for metastatic spinal tumors of lung cancer.

Methods

Study design and population

We conducted a prospective observational study to investigate the factors associated with postoperative survival time in patients diagnosed and operated on with metastatic spine tumors derived from lung cancer in a multicenter, including 39 centers. This study enrolled consecutive patients who were diagnosed and operated on with metastatic spine tumors derived from lung cancer from October 2018 to March 2021 and included 74 patients. Patients who are conservative and have many missing data were excluded. The Medical Research Ethics Committee of the Tokyo Medical and Dental University approved this study (Approval number: M2021-144), conducted following the Declaration of Helsinki. Compliance with ethical guidelines was ensured by obtaining written informed consent from all participants, or their legal representatives (when necessary), before enrollment.

Measured data

Data on the following parameters were extracted: age; sex; follow-up period; the number of patients with survival and death; chemotherapy; radiation therapy; use of molecularly targeted therapy; indications for molecularly targeted therapy; bone-modifying agents, and opioid; histological classification of the tumors; operation data, including emergency or elective, operation time, amount of bleeding, and perioperative complication; revised Tokuhashi score[13]; Tomita score[14]; Sin score[15]; Frankel classification[16]; performance status[17]; Barthel index (BI)[18]; vitality index (VI)[19]; visual analog scale (VAS); face scale; and EuroQol 5 dimensions 5-level (EQ-5D-5 L)[20]. Revised Tokuhashi score, Tomita score, BI, VI, and EQ-5D-5 L were assessed for each score. The face pain rating scale[21] was evaluated on a 10-point scale.

Statistical analysis

We analyzed the postoperative survival period. We first conducted a univariate Cox regression analysis to determine factors associated with the survival period. The multivariate Cox regression analysis included factors with p-values of <0.05 in the univariate analysis as candidates for independent factors associated with the survival period[22,23]. We considered surgery factors inappropriate for determining preoperative factors and excluded them. Finally, a backward elimination method was utilized to construct the final multivariate Cox regression model, retaining only variables with a p-value of <0.05. JMP software version 12 (SAS Institute, Cary, North Carolina, USA) was used for all statistical analyses, and a p-value of <0.05 was considered statistically significant.

Results

Patient demographics

The study population included 49 men and 25 women. The mean age at the first visit was 72 (standard deviation [SD], 37) years. The mean follow up period was 257 (SD: 190) days. A total of 42 patients reported survival and 32 patients passed away (Table 1). The mean survival period was 343 days, and the survival rate at 6 months and 1 year postoperatively was 73.1% and 56.3%, respectively (Fig. 1). The distribution of tumor histology is as follows: adenocarcinoma (71%), squamous cell carcinoma (15%), small cell carcinoma (7%), and non-small cell carcinoma (7%).

Identification of factors associated with the postoperative survival period

Univariate Cox regression analysis revealed that the survival period was associated with indications for molecular-targeted therapy ($p=0.009$), operation time ($p=0.003$), perioperative complication ($p=0.018$),

Characteristics	*N* = 74
Age, years	71.6 ± 36.7
Sex male/female	49 (66) / 25 (34)
Followup period, day	257 ± 190
survival/death	42 (57)/32 (43)

Table 1. Baseline characteristics of demographic data. Data are presented as mean ± standard deviation or n (%).

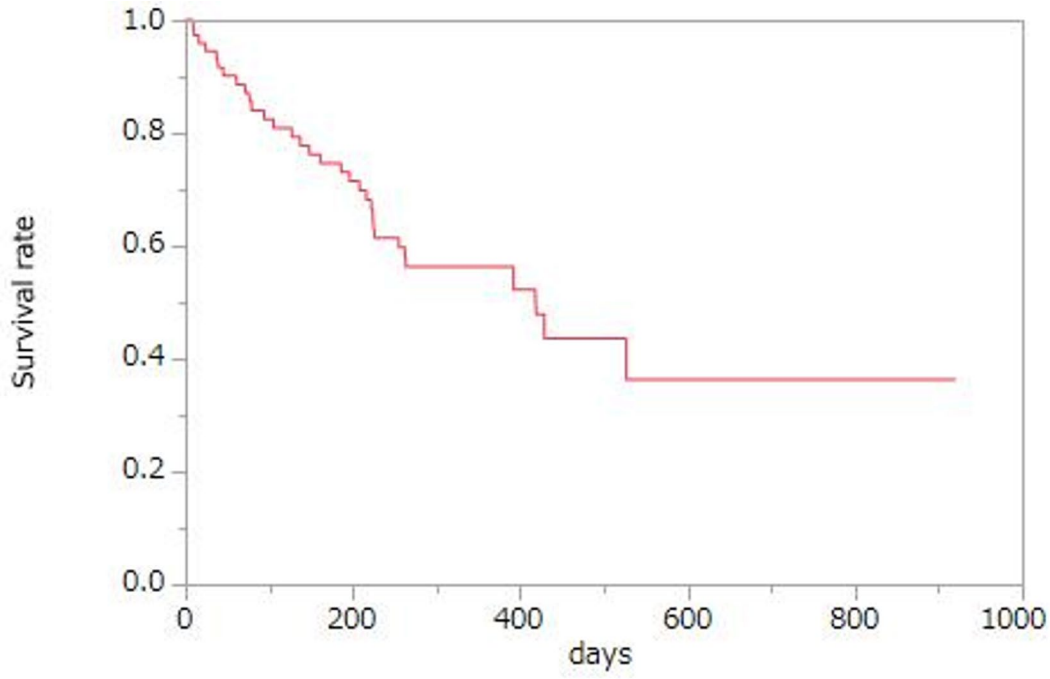

Fig. 1. Kaplane–Meier survival curve showing postoperative survival rate. The mean survival period was 343 days, and the survival rate at 6 months and 1 year postoperative was 73.1% and 56.3%, respectively.

general condition of revised Tokuhashi score ($p = 0.006$), visceral mets of Tomita score ($p = 0.040$), Frankel classification ($p < 0.001$), performance status ($p = 0.027$), BI: feeding ($p = 0.037$), BI: transfers ($p = 0.038$), BI: toilet use ($p = 0.023$), BI: bathing ($p = 0.007$), BI: mobility ($p = 0.004$), BI: stairs ($p = 0.021$), BI: total points ($p = 0.012$), VI: feeding ($p = 0.011$), VI: rehabilitation and other activities ($p = 0.002$), VI: total points ($p = 0.012$), VAS score ($p = 0.003$), face scale ($p = 0.002$), EQ-5D-5 L: mobility ($p = 0.025$), EQ-5D-5 L: usual activities ($p = 0.013$), and EQ-5D-5 L: pain/discomfort ($p = 0.013$) (Tables 2 and 3).

We investigated independent factors associated with the postoperative survival period by conducting a multivariate Cox regression analysis. We utilized a backward elimination method to establish the final multivariate model. As a result, indications for molecularly targeted therapy (hazard ratio [HR] = 0.250, 95% confidence interval [CI]: 0.101–0.573, $p < 0.001$), mobility of BI (HR = 0.890, 95% CI: 0.816–0.961, $p = 0.002$), and feeding of VI (HR = 0.231, 95% CI: 0.097–0.587, $p = 0.003$) were determined as the independent factors associated with the postoperative survival period (Table 4). Judging from the HRs of the final model, molecular-targeted therapy indications, a higher mobility score of BI, and a higher feeding score of VI were significantly associated with a longer postoperative survival period.

Discussion

This study investigated the factors related to the postoperative survival period in patients diagnosed and operated on with metastatic spine tumors derived from lung cancer. Patients with molecular-targeted therapy, high mobility scores of BI, and high feeding scores of VI had long postoperative survival periods. Previous studies revealed that good performance status[24] and molecularly targeted therapy[25] were associated with long survival in patients with lung cancer. However, this is the first report to assess prognostic factors in patients with metastatic spinal tumors derived from lung cancer in a large multicenter prospective study.

In VI, feeding was independently associated with postoperative survival period. Furthermore, univariate Cox regression analysis revealed that rehabilitation and other activities and total points were significantly associated with postoperative survival period. Previous studies revealed that 36-Item Short-Form Health Survey (SF-

Characteristics	HR	95% CI	*P*
Sex male/female	1.458	0.681–3.477	0.34
Age, years	1.002	0.994–1.007	0.51
Preoperative chemotherapy	1.767	0.860–3.560	0.12
Preoperative radiation therapy	1.004	0.437–2.117	0.99
Preoperative use of molecular-targeted therapy	0.773	0.307–1.705	0.54
Indications for molecular-targeted therapy	0.368	0.163–0.785	0.009*
Preoperative use of bone-modifying agents	0.554	0.221–1.219	0.15
Preoperative use of opioid	1.464	0.723–2.967	0.29
adenocarcinoma	0.751	0.359–1.633	0.46
squamous cell carcinoma	0.583	0.168–1.541	0.30
small cell carcinoma	2.710	0.788–7.097	0.10
emergency/elective surgery	1.330	0.640–2.678	0.44
Operation time	0.992	0.988–0.998	0.003*
Amount of bleeding	0.999	0.997–1.000	0.18
Perioperative complication	2.797	1.212–5.935	0.018*

Table 2. Univariate Cox regression analysis of demographic and treatment data. *$P < 0.05$. CI: confidence intervals; HR: hazard ratio.

36) vitality was associated with improved survival in patients who underwent hyperthermic intraperitoneal chemotherapy for peritoneal metastases[26]and mental Health-related quality of life (HRQoL) was related to improved survival in patients with bladder[27]lung, and colorectal cancer[28]. VI was first reported as a new objective scale to measure vitality associated with activities of daily living in elderly patients with dementia[19] and influences patient survival rates [19,29]. To the best of our knowledge, this study is the first to determine feeding, rehabilitation and other activities, and total points of VI as factors associated with the postoperative survival period in metastatic spinal tumors derived from lung cancer. Interestingly, only VI: feeding was determined as an independent factor. The prevalence of malnutrition in patients with spinal metastases is approximately 50–90%[30,31], but nutritional status seems to be remarkably associated with mortality after metastatic spinal tumor surgery[32,33]. Therefore, motivation for feeding seems particularly important, considering that BI: feeding is associated with survival period in univariate Cox regression analysis. Nutritional intervention is recommended to increase oral intake in patients with cancer who can eat but are malnourished or at risk of malnutrition in the ESPEN practical guideline[34]. Interventions to increase dietary motivation, in addition to preoperative nutritional interventions, may be useful for surgical patients with metastatic spinal tumors.

We revealed that indications for molecularly targeted therapy were independently associated with postoperative survival period. Molecular-targeted therapy is administered to improve survival in patients with nonsmall cell lung cancer and applied to an appropriately selected population, which has been more effective and better tolerated than conventional chemotherapy[25]. The survival periods increased and activities of daily living improved after the introduction of molecular-targeted therapy and bone-modifying agents as sufficient treatments for lung cancer-derived metastatic spine tumors[5]. While our findings regarding the prognostic significance of factors like indications for molecularly targeted therapy are consistent with previous reports, our study provides novel insights. Specifically, this is the first large multicenter prospective study to identify the prognostic significance factor of longer postoperative survival in patients undergoing surgery for metastatic spinal tumors derived from lung cancer. Interestingly, preoperative uses of molecular-targeted therapy and bone-modifying agents were not associated with postoperative survival period. Further study with a larger sample size may be warranted.

In BI, mobility was independently associated with postoperative survival period. Furthermore, univariate Cox regression analysis revealed that feeding, transfers, toilet use, bathing, stairs, and total points were significantly associated with postoperative survival period. Previous studies revealed that BI improved in patients who underwent surgery for metastatic spinal tumors [35,36]. Another study demonstrated that high BI exhibits a positive effect on overall survival and long-term survival may be achieved by rehabilitation interventions to maintain or improve ADL before they decline[37]. Skeletal-related events are significantly correlated with immobilization, loss of independence, poor quality of life, and reduced survival[38]. We revealed that BI, especially mobility was associated with postoperative survival period in metastatic spinal tumors related to lung cancer. These patients demonstrated poor prognoses[4–6]. However, considering that rehabilitation and other activities of VI are also important factors in long-term survival, rehabilitation intervention, and motivation are crucial and should be performed as early as possible.

This study has several limitations. First, the data were obtained from a multicenter, and indications for surgery depend on the judgment of each institution. Second, our sample size was relatively small. However, this is a prospective study, with almost no missing values, and significant differences were revealed.

Characteristics		HR	95% CI	*P*
Revised Tokuhashi score	General condition	0.581	0.381–0.857	0.006*
	Number of extraspinal bone metastases foci	0.885	0.596–1.343	0.55
	Number of metastases in the vertebral body	1.375	0.887–2.128	0.15
	Metastases to the major internal organs	0.775	0.514–1.133	0.19
	Spinal cord palsy	0.582	0.288–1.145	0.12
	Total points	0.865	0.726–1.016	0.079
Tomita score	Primary tumor	0.866	0.590–1.398	0.52
	Visceral mets	1.252	1.011–1.569	0.040*
	Bone mets	1.541	0.740–3.399	0.25
	Total points	1.218	1.000–1.495	0.05
Sin score		1.013	0.890–1.162	0.85
Frankel classification		0.755	0.511–1.129	< 0.001*
Performance Status		1.334	1.033–1.763	0.027*
Barthel Index	Feeding	0.895	0.817–0.993	0.037*
	Transfers	0.940	0.886–0.997	0.038*
	Grooming	0.909	0.789–1.058	0.21
	Toilet use	0.905	0.830–0.986	0.023*
	Bathing	0.807	0.671–0.945	0.007*
	Mobility	0.916	0.856–0.973	0.004*
	Stairs	0.904	0.817–0.986	0.021*
	Dressing	0.932	0.853–1.019	0.12
	Bowels	0.945	0.871–1.034	0.21
	Bladder	0.932	0.859–1.018	0.11
	Total points	0.986	0.976–0.997	0.012*
Vitality Index	Waking pattern	0.648	0.293–1.635	0.33
	Communication	0.704	0.328–1.682	0.41
	Feeding	0.331	0.157–0.762	0.011*
	On and off toilet	0.519	0.227–1.400	0.18
	Rehabilitation and other activities	0.407	0.247–0.706	0.002*
	Total points	0.761	0.630–0.938	0.012*
VAS score		1.021	1.006–1.037	0.003*
Face Scale		1.231	1.073–1.435	0.002*
EQ-5D-5 L	Mobility	1.312	1.0328–1.736	0.025*
	Self-care	1.228	0.971–1.578	0.087
	Usual activities	1.424	1.072–1.982	0.013*
	Pain/Discomfort	1.484	1.084–2.081	0.013*
	Anxiety/Depression	1.325	0.940–1.882	0.11
	Health status	0.985	0.968–1.001	0.071

Table 3. Univariate Cox regression analysis of prognostic factor and health status. *$P < 0.05$. CI: confidence intervals; EQ-5D-5 L: EuroQol 5 dimensions 5-level; HR: hazard ratio; VAS: visual analog scale.

Characteristics	HR	95% CI	*P*
Indications for molecularly targeted therapy	0.250	0.101–0.573	< 0.001*
Barthel Index Mobility	0.890	0.816–0.961	0.002*
Vitality index Feeding	0.231	0.097–0.587	0.003*

Table 4. Multivariate Cox regression analysis. *$P < 0.05$. CI: confidence intervals; HR: hazard ratio.

Conclusions

In conclusion, the present study revealed that molecular-targeted therapy indications, a higher mobility score of BI, and a higher feeding score of VI were significantly associated with postoperative survival period in metastatic spinal tumors derived from lung cancer. These factors are useful when making surgical decisions.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions
T.T. and T.H. conceived and designed the study. All authors collected the data. T.T. and T.H. prepared the manuscript, and all authors reviewed and edited the manuscript. All authors approved the final manuscript.

Declarations

Competing interests
The authors declare no competing interests.

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