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Original Article

Statistical Analysis of Prognostic Factors for Survival in Patients with Spinal Metastasis

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There are a variety of treatment options for patients with spinal metastasis, and predicting prognosis is essential for selecting the proper treatment. The purpose of the present study was to identify the significant prognostic factors for the survival of patients with spinal metastasis. We retrospectively reviewed 143 patients with spinal metastasis. The median age was 61 years. Eleven factors reported previously were analyzed using the Cox proportional hazards model: gender, age, performance status, neurological deficits, pain, type of primary tumor, metastasis to major organs, previous chemotherapy, disease-free interval before spinal metastasis, multiple spinal metastases, and extra-spinal bone metastasis. The average survival of study patients after the first visit to our clinic was 22 months. Multivariate survival analysis demonstrated that type of primary tumor (hazard ratio [HR] = 6.80, $p < 0.001$), metastasis to major organs (HR = 2.01, $p = 0.005$), disease-free interval before spinal metastasis (HR = 1.77, $p = 0.028$), and extra-spinal bone metastasis (HR = 1.75, $p = 0.017$) were significant prognostic factors. Type of primary tumor was the most powerful prognostic factor. Other prognostic factors may differ among the types of primary tumor and may also be closely associated with primary disease activity. Further analysis of factors predicting prognosis should be conducted with respect to each type of primary tumor to help accurately predict prognosis.

Key words: spine, metastasis, survival, prognostic factor, cancer

Spinal metastasis occurs in 30–60% of patients with cancer [1–3], and can result in poor prognosis [4]. There are a variety of options for the treatment of spinal metastasis. Some patients are treated non-surgically by radiotherapy or chemotherapy [5], while others undergo surgical treatments such as posterior decompression with or without instrumentation [6, 7]. Recently, the more radical operation of total en-bloc spondylectomy has been applied, with the aim of complete local control of spinal metastasis [8]. It is difficult to select the proper treatment option for patients with spinal metastasis, and predicting survival is the key factor in the selection of the best option. Many studies have been conducted on the biological characteristics of cancers or the treatment modalities that might affect the prognosis of patients with metastasis [4, 5, 9–11]. Various scoring systems for spinal metastasis have also been proposed for predicting survival and selecting the ideal treatment modality [6, 7, 12,

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13]. Although these scoring systems can be useful in predicting prognosis and deciding on proper treatment, there have been few reports using multivariate survival analysis to assess the significant prognostic factors for patients with spinal metastasis.

In this study, we analyzed the clinical features of patients with spinal metastasis who were referred to our clinic, and determined significant prognostic factors for survival using the Cox proportional hazards model.

Patients and Methods

We analyzed 143 patients with spinal metastasis originating from various cancers and sarcomas who were referred to the Department of Orthopaedic Surgery of Okayama University Hospital and Okayama Medical Center between January 1990 and December 2008. Detailed information regarding each patient's characteristics and clinical signs and symptoms were entered on an initial evaluation form. There were 91 males and 52 females. The median age was 61 years (range, 4 to 83 years). The mean follow-up period was 21 months (range, 1 to 127 months). The types of primary tumor for the 143 patients, including of 33 lung cancers, 18 prostate cancers, 14 breast cancers, and other types of cancer, are presented in Table 1. Lung, prostate, and breast cancers accounted for 46% of the total number of primary tumors in all patients.

Table 1 The primary tumors in the 143 patients

Primary lesion	Number of patients
Lung cancer	33
Prostate cancer	18
Breast cancer	14
Endometrial, cervical, ovarian, and uterine cancer	12
Renal cell cancer	10
Thyroid cancer	8
Bladder cancer	6
Colon and rectal cancer	6
Hepatocellular cancer	5
Stomach cancer	5
Bone and soft tissue sarcoma	4
Others	19
Unknown origin	3
Total	143

To localize spinal metastasis, imaging such as radiography, computed tomography (CT), and/or magnetic resonance imaging (MRI) was performed first on the symptomatic spinal level related to back pain and/or spinal cord injury. Patients with spinal metastasis then underwent systemic imaging assessment using bone scintigraphy, MRI on the entire spinal column, and/or whole-body CT.

The treatment strategy for the spinal metastasis was thoroughly discussed with the medical oncologists who took primary care of the patients, especially focusing on the patients' general condition and prognosis. Surgery was considered mainly based on the severity of intractable pain, neurological status, and/or spinal instability (Table 2). Seventy-two surgeries were performed, including 55 laminectomies and posterior stabilizations, 10 combined anterior and posterior fusions, 4 total en-bloc spondylectomies, and 3 anterior fusions only. Total en-bloc spondylectomies were performed for 2 patients with thyroid cancer, 1 with renal cancer, and 1 with prostate cancer.

Eleven prognostic factors were investigated (Table 3). Each factor was grouped in up to 3 categories for statistical analysis. Age was categorized into groups of younger than 60 years and 60 years or older [13]. Performance status (PS), assessed by the Eastern Cooperative Oncology Group (ECOG) PS scale [14], was categorized into 2 groups of PS 0 to 2 and 3 to 4. Neurological deficit was assessed using the Frankel classification of spinal cord injury; grade A: complete neurological injury, B: preserved sensation only, C: preserved motor non-functional, D: preserved motor function, E: normal motor [15]. Neurological deficit was divided into 2 categories, Frankel grades A to C and D to E. Type of primary

Table 2 Treatment

Treatment	n
Surgery + Chemotherapy + Radiotherapy	18
Surgery + Radiotherapy	20
Surgery + Chemotherapy	16
Surgery	18
Chemotherapy + Radiotherapy	38
Chemotherapy	19
Radiotherapy	8
Palliative	6
Total	143

Table 3 Distribution of potentially prognostic factors in the 143 patients

	n
Patient-related factor	
Gender	
Male	91
Female	52
Age (yrs)	
<60	89
≧60	54
Performance status	
PS 0 to 2	99
PS 3 to 4	44
Neurological deficits	
ABC	47
DE	96
Pain	
No	39
Yes	104
Primary site-related factor	
Type of primary tumor	
Slow: Breast, prostate, thyroid	39
Moderate: Other cancer and sarcoma	49
Rapid: lung, bladder, liver, colon, stomach	55
Metastasis to major organs	
No	120
Yes	23
Previous chemotherapy	
No	68
Yes	75
Skeletal metastasis-related factor	
Disease-free interval before spinal metastasis	
<12 months	85
≧12 months	58
Multiple spinal metastasis	
No	58
Yes	85
Extra-spinal bone metastasis	
No	112
Yes	31

tumor was divided into 3 groups according to growth rate of the primary disease of the Tomita classification: breast, prostate, and thyroid cancer as slow growth, other cancer and sarcoma as moderate growth, and lung, bladder, liver, colon, and stomach cancer as rapid growth [7]. Previous chemotherapy for primary cancer was classified as a primary-site related factor [13]. Disease-free interval before spinal metastasis was divided into 2 categories, less than 12 months and 12 months or more, and was classified as a skeletal metastasis-related factor [13].

A Kaplan-Meier actuarial survival curve was created using the first visit date as the starting point of follow-up. Univariate analysis was performed using a log-rank test [16]. The Cox proportional hazards model was used for the multivariate analysis. Evaluation of the effect of multiple variables on the survival of patients was carried out using a stepwise proportional hazard analysis. In all analyses, p values of less than 0.05 were considered to be statistically significant. The software program StatView version 5.0 (SAS Institute Inc, Cary, NC, USA) was used for all analyses.

Results

At the last follow-up, 14 patients (10%) were still alive. The average survival of all patients was 22 months, ranging from 1 to 127 months. One hundred and four patients complained of pain in connection with their spinal metastasis and required daily analgesics and/or narcotics. At the first physical examination, 45 patients could not walk due to muscle weakness. According to the Frankel classification, 4 patients were classified as grade A, 7 as grade B, 36 as grade C, 34 as grade D, and 62 as grade E. Twenty-three patients had metastasis to major organs at the time of diagnosis of spinal metastasis: lung (11 patients), liver (10), brain (2), and kidney (1). One patient showed metastasis to both the liver and brain.

Thirty-seven patients (26%) presented with spinal metastasis at the time of the primary diagnosis of cancer. Forty-eight patients (34%) were diagnosed with spinal metastasis less than 12 months after the primary diagnosis of cancer, and 58 patients (40%) were diagnosed at 12 months or longer after the primary diagnosis of cancer. Imaging assessment revealed that 85 patients had multiple (2 or more) spinal metastases: 2 spinal metastases in 30 patients, 3 metastases in 10 patients, and more than 4 metastases in 45 patients. Multiple spinal metastases were seen in 80% of the patients with spinal metastasis of breast cancer, 69% of the patients with prostate cancer, and 67% of the patients with bladder cancer. Thirty-one patients had bone metastasis not only to the spine but also to other bones in the extremities or trunk.

Univariate survival analysis demonstrated that type of primary tumor (Fig. 1A), metastasis to major organs (Fig. 1B), disease-free interval before spinal

metastasis (Fig. 1C), and pain with spinal metastasis were statistically significant prognostic factors for patients with spinal metastasis (Table 4). Multivariate survival analysis showed that type of primary tumor (HR = 6.80 and 1.80, $p < 0.001$), metastasis to major organs (HR = 2.01, $p = 0.005$), disease-free interval before spinal metastasis (HR = 1.77, $p = 0.028$), and extra-spinal bone metastasis (HR = 1.75, $p = 0.017$) were significant prognostic factors (Table 5).

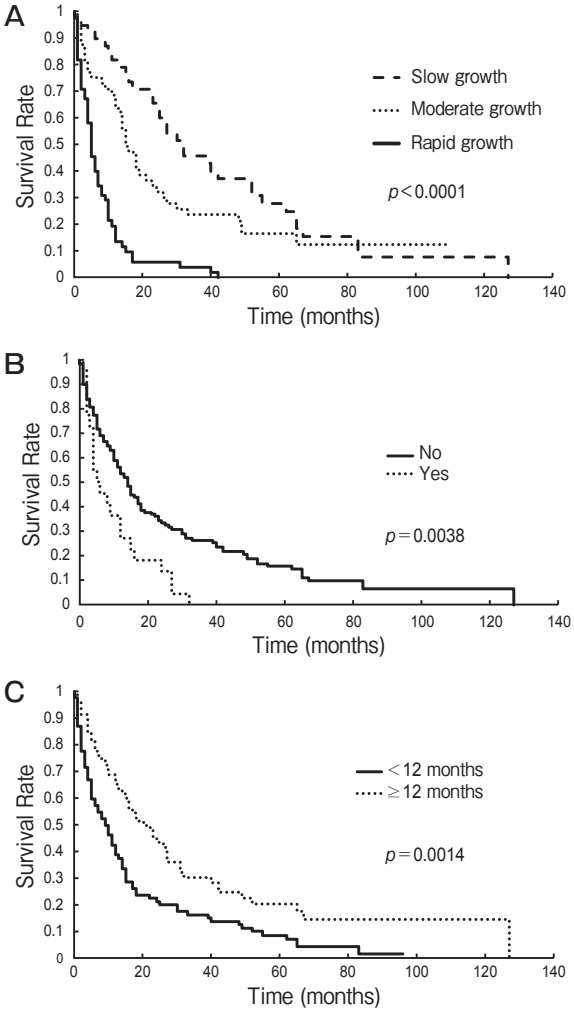

Fig. 1 Survival curves for prognostic factors in 143 patients with spinal metastasis. A, Type of primary tumor. Slow growth: breast, prostate, and thyroid cancer; Moderate growth: other cancer and sarcoma; Rapid growth: lung, bladder, liver, colon, and stomach cancer; B, Survival curves for metastasis to major organs; C, Survival curves for disease-free interval before spinal metastasis.

Discussion

Several investigators have discussed the prognostic factors for patients with spinal metastasis, and various prognostic factors have been reported as statistically significant for survival [5, 13, 17–26]. Stoll stated that the prognostic factors for a given patient could be discovered from the patient's disease history and clinical findings [4]. Several scoring assessment systems have been formulated for predicting survival and deciding on the proper treatment modality [6, 7, 12, 13]. Although scoring systems can be useful clinically, few clinicians have used multivariate analysis to analyze the statistical independence of each prognostic factor. We studied 11 factors used as components of the Tokuhashi score, the Tomita score, and the Katagiri score, and analyzed them using the Cox proportional hazards model. Our multivariate analysis of all the patients with spinal metastasis referred to our clinic identified four variables—type of primary tumor, metastasis to major organs, disease-free interval before spinal metastasis, and extra-spinal bone metastasis—as significant prognostic factors for survival.

The Tokuhashi score consists of the sum of 6 parameters. However, three of those—general condition as assessed by PS, the number of metastases in the vertebral body, and the Frankel grade—were not identified as statistically significant prognostic factors in the present study. Previous papers also demonstrated that these were less significant factors [5, 25]. Van der Linden also proposed a scoring system for patients with spinal metastasis based on multivariate analysis [27]. However, since the scores were originally developed through analysis of patients with painful spinal metastases without neurologic impairment, assessment according to the van der Linden score could be limited to such patients. The Tomita score and the Bauer score are similar assessment systems for spinal metastasis, composed of primary tumor, visceral metastasis, and number of bone metastases, since pathological fracture, as one of Bauer's variables, was evident only in the patients with metastasis in the extremities [7, 12]. Multivariate analysis in our series also showed that these 3 prognostic factors were statistically significant. Leithner *et al.* evaluated the differences between the Tomita and Bauer scoring systems for 69 patients

Table 4 Univariate analysis of prognostic factors

Variables	Hazard Ratio	95% CI	*p* value
Sex			
Male			
Female	0.505	0.346–0.737	0.0004
Age			
<60			
≧60	0.9	0.618–1.309	0.5811
Performance status			
3 to 4			
0 to 2	1.072	0.729–1.574	0.7247
Neurological deficits			
DE			
ABC	1.056	0.727–1.534	0.7732
Pain			
No			
Yes	1.531	1.018–2.304	0.0406
Type of primary tumor			
Slow			
Moderate	1.502	0.940–2.399	<0.0001
Rapid	5.013	3.083–8.150	<0.0001
Metastasis to major organs			
No			
Yes	2.012	1.251–3.236	0.0038
Previous chemotherapy			
No			
Yes	0.743	0.523–1.054	0.0963
Disease-free interval before spinal metastasis			
≧12 months			
<12 months	1.815	1.259–2.614	0.0014
Multiple spinal metastasis			
No			
Yes	1.002	0.702–1.429	0.992
Extra-spinal bone metastasis			
No			
Yes	1.076	0.71–1.631	0.7296

CI, confidence interval.

Table 5 Multivariate analysis of prognostic factors

Variables	Hazard Ratio	95% CI	*p* value
Type of primary tumor			
Slow			
Moderate	1.797	1.12–3.39	<0.001
Rapid	6.802	3.62–11.5	<0.001
Metastases to major organs			
No			
Yes	2.01	1.09–2.95	0.0051
Disease-free interval before spinal metastasis			
≧12 months			
<12 months	1.77	1.02–2.34	0.028
Extra-spinal bone metastases			
No			
Yes	1.75	1.04–2.79	0.0171

CI, confidence interval.

with spinal metastasis and showed that the Bauer score was a practical and highly predictive preoperative scoring system [25]. The Bauer score was based on multivariate analysis for several prognostic values and could be suitable for predicting prognosis.

Some authors have reported that metastasis to major organs was the significant prognostic factor for survival of patients with spinal metastasis [5–7, 13, 17, 21]. In particular, Yamashita *et al.* stated that metastasis to the major organs in patients with breast cancer affected the prognosis, rather than the extent of the spread of bone metastasis [9]. The disease-free interval before the occurrence of spinal metastasis was also reported as a prognostic factor [18, 20, 28, 29]. In our series, the patients with a disease-free interval longer than 12 months before the discovery of spinal metastasis were the patients who mainly had primary tumors with slow growth, such as thyroid and breast cancer. The disease-free interval before the occurrence of spinal metastasis might reflect the activity of the primary disease, indicating that a long interval could be a sign of low activity of the disease, thereby portending a probable long survival after spinal metastasis [18].

Extra-spinal bone metastasis seemed to be a less significant prognostic factor [9, 13, 23, 25]. Katagiri *et al.* studied the locations of skeletal metastasis for patients with bone metastasis and found that the grouping of the skeletal metastases according to site was not significantly associated with survival [13]. However, in patients with breast cancer, Yamashita *et al.* showed that widespread distribution of bone metastasis was the prognostic factor [9]. Rigaud *et al.* also demonstrated that patients with axial metastasis had a better prognosis than that of patients with appendicular metastasis in cases of prostate cancer [24]. Our univariate analysis identified extra-spinal bone metastasis as a less significant prognostic factor for survival. However, our multivariate analysis demonstrated that extra-spinal bone metastasis was one of the significant prognostic factors. The reason might be that the type of primary tumor could be a very strong prognostic factor and univariate analysis might be unable to identify its significance.

Tokuhashi *et al.* reported that the average survival rates for patients with spinal metastasis of stomach and lung cancer were statistically shorter than the survival rates of patients with thyroid, prostate, breast, and rectal cancer [6]. Many authors have also shown that the site of the primary tumor was the statistically significant factor in predicting prognosis [5, 13, 17–26]. In the present study, type of primary tumor was identified as the most powerful prognostic factor for patients with spinal metastasis. Other prognostic factors identified in the present study can differ among types of primary tumor and may also be closely associated with the activity of the primary disease. Further survival analysis with regard to each primary tumor may lead to predicting prognosis more accurately for patients with spinal metastasis.

There were some limitations in the present study. Patients referred to our clinic underwent various previous treatments, and the treatment strategies for primary cancer might have been different among the referring hospitals. Treatment of spinal metastasis also varied in our series; especially, surgical treatments were different among 2 hospitals. Treatment modality for spinal metastasis might affect patient survival. Cancers arising from a single organ, such as lung cancer and breast cancer, have different histological subtypes as well as biological activities. Furthermore, in the treatment of some types of cancer, recent advances, such as molecular-targeted drugs, have dramatically changed the patients' prognosis [30, 31]. These subtypes may have to be carefully considered when assessing the survival of patients with spinal metastasis.

In conclusion, the data of the present study identified the preoperative factors of type of primary tumor, metastasis to major organs, disease-free interval before spinal metastasis, and extra-spinal bone metastasis as independent prognostic factors for survival in patients with spinal metastasis. Although the type of primary tumor was the most significant prognostic factor, further analysis of factors predicting prognosis should be conducted with respect to each type of primary tumor.

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