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Prognostic Factors for Bone Survival and Functional Outcomes in Patients With Breast Cancer Spine Metastases

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Abstract

According to the Global Cancer Statistics 2020 report, breast cancer is the most commonly diagnosed cancer worldwide. Patients with mammary cancer live longer due to the continuous optimization of chemotherapy, targeted drugs, and hormone therapy, which will inevitably lead to an increase in the prevalence of metastatic bone tumors. Bone metastasis affects approximately 8% of patients with mammary cancer, with the spine being the most common site. Metastatic neoplasms can invade the centrum and its attachments, leading to local pain, spinal instability, vertebral pathological fractures, spinal cord compression, impaired neurological function, and paralysis, ultimately reducing the quality of life. Multidisciplinary and personalized management using analgesic drugs, endocrine therapy, corticosteroid therapy, chemotherapy, bisphosphonates, immunotherapy, targeted drugs, radiotherapy, and surgery has been advocated for the treatment of spinal metastases. Multiple paradigms and systems have been proposed to determine suitable treatments. In the early stages, the occurrence of metastasis indicates a terminal stage of the tumor process in patients with malignant tumors, implying that their lifespan is limited. As a result, the choice of treatment is heavily influenced by longevity. However, with the development of treatment methods, the lifespan of patients with tumors has considerably increased in recent years. This leads to the choice of patient's treatment, which depends not only on the patient's survival, but also on the radiotherapy or postoperative functional outcomes. Nevertheless, they fall short of determining the variables that affect survival and functional outcomes in histology-specific subgroups of breast cancer. To accurately predict the bone survival and functional outcomes of patients with breast cancer spine metastases a review of prognostic factors was performed.

Keywords

prognostic factors, functional outcomes, bone survival, breast cancer spine metastases, receptor status

Abbreviations

BCSM, breast cancer spine metastases; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; KPS, Karnofsky Performance Scale; NOMS, neurologic, oncologic, mechanical, and systemic; NSE, neurological status, stability of the spine, and epidemiological compression; PR, progesterone receptor; RT, radiotherapy; SINS, Spinal Instability Neoplastic Score; SRS, stereotactic radiosurgery

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Introduction

Global Cancer Statistics 2020 reported that breast cancer was the most common malignant tumor, with an estimated 2.3 million new cases (11.7%), and the fifth leading cause of cancer-related deaths worldwide, accounting for 6.9% of all deaths.[1] Lower mortality may be due to the biological characteristics of malignant breast tumors and the continuous optimization of chemotherapy, targeted drugs, and hormonal therapy in recent years, which will inevitably lead to an increase in

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the prevalence of metastatic tumors. The bone is the third most common site of malignant tumor metastasis after the liver and lung.[2] About 8% of breast malignant neoplasm patients have metastatic bone tumors,[3] of which the most common site is the spine.[4–8]

Like spinal metastases from other types of cancer, spinal metastases from breast cancer can also cause local pain, spinal instability, pathological vertebral fractures, spinal cord compression, neurological impairment, and paralysis, which seriously affect the quality of life and shorten the patients' lifespan. The treatment of spinal metastases requires multidisciplinary cooperation, which can be roughly divided into 2 categories: systemic and local treatment. Systemic treatment includes analgesic drug therapy, endocrine therapy, corticosteroid therapy, chemotherapy, bisphosphonates, and immune and targeted drug therapies. Local treatment includes radiotherapy (RT) and surgery. Multiple paradigms and systems have been proposed to determine the suitable treatment.[9–14] In the early stages, the appearance of metastasis indicates a terminal stage of the tumor process in patients with malignant tumors, implying that their lifespan is limited. As a result, the choice of treatment is heavily influenced by longevity. However, with the development of treatment methods, the lifespan of patients with tumors has greatly increased in recent years. The choice of treatment for patients depends not only on their survival but also on the RT or postoperative functional outcomes.[15,16] The 2 landmark evaluation systems used for determining the suitable treatments are Tomita et al[10] and Tokuhashi et al[9] scores.

Tokuhashi score was published in 1989 as a scheme for the management of patients with spinal metastasis.[9,17,18] The revised score was developed from a series that included 164 patients who underwent surgery and 82 nonsurgical patients, in which the predictive accuracy of prospective evaluation of patients was 86.4%.[19] The score included 6 items (metastases to the major internal organs, the primary site of cancer, general condition [KPS], spinal cord palsy, number of extraspinal bone metastases, number of metastases in the vertical body). According to the revised version,[19] the estimated survival period was less than 6 months when the total points were under 8 or less, more than 6 months when it was 9 to 11, and more than 12 months when it was 12 to 15. Patients with a total score of 8 or less are recommended to undergo conservative treatment or palliative surgery. Patients with a total score of 9 to 11 who have single spinal metastasis but no major internal organ metastasis are recommended to undergo vertebrectomy, and the remaining 9 to 11 patients are recommended to undergo palliative surgery. Vertebrectomy is recommended for patients with a total score of 12 or above. However, the predictive power of the Tokuhashi score of 9 to 11 in one small study was questioned,[20] and other studies showed that the Tokuhaishi score had lower prediction accuracy.[21–24]

Tomita score was proposed as a paradigm for the evaluation of the prognosis of metastatic spine tumor in 2001.[10,25] The paradigm consists of 3 factors （primary tumor, the number of spinal metastases, and visceral metastases） considered to be significantly associated with survival. Compared with the Tokuhashi score, each factor in the Tomita system was weighted by COX analysis, and the Tomita score system is more simplified. Multivariate analysis revealed that paralysis was found not to significantly affect the outcome. According to the Tomita score, the life expectancy was $\leq$ 3 months when the total points were 8 to 10, 6 to 12 months when the total points were 6 to 8, 1 to 2 years when the total points were 4 to 6, $\geq$ 2 years when total points were 2 to 4. Total resection is recommended for patients with a total score of 2 to 4, debulking for patients with a total score of 4 to 6, palliative decompression surgery for patients with a total score of 6 to 8, and terminal care for patients with a total score of 8 to 10.

Additionally, a more comprehensive management system for spinal metastases has emerged in recent years.[15] The neurologic, oncologic, mechanical, and systemic decision framework was originally proposed by the Spine Expert Group from the Memorial Sloan Kettering Cancer Center and was later improved by Bilsky and Smith.[26] According to the decision framework, conventional RT is sufficient for tumor types that are sensitive to RT (any ESCC grade). For low-grade ESCC (grade 1) and tumors that were unresponsive to RT, stereotactic RT was applied; for high-grade ESCC (2 grades 2 and 3) and tumors that were unresponsive to RT, separation surgery combined with stereotactic RT was applied; radiotherapy should be administered to patients who are not suitable for surgery. For patients with vertebral body instability, the vertebral body stabilization technique should be applied.

Separation surgery combined with stereotactic RT is also called hybrid treatment.[27] The aims of hybrid therapy for spinal metastasis are as follows: (1) to improve or maintain neurological function, (2) to provide mechanical stability, (3) to achieve long-term local tumor control, and (4) to reduce treatment-related morbidity. There is extensive level III evidence supporting the use of hybrid therapy in the treatment of metastatic spinal disease.[28–31] Laufer et al[32] applied separation surgery combined with stereotactic radiosurgery (SRS) in 186 patients with epidural compression due to spinal metastases. Forty patients received a single high-dose SRS (24 Gy), 37 patients received high-dose hypofractionated SRS (24-30 Gy in 3 fractions), and 109 patients received low-dose hypofractionated SRS (18-36 Gy in 5 or 6 fractions). The overall local tumor progression rate was 18.3% (34/186) at a median of 4.8 months (0.2-38.3 months) following SRS. The local progression rate was 16.4% at 1 year after surgery. The 1-year local progression rates were 9.0% for the single-fraction group, 22.6% for low-dose hypofractionated SRS, and 4.1% for high-dose hypofractionated SRS.

The neurological status, stability of the spine, and epidemiological compression (NSE) scoring system has been published to guide the selection of patients with spinal metastases who are suitable for surgery.[16] Neurological status was scored on a 0- to 5-point scale. A score of 0 point was assigned to patients with no neurological deficit or those with complete clinical spinal cord injury within > 72 h, 1

point to patients with nonmotor simple radicular pain, and 3 points to patients with motor nerve root injury or intractable mechanical nerve root pain. A score of 4 points was assigned to patients with complete spinal cord injury within < 72 h and 5 points to patients with incomplete spinal cord injury or cauda equina syndrome. Stability was evaluated using Spinal Instability Neoplastic Score (SINS). Patients classified under the SINS 0 to 6 category were assigned a score of 0 points, those in the SINS 7 to 12 category were assigned a score of 3 points, and those in the SINS 13 to 18.5 category were assigned a score of 5 points. The degree of epidural compression was evaluated according to the ESCC score. Patients with ESCC 0, 1a, and 1b obtained a score of 0 point, patients with ESCC 1c obtained a score of 1 point, and patients with ESCC 2 or 3 obtained a score of 3 points. Based on the NSE score, patients with total NSE scores of 0, 1, or 2 points should be treated conservatively. For patients with NSE total scores of 3 or 4 points, surgery or RT/whole-body therapy can be performed, depending on the tumor type, whether the patients have the conditions for SRS and the clinical and general conditions of the patients. For patients with a total NSE score of 5 points or above (maximum score: 13), regardless of the histological type of the tumor, surgical treatment should be performed. Cofano et al[16] reviewed 145 patients with spinal metastases who underwent surgery or conservative treatment and analyzed the consistency of NSE scores based on the patient's treatment choices. Patients were divided into the consistent group and the inconsistent group, with the consistent group accounting for 88.3%. Until the last follow-up, 89.6% of patients in the agreement group did not exhibit deterioration of neurological function, while 82% of the patients did not demonstrate the further deterioration of mechanical pain.

However, they fall short of determining factors that affect the outcome in histology-specific subgroups of breast cancer.[33] As a result, we reviewed a number of studies on variables influencing bone survival (BS) and functional outcomes of patients with breast cancer spine metastases in recent years. The objective of this review is to answer which patients were associated with better survival and functional outcomes.

Survival Parameters

The survival parameters of patients with BCSM are classified as bone survival (BS) and overall survival (OS), according to the initial events. OS refers to the time from the diagnosis of breast cancer to death, whereas BS refers to the time from the diagnosis of BCSM to death.[34] The median BS of BCSM ranged from 24 to 43.9 months.[35,36]

Prognostic Factors for BS in Patients With BSCM

Age

Patients with BCSM were aged 27 to 93 years,[33,35–41] with a median age of 53 to 58 years[33,35,37–40] and a mean age of 53.0 to 59.9 years.[36,38,40–42] Numerous observational studies have demonstrated that age does not significantly affect the survival of patients with BCSM (Table 1).[33,35,37–40,43–48] Zadnik et al[39] reported that patients older than 55 years had a median postoperative survival time that was almost 2 times longer than that of patients aged < 55 years. However, age at the time of surgery was not significantly predictive of longevity in patients with BCSM on multivariate analysis. Zadnik et al[39] determined that if a different age cutoff can be used for the analysis, it may be possible to derive the significance of age at the time of surgery.

Age is probably not a predictor of survival in patients with BCSM. However, the study by Amelot et al[36] found the significant predictive value of age for the survival of patients with BCSM and divided patients into 3 cohorts according to age; the intermediate age group was used as the reference cohort for analysis, which differed from the aforementioned other literature.[33,35,37–40,43–48] The other series[33,35,37–40,43–48] divided the patients into 2 groups according to age in the regression model. Therefore, the selection of the cutoff value and the design of the model group may be key to identifying the significance of age.

Hormone Receptor Status and Human Epidermal Growth Factor Receptor 2 Status

The hormone receptor (HR) status in patients with malignant breast tumors has an important prognostic value with regard to the risk of tumor metastasis and pattern of tumor spread.[49,50] The estrogen receptor (ER) and progesterone receptor (PR) are 2 HRs found in breast cancer. Cancer cells containing high levels of ER are called hormone-dependent tumors. Tamoxifen is an anti-estrogen drug that can compete with estradiol to binding with ER in target organs, thereby inhibiting the growth of tumor cells. Patients with ER-positive mammary cancer are more likely to develop bone metastasis.[34,49,51] The expression of human epidermal growth factor receptor 2 (HER2) is closely associated with the prognosis of patients with breast cancer. When the HER2 gene is overexpressed, cells grow abnormally and rapidly owing to excessive stimulation, eventually leading to the occurrence of breast cancer. The use of trastuzumab and pertuzumab has led to an improvement in the lifespan of HER2 (+) breast malignant tumor patients.[52–54]

ER Status. The median BS of ER (+) patients with BCSM is 32 to 76.1 months[35,36] and of ER (−) patients is 13 months.[35] Multiple studies have demonstrated that ER (+) patients with BCSM were significantly associated with better survival than ER (−) patients.[33,35,41] Wang et al[41] reported that ER (+) patients with BCSM had a postoperative median survival of 21.5 months compared to ER (−) patients who had a postoperative median survival of 11 months. Wang et al[41] suggested that Tokuhashi et al[19] gave a score based on the median survival of the primary tumor. The median survival of mammary cancer metastatic spine tumor patients was 18.6 months, giving a score of "5." The median survival of renal malignant neoplasm spinal metastasis patients and the uterine malignant tumor was more than 8 months and less than 12 months, resulting in a

Table 1. Significant Prognostic Variables for Patients With BCSM.

Studies and authors	Year	Patients (n)	Treatment	Survival measured (dependent variable)	Survival data	Significant prognostic variables
Terzi et al[37]	2020	77	Surgery	Postoperative survival for spine metastasis	• 3-year survival rate: 61% • 5-year survival rate: 43%	• Number of extraspinal bone metastases (0 vs >=1) • Neurologic status (Frankel E vs other neurologic status)
Sciubba et al[33]	2007	125	Surgery	Postoperative survival for spine metastasis	• median survival: 21 months • 1-year survival rate: 62% • 2-year survival rate: 44% • 3-year survival rate::33% • 4-year survival rate:27% • 5-year survival rate 24%	• Cervical metastasis (yes vs no) • ER status (ER [+]) vs ER [−])
Zhao et al[38]	2020	144	Surgery	Survival from the date of spinal metastasis	• mortality rate: 57%(82/144)	• Visceral metastases (yes vs no) • Preoperative Frankel Score (A-B vs C vs D-E) • ER status (ER [+] vs ER [−])
Zadnik et al[39]	2014	43	Surgery	Postoperative survival for spine metastasis	• median survival:26.8 months • 1-year survival rate: 66% • 5-year survival rate: 4%	• Postoperative adjuvant therapy (none vs single therapy vs dual therapy)
Walcott et al[40]	2011	15	Surgery	Postoperative survival for spine metastasis	• median survival:1025 days	• Change in ambulatory status (deficit with no improvement vs normal or deficit improvement) • Surgical complication (presence vs absence)
Wang et al[41]	2014	151	Surgery	Postoperative survival for spine metastasis	• Median survival: 21.2 months	• ER status (ER [+] vs ER [−]) • PR status (PR [+] vs PR [−]) • HR status (HR [+] vs HR [−])
Rades et al[43]	2015	218	RT	Survival after radiotherapy for spinal metastases	• 6-month survival rate : 69% • 12-month survival rate: 55%	• Visceral metastasis (yes vs no) • Ambulatory status before radiotherapy (ambulatory patients vs patients who were not ambulatory) • Number of involved vertebrae (1-3 vs ≥ 4)

(continued)

Table 1. (continued).

Studies and authors	Year	Patients (n)	Treatment	Survival measured (dependent variable)	Survival data	Significant prognostic variables
Rades et al[46]	2013	518	RT	Survival after radiotherapy for spinal metastases	• 6-month survival rate : 74% • 12-month survival rate: 62%	• Number of vertebrae involved (1-2 vs ≥ 3) • Ambulatory before radiotherapy (ambulatory patients vs patients who were not ambulatory) • Number of extraspinal bone metastases (1-2 vs > = 3) • Visceral metastasis (yes vs no)
Weber et al[44]	2014	145	RT	Survival after radiotherapy for spinal metastases	• 6-month survival rate : 73% • 12-month survival rate: 63%	• Ambulatory before radiotherapy (ambulatory patients vs patients who were not ambulatory) • Number of involved extraspinal organs (0 vs 1 vs 2 vs ≥3)
Rades et al[47]	2018	159	RT	Survival after radiotherapy for spinal metastases	• 6-month survival rate: 94% • 12-month survival rate: 81% • 18-month survival rate: 80% • 24-month survival rate: 67%	• Ambulatory before radiotherapy (ambulatory patients vs patients who were not ambulatory)
Rades et al[45]	2012	504	RT	Survival after radiotherapy for spinal metastases	• 12-month survival rate: 61% • 24-month survival rate: 46%	• Number of involved vertebrae（1-2 vs ≥3） • Ambulatory before radiotherapy (ambulatory patients vs patients who were not ambulatory) • Number of extraspinal bone metastases (0 vs > = 1) • Visceral metastases (0 vs > = 1)
Rades et al[48]	2005	335	RT	Survival after radiotherapy for spinal metastases	• Median survival: 20 months	• Ambulatory before radiotherapy (ambulatory patients vs patients who were not ambulatory)
Tan et al[35]	2017	185	Heterogeneous	Survival after diagnosis of spinal metastases	• Median survival: 24 months • 6-month survival rate: 90%	• ER status (ER [+) vs ER [−]) • HER2 status (HER2 [+] vs HER2[−]) • HR status (HR [+] vs HR [−]) • Nontriple negative breast cancer (nontriple-negative breast cancer vs triple-negative breast cancer)
	2014	111	Heterogeneous	Survival from the start of	• Median	• Nontriple negative breast cancer

(continued)

Table 1. (continued).

Studies and authors	Year	Patients (n)	Treatment	Survival measured (dependent variable)	Survival data	Significant prognostic variables
Bollen et al[42]				treatment for spinal metastasis	survival:18 months	(nontriple-negative breast cancer vs triple-negative breast cancer)
Amelot et al[36]	2019	123	Heterogeneous	Survival from the Spinal metastasis event	• Median survival: 43.9 months	• Age (< 60 years vs 60-75 years > 75 years) • Frankel score (A vs B vs C vs D vs E) • Nontriple negative breast cancer (nontriple-negative breast cancer vs triple-negative breast cancer)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor; HR, hormone receptor; PR, progesterone receptor; RT, radiotherapy; BCSM, breast cancer spine metastases.

score of "3." In this cohort, Wang et al[41] the median survival of ER (−) patients was also more than 8 months and less than 12 months. Therefore, it should be given a score of 3, and for the Tomita score, patients with ER (−) should be classified as the moderate growth group.

PR Status. In general, PR expression has been considered a surrogate marker for ER.[55] Wang et al[41] reported in their clinical work that PR testing is performed as a supplement to ER status when the ER test result is negative. Several reports have demonstrated that PR status is not an independent predictor for survival in patients with BCSM.[33,35,38] Sciubba et al[33] reported that the postoperative survival of PR (+) patients is 30 months and of PR (−) patients is 11 months, with no significant difference.

The findings of the Wang's et al[41] study contradict the findings of the preceding reports. The median postoperative survival of PR (+) patients with BCSM was 18.8 months and of PR (−) patients was 16.6 months. PR (+) was found to be significantly associated with improved survival. Tan et al[35] suggested that Wang et al[41] only adjusted for age and did not include other important factors in the multivariate analysis, which could explain this result.

HR Status. As previously stated, PR expression is thought to be a surrogate marker for ER.[55] Thus, patients with ER (+) and/or PR (+) are usually classified as HR (+).[41] Several studies[35,41] have found that HR status was a significant predictor of survival in patients with mammary cancer spinal metastases. In the study by Tan et al,[35] the median BS in HR (+) patients was 32 months, and the 6-month survival rate was 88. 4%. The median BS in HR (-) patients was 12 months, and the 6-month survival rate was 76. 3%. HR (+) was associated with better survival in patients with metastatic mammary cancer confined to the spinal column. Tan et al[35] demonstrated in recent studies[56–58] that the survival of ER (+) and PR (+) patients was significantly better than that of patients with ER (+) and PR (−). This result is explained by a landmark study by Mohammed et al[59] published in Natureby, in which PR expression downregulates estrogen receptor sensitivity. Therefore, it may be worthwhile to compare the survival of ER (+) and PR (+) cohorts with ER (+) and PR (−) cohorts rather than the current HR (+)/(−) cohorts.

HER2 Status. Among the previously reported clinical series of patients with breast cancer, HER2 (+) patients account for 20% to 30%.[60] In the studies conducted by Tan et al[35] and Zhao et al,[38] HER2 (+) status was significantly associated with greater survival in patients with BCSM. Tan et al[35] reported that HER2 (+) patients had a median BS of 35 months and a 6-month survival rate of 89.8%. Patients with HER2 (−) status had a median BS of 20 months and a 6-month survival rate of 81.0%.

According to another study by Wang et al,[41] HER2 status was found not to be an independent predictor for the survival of BCSM. The median postoperative of Her2 (+) patients was found to be 23.1 months and of Her2 (−) patients was found to be 21. 3 months.

Triple-Negative Breast Cancer (Basal). The triple-negative breast cancer subtype refers to ER (−), PR (−), and HER2 (−), which are highly aggressive, with rapid growth, a high rate of chemoresistance and tumor recurrence, and a high risk of distant metastasis.[61] When compared with other HR (+) and HER2 (+) breast cancer patients, the treatment options for triple-negative breast cancer patients are limited.[62] Patients with triple-negative mammary cancer spinal metastasis had a median BS of 11 to 17.4 months.[35,36] Patients with triple-negative mammary cancer spinal metastasis had significantly worse survival than those with receptor-positive subtypes.[35,36,42] According to the study conducted by Bollen et al,[42] the median survival times were 23.4 months and 5.5 months in the receptor-positive cohort and triple-negative breast cancer group, with a significant difference in survival. The relatively poor survival outcomes of patients with triple-negative breast cancer suggest that surgeons should distinguish between them in models evaluating the survival of patients with

spinal metastases. Surgeons should carefully select the treatment options for these patients.

Karnofsky Performance Scale

The Karnofsky Performance Scale (KPS) is a tool used for assessing functional status on an 11-point scale ranging from 0 (death) to 100 (normal without any discomfort).[63] The system assesses the general health of patients and their ability to tolerate the side effects of treatment. KPS is not an independent predictor of survival in patients with BCSM.[35,39,40] In the study conducted by Tan et al,[35] patients were divided into 3 cohorts according to their KPS score: those with poor KPS scores, those with medium KPS scores, and those with good KPS scores. Multivariate regression analysis was carried out, and patients with a poor KPS score were assigned as the reference group; results showed no significant difference between the 3 groups. Tan et al[35] reported that 84.3% of patients had good KPS scores. An imbalance in the proportion of patients may affect the analytical outcome. In the study by Zadnik et al,[39] KPS was not an independent predictor of postoperative survival, of which the median postoperative survival of patients with preoperative KPS score of < 70 was 25.9 months, while that of patients with a preoperative KPS score of > 70 was 27.3 month. Zadnik et al[39] suggested that multivariate regression analysis using 40 or 50 as the cutoff value may be more helpful in exploring the statistical significance of this factor; however, the small study sample with poor general conditions limited the feasibility of this assumption.

Cervical Vertebra Metastasis

Whether cervical spinal metastasis is an independent predictor of survival in patients with BCSM remains unclear. In the study conducted by Sciubba et al,[33] the postoperative survival of patients with cervical spine surgery was 6.8 months, while that of patients with noncervical surgery was 25.1 months. Cervical metastasis is an independent predictor of postoperative survival in patients with BCSM. Sciubba et al[33] reported that this outcome may be due to the following 3 points: First, cervical and cervicothoracic metastases may occur at the later stages of breast cancer. However, the OS of patients with mammary cancer with and without cervical metastases is similar; therefore, the BS of patients with cervical metastases is shorter. Another reason may be the delayed detection of cervical tumors. In the study by Sciubba et al,[33] the median times from diagnosis of malignant breast tumors to surgery were 50 months for patients with cervical tumors and 31 months for patients without cervical tumors. This difference could be due to the fact that the cervical spinal canal is wider than the thoracic spinal canal so that cervical metastatic tumors take a longer time to grow and cause clinical signs and symptoms; Furthermore, cervical metastases from breast cancer are extremely difficult to detect by bone scintigraphy.[64] Third, it may be due to the higher complication rate of cervical spine surgery; however, in the study conducted by Sciubba et al,[33] the risk of surgical complications in cervical spine metastasis patients was similar to that in noncervical spine patients; therefore, this cause is less likely.

Several reports have demonstrated that cervical metastasis was not an independent predictor for patients with BCSM.[38, 39] Zadnik et al[39] reported, that the median postoperative survival of breast cancer metastatic spine tumor patients was 6.5 months for patients with lumbar spine surgery, 29.6 months for patients with cervical spine surgery, 27.3 months for patients operated on the thoracic spine, with a nonsignificant difference. The median survival time of patients with the cervical region was the longest and of patients with the lumbar region was the shortest.

Visceral Metastasis

The impact of visceral metastases on the survival of patients with spinal metastases has been identified in the Tokuhashi et al[9,19] and Tomita et al[10] systems. The incidence of visceral metastasis in patients with BCSM is 20.8% to 86.5%.[33,35,37–39,42,43,45,46,48] Visceral metastasis is an independent prognostic factor for survival in patients with BCSM.[38,43,45,46,48] In a study by Rades et al,[45] the 6-month survival rate of patients without visceral metastasis was 90%, and the 12-month survival rate without visceral metastases was 82%. Patients with visceral metastasis had a 6-month survival rate of 43% and a 12-month survival rate of 18%. Visceral metastasis is an independent predictor of survival in patients with BCSM.

The lack of a significant effect of visceral metastasis on survival of BCSM patients in many reported series[33,35,39] differs from the Tokuhashi score,[9,19] Tomita score,[10] and other reports concerning metastatic spinal tumor from varied pathology.[65–70] Tan et al[35] reported that patients with visceral metastasis were divided into 3 groups: removable visceral metastasis, unremovable visceral metastasis, and no visceral metastasis, with the nonsignificant differences between the 3. Tan et al[35] estimated that 86.5% of patients in this study had visceral metastases. The imbalance in the proportion of patients in different groups affected the significance of visceral metastases.

Number of Vertebrae Involved

The number of vertebrae involved is also considered when calculating the Tokuhashi score.[9,19] Several studies have determined that the number of involved vertebrae is an independent predictor of survival in patients with BCSM.[38,43,45] Rades et al[45] reported that patients with 1 to 3 involved vertebrae had a 6-month BS rate of 79% and a 12-month BS rate of 66%. Patients with ≥ 4 involved vertebrae had a 6-month BS rate of 56% and a 12-month BS rate of 40%. The survival of patients with ≥ 4 involved vertebrae was significantly worse than that of patients with 1 to 3 involved vertebrae.

In contrast to the scoring systems used by Tokuhashi et al[9,19] and Tomita et al,[10] the number of vertebrae is not a significant factor for survival in patients with breast neoplasm spinal

metastasis.[33,35,36,44,46–48] According to the study conducted by Sciubba et al,[33] the median postoperative survival of patients with one involved vertebra was 22.9 months, that of patients with 2 involved vertebrae was 17.0 months, and that of patients with 3 involved vertebrae was 16 months, with no significant difference between the 3. Sciubba et al[33] determined that, although the number of vertebrae involved may not affect the patient's survival, the presence of multiple lesions can determine the surgical approach and reconstruction.

Extraspinal Bone Metastasis

The incidence of extraspinal bone metastasis in patients with BCSM is 28% to 93.0%.[33,35,37,39,43,45,46,48] Extraspinal bone metastasis is an independent prognostic factor for survival in patients with BCSM.[37,45,46] Rades et al[45] reported that patients with extraspinal bone metastases had a 1-year survival rate of 55% and a 2-year survival rate of 39%. Patients without extraspinal bone metastases had a 1-year survival rate of 70% and a 2-year survival rate of 57%. Extraspinal bone metastasis is an independent prognostic factor for survival after RT. Terzi et al[37] reported that the extraspinal bone metastasis of breast cancer is usually an indication that the tumor has advanced, is progressing, or is unresponsive to treatment.

Several reports have demonstrated that extraspinal bone metastasis is not an independent predictor of survival when using multivariate analysis.[33,35,38,43,48] Rades et al[48] reported that patients with extraspinal bone metastases had a 2-year postradiotherapy survival rate of 36% and a 6-month postradiotherapy mortality rate of 29%. Patients without extraspinal bone metastases had a 2-year mortality rate after radiotherapy of 58% and a 6-month mortality rate after radiotherapy of 32%. Extraspinal bone metastasis is not an independent prognostic factor for survival after radiotherapy.

Neurological Status

The rapid deterioration of the neurological status may be due to the rapid growth of aggressive tumors, implying an earlier death. [48] At present, there are 2 more recognized nerve function classification standards: the Frankel score[71] and the ASIA score. Previous authors have noted that neurological status may have a significant influence on the survival of patients with spinal metastasis regardless of the type of primary tumor.[72,73] Several studies have demonstrated that neurological status is a predictive factor for survival in patients with BCSM.[37,43–47] Rades et al[45] reported that patients who were not ambulatory before radiotherapy had a 1-year survival rate of 28% and a 2-year survival rate of 12%. Patients who were ambulatory before radiotherapy had a 1-year survival rate of 72% and a 2-year survival rate of 58%. Neurological status before radiotherapy is an independent predictor for survival after radiotherapy.

Several studies have demonstrated that neurologic status is not an independent prognostic factor for survival in patients with BCSM.[33,35,38,48] Sciubba et al[33] reported that the preoperative Frankel grade was not associated with survival difference (3.1 vs 21.1 vs 21.5 months). Pre-operative neurological status of patients with spinal metastasis from breast cancer was found not to be a prognostic factor for postoperative survival.

Spinal Instability Neoplastic Score

The Spinal Instability Neoplastic Score (SINS) system consists of 6 items: nature of the lesion (lytic osteoblastic mixed), nature of the pain, degree of vertebral body collapse, radiographic spinal alignment, posterolateral involvement of the spinal elements, and anatomic location of metastases.[74] This system aimed to determine the surgical strategy and does not predict the survival of patients postoperatively. Therefore, few studies have explored whether SINS is a survival prognostic factor for spinal metastasis in breast cancer. In a study that did not differentiate between primary tumor types that metastasized to the spine, the 6-month postoperative survival rates were 80% in patients with SINS 7% to 12%, and 37% in patients with SINS 13 to 16. The survival difference of patients in the SINS 7 to 12 group was significantly different from that of the SINS 13 to 16 group.[75] Only one study included in this review explored this factor. Zadnik et al[39] suggested that the items in the SINS assess the patient's disability status. Therefore, survival analysis of this factor was used to determine whether spinal instability is a prognostic factor for breast cancer metastasis. The median survival times were 12.7 months for the SINS 13 to 18 group and 28.1 months for the SINS 7 to 12 group, with no significant difference. The absence of significant differences was probably due to the small sample size. Although no statistical difference was observed between the 2 groups, the median survival of the former was only half of the median survival of the latter.

Prognostic Factors for Functional Outcomes in Patients With BCSM

With the continuous development of treatment methods, the survival of patients with BCSM has been extended, and the treatment of spinal metastasis depends not only on the survival of the patient, but also on the patient's RT or postoperative functional results.[15,16] The functional outcomes mainly include pain status[76] and motor function[77–80] after treatment. The dependent variable discussed in this article was motor function after RT (MFAR).

Age

The predictive value of age in patients with spinal metastasis whose primary tumor types are not distinguished is limited.[78] Age is not an independent prognostic factor of MFAR in patients with BCSM (Table 2).[45,47,48] The study conducted by Rades et al[48] evaluated the predictive value of age for MFAR in patients with BCSM. The postoperative walking function

was divided into 3 categories: (1) improvement of motor function, (2) absence of changes in motor function, and (3) deterioration of motor function. In patients aged ≤ 60 years, the rate of motor function improvement after RT was 33%, the rate of consistent motor function after RT was 56%, and the rate of motor function deterioration after RT was 11%. Moreover, the rate of motor function improvement after RT in patients aged > 60 years was 29%, the rate of consistent motor function after RT was 59%, and the rate of motor function deterioration after RT was 12%. No significant difference was observed in walking function or numerical values between the 2 groups after RT, suggesting that the predictive value of age for walking function in patients with BCSM after RT was also limited.

Visceral Metastasis

Visceral metastasis is an independent prognostic factor for MFAR in patients with spinal metastases from multiple primary tumor types.[78] Rades et al[45] determined that the rate of motor function improvement after RT in patients without visceral metastases was 38%, the rate of consistent motor function after RT was 57%, and the rate of motor function deterioration after RT was 5%. The rate of motor function improvement after RT in patients with visceral metastasis was 26%, the rate of consistent motor function after RT was 53%, and the rate of motor function deterioration after RT was 21%. Visceral metastasis is an independent prognostic factor for MFAR in patients with BCSM. The presence of visceral metastases indicates an advanced stage of the disease and indicates that the cancer is more aggressive and difficult to treat. Rades et al[45] determined that decompression surgery should be performed after RT in patients with visceral metastasis.

Time of Motor Deficit Development

Time of motor deficit development refers to the time from the onset of any symptoms to the occurrence of motor defects before RT.[81] A previous study involving 2096 patients with multiple primary tumor types showed that the development of motor deficits was an independent prognostic factor for postoperative walking function in patients with BCSM.[78] Multiple studies have demonstrated that the time of motor deficit development is an independent prognostic factor for MFAR in patients with BCSM.[45,47,48] In a study by Rades et al,[48] 335 patients with BCSM were included. When the motor deficits developed within 1 to 7 days, the rate of movement function improvement after RT was 10%, the rate of consistent movement function after RT was 57%, and the rate of movement function deterioration after RT was 33%. When the motor deficits developed within 8 to 14 days, the rate of motor function improvement after RT was 29%, the rate of consistent motor function after RT was 55%, and the rate of motor function deterioration after RT was 15%. When the motor deficits developed in > 14 days, the rate of motor function improvement after RT was 10%, the rate of consistent motor function after RT was 57%, and the rate of motor function deterioration after RT was 33%. Rades et al[48] determined that this result could be explained by the decreased arterial and venous blood flow due to tumor growth and compression of vessels adjacent to the spinal cord.[82,83] Acute deterioration of motor function may be due to interruption of arterial circulation and spinal cord infarction. The gradual development of neurological deficits is thought to be caused by venous congestion. It may also be due to the slow development of motor defects, indicating weak invasiveness and slow tumor growth.

ECOG Score

In a previous study on the prognostic factors for MFAR in patients with spinal metastases from multiple primary tumor types, multivariate analysis showed that the ECOG score had a significant effect on walking function after RT.[78] However, multiple studies have shown that the pre-RT ECOG score is not an independent prognostic factor for MFAR in patients with BCSM.[45,47,48] A study by Rades et al[45] included 504 patients with BCSM. For patients with an ECOG score of 1 to 2 before RT, the rate of motor function improvement after RT was 35%, the rate of consistent motor function after RT was 60%, and the rate of motor function deterioration after RT was 5%. For patients with an ECOG score of 3 to 4 before RT, the rate of motor function improvement after RT was 57%, the rate of consistent motor function after RT was 48%, and the rate of motor function deterioration after RT was 20%. Although no significant difference was observed between the 2 groups, the walking function of the latter was worse than that of the former.

Ambulatory Status Prior to RT

In a previous study on the prognostic factors for MFAR in patients with spinal metastases from multiple primary tumor types, multivariate analysis showed that the ambulatory status prior to RT had a significant effect on walking function after RT in patients with BCSM.[78] Two studies[45,48] have shown that the ambulatory status before RT was an independent prognostic factor for motor function after therapy in patients with BCSM. A retrospective study by Rades et al[45] evaluated the predictive value of ambulatory status prior to RT for MFAR in patients with BCSM. The rate of motor function improvement after RT in patients in the nonambulatory group was 40%, the rate of consistent motor function after RT was 41%, and the rate of motor function deterioration after RT was 19%. The rate of motor function improvement after RT in the walking group was 32%, the rate of consistent motor function after RT was 60%, and the rate of motor function deterioration after RT was 8%. No significant differences were found between the 2 groups. A study by Dirk included 159 patients with BCSM. The rates of motor function improvement after RT were 39% in the nonambulatory group before RT and 40% in the ambulatory group before RT.[47] No significant differences were found between the 2 groups.

This result can be due to the fact that the dependent variable in the third study was motor function improvement after RT,

Table 2. Significant Prognostic Variables for Functional Outcomes in Patients With BCSM.

Studies and authors	Year	Patients(n)	Treatment	Functional outcomes measured (dependent variable)	Functional outcome data	Significant prognostic variables
Rades et al[47]	2018	159	RT	MFAR	• Improvement rate of MFAR: 30.8%	• Time developing motor deficits (1-7 days vs 8-14days vs >14 days)
Rades et al[45]	2012	504	RT	MFAR	• Improvement rate of MFAR: 33.9% • Unchanged rate of MFAR: 55.8% • Deterioration rate of MFAR: 10.3%	• Ambulatory before radiotherapy (ambulatory patients vs patients who were not ambulatory) • Visceral metastasis (yes vs no) • Time developing motor deficits (1-7 days vs 8-14 days vs > 14 days)
Rades et al[48]	2005	335	RT	MFAR	• Improvement rate of MFAR: 31.3% • Unchanged rate of MFAR: 57.3% • Deterioration rate of MFAR: 11.3%	• Ambulatory before radiotherapy (ambulatory patients vs patients who were not ambulatory) • Time developing motor deficits (1-7 days vs 8-14 days vs > 14 days)

Abbreviations: MFAR, motor function after radiotherapy; RT, radiotherapy; BCSM, breast cancer spine metastases.

whereas the dependent variables in the first 2 studies were motor function improvement after RT, motor function deterioration after RT, and consistent motor function after RT. The former had a more comprehensive evaluation of motor function changes after RT, which might explain why the latter did not achieve statistical significance.

Limitations

Firstly, this article is a literature review without systematic retrieval, which may lead to literature bias. Another limitation was that all studies included in this article were retrospective studies with a low level of evidence. In addition, despite numerous studies on age, HER2 status, KPS, cervical vertebral metastasis, visceral metastasis, number of involved vertebrae, extraspinal bone metastasis, and neurological status, the results and conclusions remain inconsistent. We deeply regret that we fail to find a reasonable explanation. Finally, in this study, there are too few studies on the prognostic factors for functional outcomes in patients with BCSM.

Summary and Prospect

In summary, the survival and outcomes of patients with BCSM are affected by several factors. In this review, the prognostic factors affecting the survival of patients with BCSM were ER status (ER [+] patients have a better prognosis compared with ER [−] patients), HR status (HR [+] patients have a better prognosis compared with HR [−] patients), and triple-negative breast cancer (nontriple-negative breast cancer has a better prognosis than triple-negative breast cancer). PR status and KPS were not independent prognostic factors for survival in patients with spinal metastases from breast cancer. Despite numerous studies on age, HER2 status, KPS, cervical vertebral metastasis, visceral metastasis, number of involved vertebrae, extraspinal bone metastasis, and neurological status, the results and conclusions remain inconsistent and require further verification. For functional outcomes, the prognostic factors affecting MFAR in patients with BCSM are a time of motor deficit development (1-7 days vs 7-14 days vs > 14 days), ambulatory status prior to RT (ambulatory patients have a better prognosis), and visceral metastasis (patients without visceral metastasis have a better prognosis). Age and ECOG score were not independent prognostic factors for MFAR in patients with BCSM. However, studies on the prognostic factors of functional outcomes in patients with BCSM are limited, and further research is needed.

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