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Survival outcomes and prognostic factors of breast cancer spinal metastases: a retrospective study

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Abstract

Purpose To investigate survival-related factors in patients with breast cancer spinal metastases (BCSM) within the context of multidisciplinary treatment.

Methods A retrospective cohort of 78 cases from July 2010 to December 2021 was recruited. These patients underwent surgery-based multidisciplinary treatment. Collected data included demographics, pathologies, symptoms, surgery-related data, adjuvant therapies, postoperative events, and survival data. The primary outcome was overall survival (OS). Kaplan–Meier survival curves were plotted. Univariate analysis employed the log-rank test, and post-hoc multivariate analysis utilized the Cox regression model.

Results The mean age was 50.9 years. 72 cases (92.3%) reported locoregional pain, and 30 cases (38.5%) presented with neurological dysfunction. The primary pathological subtype was invasive ductal carcinoma (83.3%). Surgical procedures: total *en-bloc* spondylectomy (6.4%), debulking surgery (61.5%), palliative surgery (32.1%). Postoperatively, both pain and neurological function significantly improved ($P < 0.05$). Radiotherapy, endocrine therapy, chemotherapy/targeted therapy were given to 56.4%, 60.3%, 61.5% patients, respectively. The estimated OS was 50.0 months. Tomita's scores ($P = 0.355$) and Tokuhashi's scores ($P = 0.461$) showed no significant OS association. Univariate analysis indicated that preoperative neurological dysfunction ($P = 0.003$), postoperative neurological dysfunction ($P = 0.051$), adjuvant endocrine therapy ($P = 0.025$), and hormone receptor expression status ($P = 0.009$) were associated with patient survival. Multivariate analysis identified endocrine therapy as an independent protective factor for prognosis (aHR = 0.070, 95% CI 0.007–0.727, $P = 0.026$).

Conclusions Patients with BCSM have experienced prolonged survival. Neurological status, adjuvant anti-drugs, and expression of hormone receptors played crucial roles in predicting survival. Conventional prognostic systems may require modification to incorporate these factors. However, this study has limitations inherent to its retrospective design, single-center cohort, and relatively small sample size, which may affect generalizability.

Keywords Spinal metastasis · Breast cancer · Surgery · Survival · Prognostic analysis

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1 Introduction

Breast cancer stands as the most prevalent malignancy among women, and spinal metastasis commonly manifests in the advanced stages of the disease [1, 2]. Breast cancer spinal metastases (BCSM) often lead to severe skeletal-related events (SRE), such as vertebral fractures and paralysis [3]. Management typically involves a multidisciplinary approach, encompassing endocrine therapy, targeted therapies, radiotherapy, and spine surgery [4]. Surgical interventions, specifically, have demonstrated efficacy in alleviating pain and restoring spinal stability for affected individuals [2, 5]. However, not all patients derive equal benefits from surgical intervention. A comprehensive exploration of prognosis-related factors becomes imperative in determining the appropriateness, timing, and modality of surgery. Previous studies have suggested that age, pathological subtypes, and patients' general conditions may influence survival outcomes [6–8]. Additionally, factors such as visceral involvement, surgical strategies, and neurological status have been recognized as contributors to prognosis [9, 10].

Despite advancements, there remains a dearth of high-level evidence guiding the selection of surgical procedures, the administration of adjuvant therapies, and the customization of treatment regimens. In this study, we retrospectively reviewed a cohort of 78 BCSM cases spanning the past decade, elucidated treatment outcomes, and conducted a thorough survival analysis.

2 Materials and methods

2.1 Patients' inclusion

This retrospective cohort study focused on patients with BCSM who underwent surgery and received adjuvant therapies at our hospital between January 2010 and December 2021. Ethical approval was obtained from our Institutional Ethics Committee, and all patients provided informed consent. Inclusion criteria comprised (1) pathologically confirmed BCSM, (2) initial surgery on spinal metastatic lesions conducted at our center, (3) regular follow-up, and (4) availability of complete clinical data. Exclusion criteria encompassed (1) loss to follow-up, (2) absence of a pathological diagnosis, and (3) concurrent presence of other malignancies.

2.2 Data collection

Clinical records of enrolled patients were thoroughly reviewed. Key data subsets included demographics, details regarding primary breast lesions and treatments, surgical procedures, adjuvant therapies, and follow-up information. The histological subtypes were stratified into two categories based on invasive potential and metastatic behavior: 1) invasive subtype: includes invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), and other conventional invasive variants; and low-invasive subtype: encompasses histological variants with indolent behavior: papillary carcinoma, mucinous adenocarcinoma, and encapsulated papillary carcinoma. Pain levels were assessed using the visual analog scale (VAS). Neurological function was assessed using the American Spinal Injury Association (ASIA) Impairment Scale [11].

Tumor-related details, including treatment of primary breast lesions, history of adjuvant therapy, systemic metastatic sites (lymph nodes, lung, liver, etc.), and the interval time to spinal metastasis, were recorded. Additionally, patients' Karnofsky performance score (KPS), spinal instability neoplastic scores (SINS), and Tomita's [12] and Tokuhashi's [13] prognosis scores were assessed. To systematically evaluate the prognostic impact of surgical strategies in BCSM management, we stratified patients based on intervention radicality, consistent with the NOMS (Neurologic, Oncologic, Mechanical, and Systemic) decision framework [14]. Specifically, we described non-resective interventions as palliative surgery, and cytoreductive interventions as debulking surgery.

The primary outcome of this study was the survival status of patients. We also explored clinical factors associated with patient survival.

2.3 Definition of key terms

1) Neurological dysfunction: defined as impaired ambulatory function corresponding to ASIA Impairment Scale grades A-C.
2) Solitary spinal lesion: presence of a single radiographically confirmed vertebral metastasis, with no concurrent extraspinal bone metastases.
3) Other bone metastases: radiographic evidence of metastatic involvement in non-spinal skeletal sites (e.g., pelvis, ribs, long bones).

2.4 Statistical analysis

Statistical analysis was conducted using SPSS for Windows, version 26.0 (IBM Corp., New York, USA). Categorical variables were presented as n (percentage). The distribution normality of continuous variables was examined using the Shapiro—Wilk test. For variables with a normal distribution, they were presented as mean ± standard deviation (SD), while for those with a non—normal distribution, they were presented as median (inter—quartile range, IQR). Survival was presented as the median value with a 95% confidence interval (CI). Paired Student t-tests were employed for comparisons before and after the operation, while unpaired Student t-tests were used between different groups. Survival analyses followed a two-phase approach [15]. Kaplan–Meier curves were plotted for each covariate, and inter-group differences assessed via log-rank test. Variables with $P < 0.05$ were considered candidate predictors. A Cox proportional hazards regression with backward elimination was performed to identify independent prognostic factors. We displayed the hazard ratio (HR) of each variable along with its 95% CI. Statistical significance was set at $P < 0.05$.

3 Results

3.1 Demographics and clinical features

A total of 78 patients with BCSM were included, with a mean age of 50.9 years (Table 1). Notably, 73.1% of patients had a history of breast surgery with or without adjuvant therapies. The median interval before symptomatic spinal metastasis was 48.0 (78.0) months.

Locoregional pain at spinal metastatic sites was reported by 92.3% of cases, with a median VAS score of 6. Neurological dysfunction symptoms were present in 38.5% of patients. The median KPS was 70 (30). Preoperative imaging revealed 23.1% presenting solitary vertebral lesions, and 24.4% had coexisting visceral metastasis.

3.2 Surgery and adjuvant therapies

Five patients (6.4%) underwent total *en-bloc* spondylectomy (TES), and the median bleeding volume was 2100 (1675) ml. 48 patients (61.5%) underwent debulking surgery, and the median bleeding volume was 400 (638) ml. 25 patients (32.1%) underwent palliative surgery, and the median bleeding volume was 100 (350) ml. Significant differences in bleeding volumes were observed among the three surgical methods ($P < 0.001$).

Post-operation, 56.4% received radiotherapy, 60.3% received endocrine therapy, and 61.5% received chemotherapy and/or targeted treatment. Additionally, 61.5% were administered zoledronic acid or denosumab.

3.3 Pathological subtypes and biomarkers test

Invasive ductal carcinoma was the most prevalent subtype (83.3%). Other subtypes included invasive lobular carcinoma (5.1%), papillary carcinoma (2.6%), and mucous adenocarcinoma (7.7%). Immunohistochemistry tests, including ER, PR, HER-2, and Ki-67 biomarkers, were conducted for 67.9% of patients. Among these patients, there were 2 cases of Luminal A, 1 case of Luminal B, 28 cases of HER2 (+) and 3 cases of triple-negative breast cancer.

Table 1 Demographic and clinical characteristics of the cohort

Items	Values
Age (years), mean ± SD	50.9 ± 11.9
Follow-up (months), median (IQR)	32.0 (40.0)
History of breast surgery, n (%)	57 (73.1%)
Interval time* (months), median (IQR)	48.0 (78.0)
Local pain (VAS score), median (IQR)	6 (2)
Neurological dysfunction, n (%)	30 (38.5%)
Karnofsky performance score, median (IQR)	70 (30)
Involved spinal segments, n (%)	
Cervical	30 (38.5%)
Thoracic	52 (66.7%)
Lumbar	30 (38.5%)
Sacrum	8 (10.3%)
Solidary spinal lesion, n (%)	18 (23.1%)
Systemic metastasis status, n (%)	
Spine only	30 (38.5%)
Other bones	48 (61.5%)
Visceral	19 (24.4%)
Pathological subtypes, n (%)	
Invasive ductal carcinoma	65 (83.3%)
Invasive lobular carcinoma	4 (5.1%)
Papillary carcinoma	2 (2.6%)
Mucous adenocarcinoma	6 (7.7%)
Others	1 (1.3%)
Spinal instability neoplastic scores, n (%)	
Stable (= < 6)	3 (3.9%)
Potentially unstable (7–12)	45 (57.7%)
Unstable (> = 13)	30 (38.5%)
Epidural spinal cord compression grades, n (%)	
No compression (0–1)	35 (48.7%)
Cord compression (2–3)	43 (55.1%)
Tomita's score, n (%)	
2–3	51 (65.4%)
4–5	9 (11.5%)
6–7	18 (23.1%)
Tokuhashi's score, n (%)	
0–8	15 (19.2%)
9–11	25 (32.1%)
12–15	38 (48.7%)
Surgical methods, n (%)	
Total *en-bloc* spondylectomy	5 (6.4%)
Tumor-debulking surgery	48 (61.5%)
Palliative decompression	20 (25.6%)
Percutaneous vertebroplasty	5 (6.4%)
Operation duration (min), median (IQR)	153.5 (113.0)
Estimated blood loss (mL), median (IQR)	350 (588)
Adjuvant therapy after the operation, n (%)	
Radiotherapy	42 (53.8%)
Hormone therapy	47 (60.3%)
Chemotherapy/target therapy	48 (61.5%)
Zoledronic acid or denosumab	48 (61.5%)

SD stands for standard deviation; IQR, inter-quartile range; VAS, visual analogue scale

*This term pertains to the time interval between the initial breast surgery and the subsequent surgery for spinal metastasis

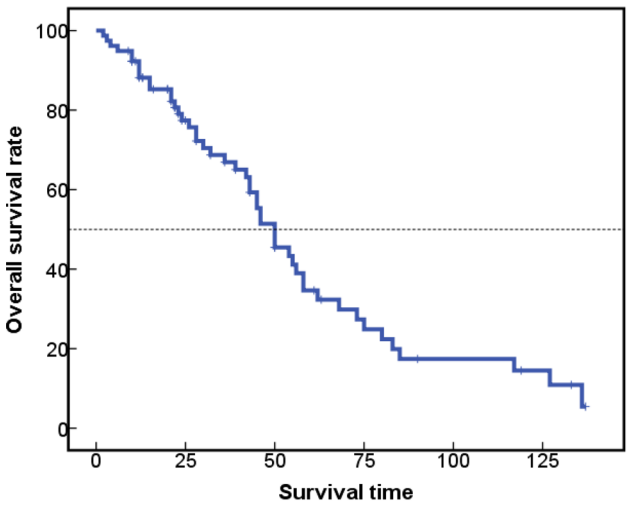


Fig. 1 Kaplan–Meier survival curve of the cohort

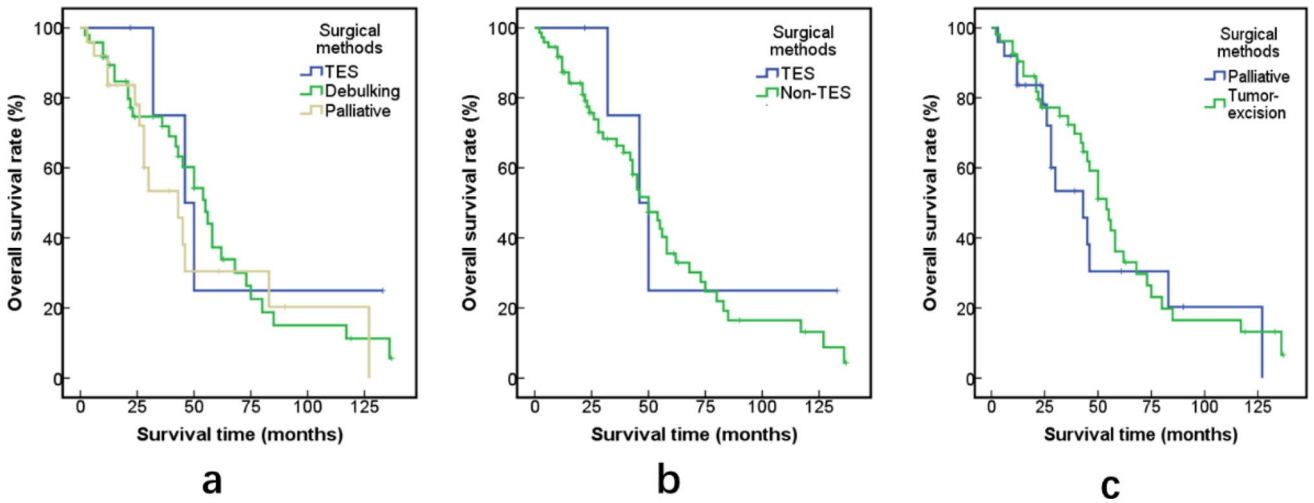


Fig. 2 **a**, Kaplan–Meier survival curves of the subgroups of the three surgical methods; **b**, survival curves of TES subgroup versus non-TES subgroup; **c**, survival curves of palliative subgroup versus tumor-excision subgroup

3.4 Treatment outcomes

Six months post-operation, symptomatic improvement was evident, with a median VAS value of 1 (2) for local pain and a median postoperative KPS of 90 (20), both significantly different from preoperative values ($P < 0.001$). Patients with neurological deficits before surgery showed improvement in ASIA grades, resulting in 79.5% maintaining intact or slightly impaired neurological function (ASIA D and E), while 20.5% were still rated as ASIA A-C grades. Median survival times for the two groups were 50.0 months and 15.0 months, with a marginal difference ($P = 0.051$).

3.5 Survival outcomes and associated factors

The median follow-up time was 32.0 (40.0) months. By the last follow-up, 38.5% of patients survived. Survival rates were 94.9% at 6 months, 92.3% at 12 months, 69.4% at 36 months, and 47.0% at 60 months. Median OS time was 50.0 months (Fig. 1). We conducted the survival analysis of the three surgical methods, and found they had similar survival time ($P = 0.605$, Fig. 2a). Furthermore, TES and non-TES subgroups had similar survival time ($P = 0.0507$, Fig. 2b); tumor-excision and palliative subgroups had similar survival as well ($P = 0.379$, Fig. 2c). The three subgroups of Tomita's scores had

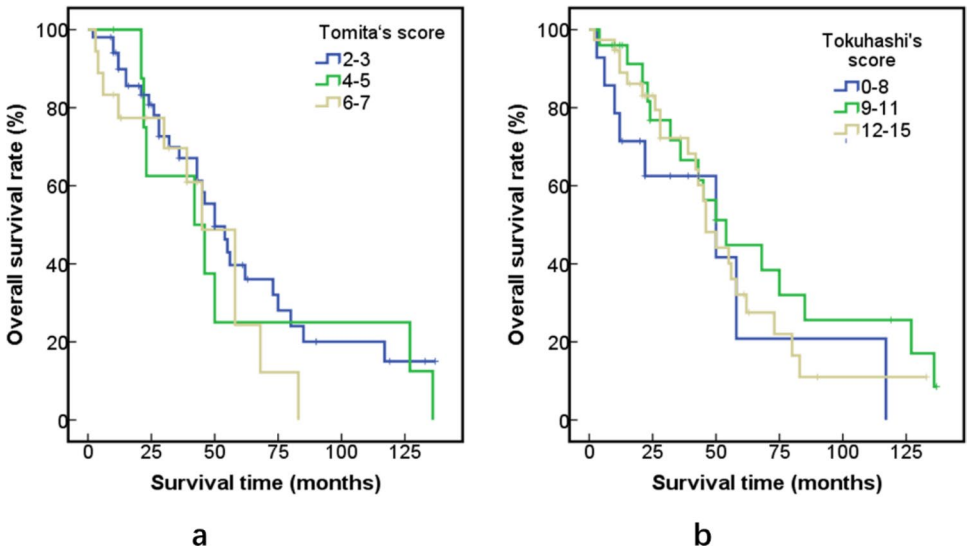


Fig. 3 **a** Kaplan–Meier survival curves of the three subgroups of Tomita's scores; **b** survival curves of the three subgroups of Tokuhashi's scores

similar survival curves ($P=0.355$, Fig. 3a). Besides, the three subgroups of Tokuhashi's scores had similar survival curves ($P=0.461$, Fig. 3b).

Univariate analysis identified preoperative neurological dysfunction ($P=0.003$), postoperative neurological dysfunction ($P=0.051$), adjuvant endocrine therapy ($P=0.025$), and hormone receptors expression status ($P=0.009$) as associated with patient survival (Table 2). Multivariate analysis confirmed endocrine therapy as an independent protective factor for patient prognosis (aHR = 0.070, 95% CI: 0.007–0.727, $P=0.026$) (Table 3).

4 Discussion

In the last three decades, spinal metastasis was traditionally associated with a short life expectancy [16]. Contemporary approaches favor multidisciplinary collaboration, often including surgery, or even radical procedures, for selected patients with BCSM. Apart from pain relief and neurological salvage, surgery facilitates the implementation of adjuvant anti-tumor drugs and high-dose radiotherapy [17]. In our cohort, the median OS time for 78 patients was 50.0 months, with survival rates at 1, 3, and 5 years after BCSM surgery at 92.3%, 69.4%, and 47.0%, respectively. This compares favorably with prior literature reporting a median OS time of 21.7 months and survival rates of 61% at 3 years and 43.3% at 5 years [9, 18].

Generally, we undertook surgical treatment for BCSM patients presenting with: imminent or progressive neurological deficit, pathological fracture and mechanical instability, and intractable pain. Post-surgery, we observed significant improvements in KPS score, VAS, and ASIA score compared to preoperative status. Importantly, patients with better neurological status exhibited longer survival times (Table 2). Severe neurological dysfunction, represented by ASIA grade A-C, not only signifies the loss of ambulatory function but also indicates a heightened risk of complications such as pressure sores, deep vein thrombosis, and pneumonia. Furthermore, ambulatory patients are more amenable to and compliant with adjuvant therapies.

Histopathological and molecular classification of primary breast cancer has historically played a pivotal role in prognostic stratification [19]. In our study, invasive non-specific carcinoma, primarily invasive ductal carcinoma, accounted for 88.5% of cases. The average survival time for invasive non-specific carcinoma was shorter than that for invasive specific cancer (50.2 months *versus* 76.7 months). This disparity may be attributed to the aggressive nature of invasive non-specific carcinoma, characterized by rapid disease progression, frequent recurrence, and high risk of metastasis [20]. ER, PR, Her-2 and Ki-67 are assumed as the most important prognostic indicators for breast cancer [21]. ER (+) and PR (+) breast cancer represents the largest pathological subtype. Compared with ER, PR may have limited practicability as a predictive marker of endocrine therapy response [22]. This study found positive expression of ER and PR was associated

Table 2 Univariate analysis of the factors associated with the survival

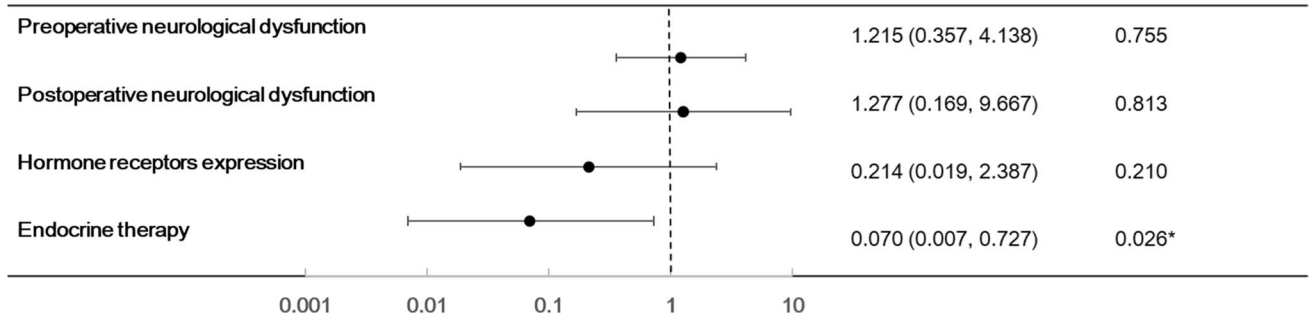
Factors	n (%)	Overall survival (months), median (95% CI)	*P* value
Age (years)			0.377
≤ 50	38 (48.7)	50.0 (44.1, 55.9)	
> 50	40 (51.3)	50.0 (33.0, 67.0)	
Surgical history of breast cancer			0.429
Yes	57 (73.1)	43.0 (23.1, 62,9)	
No	21 (26.9)	50.0 (38.2, 61.8)	
Preoperative neurological dysfunction (ASIA grades)			0.003*
Yes (A-C)	16 (20.5)	23.0 (0.3, 45.7)	
No (D, E)	62 (79.5)	54.0 (42.6, 65.4)	
Solidary spine lesion			0.148
Yes	18 (23.1)	56.0 (45.1, 66.9)	
No	60 (76.9)	45.0 (35.8, 54,2)	
Visceral metastasis			0.227
Yes	19 (24.4)	45.0 (29.9, 60.1)	
No	59 (75.6)	50.0 (39.3, 60.7)	
Surgical methods			0.687
Total *en-bloc* spondylectomy	5 (6.4)	46.0 (28.4, 63.6)	
Tumor-debulking	48 (61.5)	55.0 (43.7, 66.3)	
Palliative	25 (32.1)	43.0 (24.1, 61.9)	
Postoperative neurological dysfunction (ASIA grades)			0.051*
Yes (A-C)	16 (20.5)	15.0 (8.6, 21.4)	
No (D, E)	62 (79.5)	50.0 (40.5, 59.5)	
Pathological subtypes			0.664
Invasive subtype	69 (88.5)	50 (40.7, 59.3)	
Low-invasive subtype	9 (11.5)	32 (22.0, 42.0)	
Postoperative Karnofsky performance score			0.926
≥ 70	54 (69.2)	62.0 (36.8, 87.2)	
< 70	24 (30.8)	46.0 (40.0, 52.0)	
Adjuvant radiotherapy			0.197
Yes	42 (53.8)	56.0 (45.0, 67.0)	
No	36 (46.2)	42.0 (29.8, 54.2)	
Adjuvant hormone therapy			0.025*
Yes	47 (60.3)	54.0 (44.6, 63.4)	
No	31 (39.7)	43.0 (26.0, 60.0)	
Chemotherapy and/or target therapy			0.235
Yes	48 (61.5)	50.0 (40.1, 59.9)	
No	30 (38.5)	45.0 (22.6, 67.4)	
Hormone receptors expression			0.009*
Positive	48 (90.6)	43.0 (38.7, 47.3)	
Negative	5 (9.4)	21.0 (0, 44.4)	
HER-2 expression			0.850
Positive	41 (91.1)	50.0 (43.7, 56.3)	
Negative	4 (8.9)	73.0 (-)	
Ki-67 expression[#]			0.416
> 40% (high)	16 (38.1)	39.0 (16.7, 61.3)	
10–40% (moderate)	17 (40.5)	50.0 (31.2, 68,8)	
< 10% (low)	9 (21.4)	46.0 (-)	

[*]Statistically significant at $P < 0.05$. Analysis was performed using Log-rank test

[#]rated according to St Gallen consensus classification [24]

Table 3 Multivariate Cox regression analysis of associated factors affecting survival

Factors	aHR (95% CI)	*P* Values
Preoperative neurological dysfunction	1.215 (0.357, 4.138)	0.755
Postoperative neurological dysfunction	1.277 (0.169, 9.667)	0.813
Hormone receptors expression	0.214 (0.019, 2.387)	0.210
Endocrine therapy	0.070 (0.007, 0.727)	0.026*



aHR stands for adjusted hazard ratio; CI, confidential interval. Specifically, aHR < 1 indicates reduced mortality risk; aHR > 1 indicates increased risk

*Significant at $P < 0.05$

with longer survival (Table 2). ER and PR positivity indicates sensitivity to endocrine therapy, contributing to improved survival [21–23]. The observed association between endocrine therapy and survival outcomes in BCSM patients may be attributed to the intricate interplay between hormone receptor signaling and tumor biology. In hormone receptor-positive (HR +) breast cancers, hormone therapies such as selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) suppress estrogen-driven proliferation by blocking ERα-mediated transcriptional activity [24]. In BCSM cases, the presence of hormone receptors, such as ER and PR, is associated with enhanced sensitivity to endocrine therapy, resulting in prolonged survival.

While HER2-targeted agents have markedly enhanced the prognosis of HER-2 positive breast cancer, HER-2 positivity remained associated with a relatively poorer prognosis [25]. In our study, the median survival of HER-2 positive patients was insignificantly shorter than that of HER-2 negative patients. Notably, the correlation between survival and different expression levels of Ki-67 did not reach statistical significance, possibly attributed to the small sample size and ongoing controversies regarding the prognostic utility of Ki-67 grading [26–28]. Emerging evidence advocates for molecular subtyping (Luminal A/B, HER2 +, TNBC) in metastatic breast cancer prognostication [21, 27, 29]. Although our study primarily employed traditional biomarker categories (HR/HER2), the observed survival advantage in HR + patients parallels Luminal subtype outcomes, suggesting conserved biological drivers. While clinical stage and tumor burden remain important, contemporary guidelines prioritize molecular subtyping over traditional anatomic staging for metastatic breast cancer prognostication [21, 27, 30, 31]. We advocate integrating immunophenotypic profiling (ER/PR/HER2/Ki-67) with spinal metastasis characteristics (e.g., lesion number, neurological status) to optimize BCSM management.

Various scoring systems for BCSM have been employed clinically [12, 13], aiding in survival prediction and treatment planning. Tomita's system is designed to establish a simplified connection between easily obtainable factors and ultimate survival outcomes [12]. Usually, a higher Tomita score means a worse prognosis. In our study, both Tomita's and Tokuhashi's systems failed to demonstrate a significant association with patients' survival in our study (Fig. 3), underscoring the limitations of conventional prognostic systems in guiding treatment decisions for BCSM in current practice.

TES procedure, with its potential for complete tumor removal, is associated with a higher risk of complications [32]. Our study revealed no significant difference in median OS times between TES and non-TES cases (Fig. 2b). Nevertheless, TES was associated with higher estimated blood loss, raising doubts about whether patients with spinal metastasis can truly benefit from this procedure. This result can be attributed to several factors. Firstly, only a small proportion of patients with BCSM presented with solitary spinal lesions suitable for TES (23.1%, Table 1). Additionally, many patients have undetectable, occult lesions, even with advanced imaging techniques like [18F]FDG PET/CT [33], which may affect the completeness of tumor resection. Furthermore, TES is a highly invasive procedure associated with substantial surgical risks [34]. The occurrence of severe postoperative complications may adversely impact patient prognosis, potentially overshadowing the potential benefits of complete tumor removal. Debulking surgery effectively removes the compression between spinal metastases and the spinal cord [35], making it a suitable option for patients experiencing severe squeezing of the spinal cord. This procedure, a less invasive alternative, when combined with stereotactic radiotherapy, showed promising outcomes in terms of both survival and local control for BCSM patients (Table 2).

The limitations of this study include its retrospective design, which inherently introduces the risk of selection bias and limits the ability to establish causal relationships. The relatively small sample size may also reduce the statistical power of some analyses and limit the generalizability of the findings. Additionally, despite efforts to include relevant patient data, the single-center nature of the study may not fully represent the broader population of breast cancer spinal metastasis patients. These limitations highlight the need for larger, multi-center, prospective studies to validate the findings and minimize biases.

5 Conclusions

The contemporary approach to BCSM treatment emphasizes multidisciplinary collaboration. Surgery, in addition to effectively managing pain and improving neurological function, significantly enhances patients' likelihood and tolerance of adjuvant drug therapy and radiotherapy. Limited tumor-excisional surgery options can achieve satisfactory survival outcomes while maintaining perioperative safety. Conventional prognostic systems exhibit limited predictive value for patient survival, highlighting the need for new systems that incorporate neurological status, hormone receptor expression, and adjuvant anti-tumor drug considerations. Postoperative adjuvant therapies, particularly endocrine therapy, demonstrate a positive correlation with patient survival.

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Author contributions P. Hu and X. Wu played instrumental roles in the study's conception and design, patient review, clinical data collection and processing, and manuscript drafting. Y. Li contributed in methodological demonstration, data collection and visualization. S. Zeng took charge of data collation and conducted the statistical analysis. Y. Xiao contributed expertise in analyzing the pathological results of breast cancer. F. Wei, in addition to designing the study, patient selection, and data processing, provided overall supervision for the research endeavor. X. Liu and Z. Liu took on supervisory roles in data collection and processing. All authors actively participate in reviewing the manuscript, agree on its content and endorse its publication.

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Data availability The data set used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate The study was approved by the institutional ethics committee of Peking University Third Hospital (approval number: M2023797), and performed in accordance with the ethical standards of the Declaration of Helsinki (1964) and its subsequent amendments. Informed consent was obtained from all individual participants included in the study.

Competing interests The authors declare no competing interests.

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