ORIGINAL ARTICLE



Spine Surgery in Patients with Metastatic Breast Cancer: A Retrospective Analysis

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BACKGROUND: Pathologic or iatrogenic symptomatic spinal lesions are common in metastatic breast cancer. Given the longer duration of overall survival provided by modern oncologic therapies, a prompt and effective treatment of such lesions may have a significant impact on patient's quality of life, improving pain and preventing deterioration of neurologic functions.

METHODS: A retrospective review was conducted on patients with breast cancer operated to the spine between 2005 and 2013. The series includes 41 patients and 57 vertebral levels treated (4 cervical, 35 dorsal, and 18 lumbar). There were 28 patients who received palliative surgery and 13 who received excisional surgery, according to their clinical conditions, Spinal Instability Neoplastic Score, and Tokuhashi scores.

■ RESULTS: Of the 41 patients, 38 presented with a median survival of 50 months (95% confidence interval [Cl], 39–61), still preserving a Karnofsky Performance Status Scale score ≥60 and a retained ability to ambulate independently. The median overall survival after the first spine surgery was also 50 months (95% Cl, 35–65), suggesting that in this cohort of patients, a reasonable quality of life was preserved almost to the end of their clinical history. In patients treated with palliative surgery, the median survival was 37 months (95% Cl, 26–48). In those treated with complex surgery, it was 57 months (95% Cl, 41–73; P = 0.03).

CONCLUSIONS: Major excisional surgery, albeit associated with an increased length of hospital stay, allowed in our

Key words

- Breast cancer
- Kyphoplasty
- Somatectomy
- Spine surgery

Abbreviations and Acronyms

ASIA: American Spinal Injury Association BKP: balloon kyphoplasty CI: confidence interval CT: computed tomography ES: estrogen KPS: Karnofsky Performance Status Scale LOS: length of hospital stay MRI: magnetic resonance imaging PgR: progesterone series a prolonged survival compared with less aggressive types of surgery. However, percutaneous or open balloon kyphoplasty techniques have expanded indications for palliative surgery and even patients with lower Tokuhashi scores may benefit from rapid and sustained pain relief, preservation of neurologic function, and early mobilization.

INTRODUCTION

B reast cancer is the most common malignancy and the second cause of cancer-related death in women living in developed countries.^{1,2} In Italy, approximately 34,500 new cases are diagnosed every year (27% of all malignant tumors in women), and 11,000 annual deaths are related to breast cancer.³ Metastases to the spine are reported in up to 80% of patients affected by this tumor.⁴⁻⁶

They represent an early and predominant manifestation of breast cancer, and they often remain confined to the skeleton for a prolonged period of time. Patients with bone-only metastases may survive for many years, and even in advanced disease, they may still retain a reasonable clinical functional status. This holds especially true for tumors that express hormone receptors and are well differentiated.⁴⁻¹¹

With the help of new therapies as molecular target agents, hormones, and bisphosphonates, the prognosis after development of bone metastases in breast cancer is significantly better than after a recurrence in visceral sites, with a reported median survival of up to 24-48 months, whereas the survival rate at I year can reach 77.7%.^{6,7,12,13}

RT: radiotherapy SINS: Spinal Instability Neoplastic Score VAS: visual analog scale

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Citation: World Neurosurg. (2016) 90:133-146. http://dx.doi.org/10.1016/j.wneu.2016.02.065

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

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Moreover, up to one-third of vertebral fractures occurring in patients with cancer are reported to be osteoporotic or iatrogenic in nature, mainly related to prolonged chemotherapies, corticosteroid or hormonal therapy, and the overall reduction of mobility.¹⁴

Unfortunately, between 15% and 30% of these spinal lesions ultimately become symptomatic because of mechanical instability or epidural compressions.^{2,5,10}

These complications may cause severe pain and neurologic deficits which lead to a significant deterioration of quality of life, often requiring urgent radiotherapic or surgical treatments.^{1,10,15,16}

Because Patchell et al.,¹⁷ in a recent prospective, randomized trial, firmly established the efficacy of surgery associated with radiotherapy (RT) in cases of focal metastatic spinal cord compression, and the survival prognosis is an essential prerequisite to consider in any operative treatment, an aggressive approach seems particularly justified in patients with breast cancer. The aim is to achieve histologic diagnosis, the maximum palliative effect, the reduction of pain, and the maintenance or restoration of spinal stability, with a minimum of operative morbidity and mortality.^{10,16-18}

Neurosurgery can presently offer a large armamentarium of techniques for the heterogeneous clinical conditions affecting patients with spinal metastases. Different surgical options, such as posterior decompression, vertebroplasty, balloon kyphoplasty (BKP), spine fixation with rods and pedicular screws, or radical vertebrectomy, are increasingly used to improve the patients' quality of life in combination with other adjuvant chemo- and radiotherapic regimens.

Despite the high incidence of lesions to the spine in breast cancer, few series specifically address the topic of their surgical treatment.

We review the clinical results and outcomes reported in the literature in such patients, and we present our own experience.

Particular emphasis has been dedicated to the role that the closed and open BKP techniques have gained in the last decade at our institution, alone or in conjunction with other spine tumor treatment modalities, to further expand the indication of surgery and efficaciously deal with the more controversial cases.

MATERIALS AND METHODS

A retrospective review was conducted on patients with breast cancer operated to the spine, between December 2005 and December 2013, at "Regina Elena" National Cancer Institute. Follow-up was pursued until December 2014.

The series include 41 patients with a median age of 58 years (range, 34–84 years).

Medical records were reviewed to analyze medical history, histology of the tumor including hormonal receptors status, neuroimaging, type of surgery (complex stabilizations vs. less aggressive percutaneous/open kyphoplasty or decompressive only laminectomy), and follow-up.

Spinal metastases were diagnosed by magnetic resonance imaging (MRI) and computed tomography (CT). Bone scintig-raphy, positron emission tomography–CT, and/or total body CT scan were performed in all cases.

Pre- and postoperative spine pain levels, measured with the 10-point verbal visual analog scale (VAS), neurologic impairment evaluated with American Spinal Injury Association (ASIA) grade, and Karnofsky Performance Status Scale (KPS) were compared in all patients prior to being submitted to surgery, at discharge, and at last follow-up examination in the neurosurgical outpatient clinic, before severe deterioration of their general or neurologic conditions occurred, preventing further evaluation.^{19,20}

The Spinal Instability Neoplastic Score (SINS) was used to define the degree of instability of the vertebral lesions.²¹

Length of hospital stay (LOS), operative complications, the median overall survival of patients after the original breast cancer diagnosis and the median survival after the first spinal surgery were also evaluated.

In this cohort of patients, indication for surgery included uncontrolled pain (n = 34), spinal mechanical instability (n = 35), neurologic symptoms caused by spinal cord or radicular compression (n = 21), and previous ineffective RT (n = 3). More than one indication were observed in several cases.

Exclusion criteria for surgery were also restricted and included absence of mechanical instability of the spine or relevant spine deformity; presence of severe associated comorbidities, such as symptomatic infective, cardiovascular, cerebrovascular, pulmonary, renal, and hematologic diseases, leading to unstable general medical conditions; and an estimated survival of less than 3 months based on comprehensive oncologic clinical judgment and Tokuhashi modified score.

A total of 57 vertebral levels in 41 operative sessions were treated: 4 cervical, 35 dorsal, and 18 lumbosacral lesions.

The surgical approach was determined by the anatomic location and extent of the disease with the aim, whenever possible, to remove the larger part of the tumor tissue, to increase the stability of the spine, and to decompress the neural structures.

Most of the lesions were located in the anterior vertebral column (vertebral body or pedicles): they involved only the soma of one or more vertebrae or they presented an anterolateral extension in the vertebral canal, compressing unilaterally the cord or the roots.

In 4 cases, the tumor tissue had a prevalent posterior/posterolateral distribution requiring a simple decompressive hemilaminectomy.

Excisional Surgery

If the general condition and prognosis of the patient were evaluated as good (more than 12 months of survival), the Tokuhashi modified score was at least 12, and the extent of the disease was limited to one vertebral body with spine instability, an aggressive surgical attitude was selected, including somatectomy associated with circumferential stabilization through complex anterolateral, posterolateral transpedicular, or combined approaches.^{1,22}

To achieve anterior stabilization after somatectomy, titanium mesh or expandable cages were used. We used at the cervical levels, through an anterior approach, ADDPlus mesh (Ulrich GmbH, Ulm, Germany). At the dorsal levels, through a posterior bilateral transpedicular approach, Monarch cages (DePuy Spine, Johnson & Johnson, New Jersey, USA) were used. More recently, through a lateral transthoracic approach, the hydraulic expandable cage Hydrolift (B. Braun Melsungen AG, Germany) was used. At the lumbar levels, through a lateral retroperitoneal approach or an anterior transperitoneal approach, Hydrolift expandable cages (B. Braun Melsungen AG, Germany) were also used. Posterior only or circumferential stabilization required lateral mass screws and rods at the cervical spine and transpedicular screws and rods at the thoracic and lumbar spine (Aesculap S4; S4 Spinal System, BBraun, Melsungen AG, Germany) (Figures 1 and 2).

Palliative Surgery

BKP involved the use of a balloon, associated with injection of polymethylmethacrylate, and more recently, purified silicone VK100 (BonWRX, Phoenix, Arizona, USA).

Single- or multilevel percutaneous kyphoplasty were offered to patients with metastatic lesions that caused compression vertebral fractures, without violation of the spinal canal; with plurimetameric vertebral involvement; and with an advanced stage of disease affecting the prognosis in patients whose general conditions precluded more complex surgery and/or with a modified Tokuhashi score <12.

In the same clinical setting, an open BKP, consisting of decompressive unilateral hemilaminectomy associated with a contralateral percutaneous kyphoplasty, was taken in consideration whenever the posterior wall of the vertebrae was violated with extruded soft neoplastic tissue, causing a unilateral compression of the roots and medulla. In these cases, a Tokuhashi modified score \geq 9 was not always deemed essential to undertake such palliative surgery (Figure 3).



Figure 1. (A) Sagittal T1 weighted, (B) sagittal T2 weighted, and (C) axial T1 weighted magnetic resonance imaging of a C5-C6 metastatic breast cancer lesion in a 61-year-old patient causing spinal instability and severe pain. The cervical spine had been already treated with radiotherapy. An anterior somatectomy and a posterior decompression and stabilization was

performed. (**D**) Intraoperative view of the posterior decompressed cervical medulla, (**E**) postoperative cervical radiography, and (**F**) sagittal T2 weighted magnetic resonance imaging scan demonstrating the decompressed medulla and the surgical construct. Complete postoperative resolution of pain was achieved.



Finally, a simple decompressive hemilaminectomy was performed only if the tumor presented an extension limited to the posterior/posterolateral vertebral body (Figure 4).

Tumor growth at the operation site was considered a local recurrence.

All of the patients received postoperative adjuvant chemotherapy and bisphosphonates, and 26 of the patients received postoperative RT.

Most of the patients were followed in our outpatient clinic until they maintained a reasonable quality of life: KPS score \geq 60 and retained ability to ambulate independently either alone or with crutches.

Descriptive statistics were used to describe the patient characteristics. Continuous variables are presented as median (range). Proportions are presented as numbers and percentages. The χ^2 test or Fisher exact test, when appropriate, was used to estimate all associations between categorical variables. The Mann-Whitney U test was used for comparing quantitative variables. Comparisons between the continuous variables at each time were performed by the Friedman test.

Survival rates and comparisons were estimated by the Kaplan-Meier survival curves and the log-rank test. Follow-up was estimated by the Kaplan-Meier reversed method.

All tests were 2-sided, and $P \leq 0.05$ was considered to be statistically significant.

The statistical software package used for this analysis was SPSS for Windows version 21.0 (IBM Corporation, Armonk, New York, USA).

RESULTS

There were 41 patients with breast carcinoma who underwent surgical procedures related to epidural spinal cord compression, spine mechanical instability, or excruciating pain. Demographic and clinical characteristics of this cohort of the patients are summarized in Table 1.

The median duration of follow-up in our patients from first spinal surgery was 55 months (95% confidence interval [CI], 43–67), and the median duration of follow-up from diagnosis of breast cancer was 168 months (95% CI, 110–226).

One patient was lost at follow-up soon after surgery.

There were 24 patients (59%) who died during the follow-up, most of them (n = 22; 92%) because of progression of their systemic disease.

In 39 cases the histology of breast cancer was a ductal infiltrative carcinoma; in 2 cases it was a lobular infiltrative carcinoma.

The patients were also stratified as having estrogen (ES), progesterone (PgR), or human epidermal growth factor 2 subtype receptors (HER2).

Synchronous metastases were observed in 5 out of the 41 patients (12%).

Figure 2. (A) Sagittal, (B) coronal T2 weighted, and (C) sagittal computed tomography scan imaging of a single L3 metastatic lesion in a 45-year-old patient with breast cancer. (D) Positron emission tomography scan demonstrating a broad pathologic fluorodeoxyglucose (18F) hyperfixation in L3. This patient suffered excruciating lumbar pain, resistant to pharmacologic therapy. Because the Tokuhashi score was 13, the posterior vertebral wall was breached, and the overall prognosis based on

Of the patients, 36 (88%) presented only bone metastatic disease, and 5 (12%) had osseous and visceral metastases.

Of the patients, 24 had tumor involvement of only 1 vertebral body, as diagnosed through MRI and scintigraphy. The remaining 17 patients had other multiple metastatic lesions of the spine, at least one of which was symptomatic.

Twenty patients did not present with neurologic deficits; their main symptom was pain. The other 21 patients presented with neurologic deficits, including mild paraparesis in 14 patients (ASIA grade D) and severe paraparesis in 7 patients (ASIA grade B or C).

Of the patients, 27 were operated on at 1 vertebral level, and 11 were operated on at multiple contiguous vertebral levels. Three patients were operated on in the same surgical session at distant not contiguous vertebral levels, with a percutaneous BKP associated with an open BKP in 2 cases and with a percutaneous BKP associated with a laminectomy and posterior stabilization in 1 case.

One patient was operated on twice at the same level, and another patient was operated on 3 times at different dorsal levels for symptomatic recurrences.

No patient received preoperative embolization.

The median interval between diagnosis of breast cancer and the first spine surgery for metastases was 60 months (range, o-228 months).

The median Tokuhashi modified score of the 41 patients was 12: 2 cases had Tokuhashi scores between 0 and 8, 17 cases had Tokuhashi scores between 9 and 11, and 22 cases had Tokuhashi scores between 12 and 15.

This series includes 28 cases of palliative surgery (percutaneous BKP: n = 14; open BKP: n = 10; decompressive hemilaminectomy: n = 4) and 13 cases of excisional surgery (posterior stabilization: n = 3; vertebrectomy/somatectomy, n = 10).

The median SINS score was 10 (range, 5-17). In the palliative surgery group it was 10 (range, 5-14), and in the complex surgery group it was 14 (range, 5-17; P < 0.0001).

Complications were observed in 6 cases (14.6%): a cerebrospinal fluid leak and a myocardial infarction which occurred postoperatively and an instrumentation failure 9 months after surgery in 3 patients who underwent excisional surgery (3/13; 23%); and a wound surgical revision for diastasis of its margins, a significant but asymptomatic intradiskal leakage and an intracanalar cement leakage causing a further neurologic deterioration from ASIA grade D to C in another 3 different patients who underwent palliative surgery (3/28; 10.7%). This difference was not statistically significant (P = 0.36).

In 33 patients, histologic diagnosis confirmed metastatic lesion. In 8 cases, the histologic examination was negative for tumor localization and the final diagnosis was osteoporosis, with evidence of severe loss of connected trabecular bone.

The patients' median LOS was 5 days (range, 2–30 days).

comprehensive oncologic judgement appeared to be good, it was decided to perform an excisional surgery. (**E**) Operative lateral position of the patient for L3 somatectomy through a left lateral approach, followed by a posterior standard stabilization. (**F**) Intraoperative view after somatectomy and intersomatic expandable cage insertion (**G**) Postoperative radiograph. (**H**) Tridimensional reconstructed computed tomography scan showing the final circumferential stabilization.





The median LOS in palliative surgery was 3.5 days (range, 2-25 days), whereas it was 10 days (range, 5-30 days) in complex surgery. This difference was statistically significant (P < 0.0001).

All of the 20 patients with ASIA grade E before surgery did not change their ASIA grade. Among the 21 patients with neurologic deficits before surgery, 11 (52%) improved, 9 remained unchanged (43%), and only 1 (5%) further deteriorated.

As such, most patients preserved or improved their ASIA grade after surgery, and this result was maintained until the last neurosurgical follow-up before systemic deterioration occurred (P < 0.0007). Preoperatively, patients with ASIA grade E represented 48.8% of the series, postoperatively they represented 58.5%, and at the last follow-up they reached 72.5%. One patient was lost at follow-up (Figure 5).

The median preoperative KPS score was 60 (range, 40–80). The median postoperative KPS score was 70 (range, 50–90). At the last follow-up, the KPS score was 75 (range, 50–100).

This difference was significant (P < 0.0001). Concerning the KPS score, we did not observe statistically significant differences between the subgroups of patients who underwent palliative and complex surgical procedures in the 3 observation times (preoperative: P = 0.32; postoperative: P = 0.24; follow-up: P = 0.10).

The median VAS preoperative score was 80 (range, 60–90). The median VAS postoperative score dropped to 40 (range, 10–80). At the last follow-up the median VAS score was 30 (range, 0–70).

This difference was again significant (P < 0.0001). Concerning the VAS score, no statistically significant differences between the palliative and the complex surgical procedures subgroups of

Table 1. Demographic and Clinical Characteristics of 41	
Patients with Breast Cancer Who Underwent Surgery for Spi	in
Metastases	

Characteristic	Value
Median age (range) (years)	58 (34-84)
Median follow-up from primary breast diagnosis (range) (months)	168 (110—226)
Median follow-up from first spinal surgery (range) (months)	55 (43—67)
Histology of breast cancer	Ductal infiltrative: 39 (95) Lobular infiltrative: 2 (5)
Receptors status	
ES+	30 (73)
PgR+	29 (71)
HER2+	9 (22)
ES—	11 (27)
PgR—	12 (29)
HER2—	32 (78)
Triple negative ES—PgR—HER2—	7 (17)
Synchronous metastases	5 (12)
Other sites of metastases at time of surgery	Skeletal metastases only: 36 (88) Skeletal and visceral metastases: 5 (12)
Number of vertebral involvement	Only 1:24 (59)
	Multiple:17 (41)
Number of levels surgically treated	57 in 41 patients
	Only 1:26 (63)
	Multiple:15 (37)
Site of treated vertebrae	
Cervical	4 (7)
Thoracic	35 (61)
Lumbar	18 (32)
Median time between primary breast cancer diagnosis and spine surgery (range) (months)	60 (0—228)
Median Tokuhashi score	12
Patients stratification based on Tokuha	ashi score
0—8	2 (5)
9—11	17 (41)
12—15	22 (54)
Median SINS score	10 (palliative surgery: 10; excisional surgery: 14)
Preoperative ASIA grade	
А	0
	Continues

Table 1. Continued				
Characteristic	Value			
В	1 (2)			
С	6 (14)			
D	14 (34)			
E	20 (49)			
Palliative surgery	28 (68)			
Complex excisional surgery	13 (32)			
Metastatic lesion confirmed at diagnosis	33 (80)			
Metastatic lesion not confirmed at diagnosis	8 (20)			
Median LOS (range) (days)	5 (2–30) (palliative surgery: 3.5 [2–25]; excisional surgery: 10 [5–30])			
Median overall survival (months)	114 (95% Cl, 78—150)			
Median survival after spine surgery (months)	50 (95% Cl, 35—65)			
Median survival with retained ambulatory capability and KPS score \geq 60 (months)	50 (95% Cl, 39—61)			
Values are n (%) or as otherwise indicated.				

ES, estrogen; PgR, progesterone; HER2, human epidermal growth factor 2 subtype; SINS, Spinal Instability Neoplastic Score; ASIA, American Spinal Injury Association; LOS, length of hospital stay; CI, confidence interval; KPS, Karnofsky Performance Status Scale

patients were observed in the 3 observation times (preoperative: P = 0.53; postoperative: P = 0.94; follow-up: P = 0.24) (Figure 6).

The median overall survival of this cohort of patients was 114 months (95% CI, 78–150), whereas the median survival after the first spine surgery was 50 months (95% CI, 35-65).

In patients with positive histology, the median survival after surgery was 50 months (95% CI, 34–66). In patients with negative histology, it was 57 months (95% CI, 34–80; P = 0.28).

Patients with concomitant visceral and osseous metastases presented a median survival after surgery of 37 months (95% CI, 1-74); patients affected by osseous metastases only had a median survival of 50 months. This difference showed a trend toward significance (95% CI, 32-78; P = 0.06).

In patients treated with palliative surgery, the median survival after surgery was 37 months (95% CI, 26-48). In those patients treated with complex surgery it was 57 months (95% CI, 41-73). This result was statistically significant (P = 0.03) (Figure 7).

The median overall survival in patients without surgical complications was 54 months (95% CI, 36-72), whereas the median overall survival in patients with surgical complications was 30 months (95% CI, 1-63) This difference was statistically significant (P = 0.03).

We did not observe any statistical difference in survival after surgery among patients with positive or negative hormonal receptors (ES: P = 0.17; PgR: P = 0.23) and human epidermal



growth factor 2 receptors (P = 0.52), among subgroups of patients with different Tokuhashi scores (0-8, 9-11, and 12-15; P = 0.20), between patients operated on 1 vertebral level versus patients operated at multiple vertebral levels (P = 0.66), and between patients who presented an elapsed time from diagnosis of primary breast cancer and the occurrence of symptomatic spine metastases superior of 3 years (P = 0.98).

The median survival of 38 out of 41 patients, who preserved a reasonable quality of life (KPS score \geq 60) and a retained ability to ambulate independently, either alone or with crutches, was 50

Variables		Median (range)	р
VAS	Pre	80 (60-90)	-0.0001
	Post	40 (10-80)	<0.0001
	FU	30 (0-70)	
KPS	Pre	60 (40-80)	-0.0001
	Post	70 (50-90)	<0.0001
	FU	75 (50-100)	

Figure 6. Temporal evolution of Karnofsky Performance Status Scale (KPS) and visual analog scale (VAS) scores in 41 patients as evaluated preoperatively, postoperatively, and at the last follow-up (FU). months (95% CI, 39–61). The median overall survival after the first spine surgery was also 50 months (95% CI, 35–65), suggesting that in such patients, the surgical treatment was able to preserve their quality of life, almost until the end of their clinical history.

DISCUSSION

The incidence of breast cancer has continued to rise in Western countries in the last decades. This event could be explained by





a real increment, an increase in the number of early diagnoses because of screening campaigns, and the elevation of the mean life expectancy in women.³

Because of current palliative therapeutic strategies, which combine RT, surgery, systemic chemotherapy, hormonal, and molecular-targeted treatments, the reported 5-year survival rate has risen to >80%, and quality of life has progressively become an essential issue to deal with.^{2,8,23}

Steinauer et al.,¹² analyzing prospectively 340 patients from the Basel Breast Cancer Database, found that at least 70% of patients developed bone metastases during their disease course, and in approximately one-quarter of the cases, these were the only metastatic sites. Similar results were obtained by other studies: patients with bone-only metastases ranged between 21% and 37% of the total.^{4,24-28}

Bone metastases appear more frequently than the development of visceral metastases in well differentiated tumors with ES and PgR positive receptors. On the contrary, spread to the liver is more likely in ES and/or PgR receptor negative tumors.^{4,6,10,25,26,28,29}

A median overall survival of 24–54 months has been reported in patients after diagnosis of a first recurrence in the skeleton as the only metastatic site, compared with 3–19.5 months in those affected by visceral metastases.^{7,9,12,25,27,30} Solitary bone metastasis, ES positivity, and bisphosphonate treatment were significantly associated with longer overall survival in the Ahn et al. review²⁵ of 110 patients with breast cancer affected by bone-only metastasis.

The diagnosis of synchronous metastases limited to the skeleton may also portend a better prognosis than in cases with extraskeletal synchronous metastases (median survival, 33 months vs. 9 months), further underlining the unique tumor biology of this subset of patients with breast cancer.^{7;9;10,27,31}

Spinal metastases are observed in 82% of patients with skeletal impairment. They involve more frequently the posterior half of the vertebral body, and up of 30% of them become symptomatic with the occurrence of severe back pain, mechanical vertebral instability, and/or neurologic dysfunction.^{1,6,8,9,23,24,26,27,32-35}

The median time from diagnosis of primary breast cancer to first spinal surgery for metastatic disease has been reported in different studies between 48 and 60 months.^{7,10,36} The thoracic spine is the most common site of compression (71%) followed by the lumbosacral (20%) and cervical column (9%).³³

Because breast cancer has a variable and often long clinical course, and particularly patients with bone metastases seem to have an indolent and protracted illness, the occurrence of symptomatic vertebral compression fractures of pathologic, osteoporotic, or iatrogenic origin may significantly undermine the ability of the patients to conduct an independent life and to sustain further cancer treatments. For such reasons, these complications may deserve an aggressive approach calling neurosurgeons and radiotherapists to play an active role in their treatment, with the aim to assure a prolonged survival with minimum cancer-related morbidity.^{10,28,37}

Treatment Options

Medical therapies of spine metastases include systemic chemotherapy, endocrine therapy, steroids, analgesics, and bisphosphonates. The latter seems highly effective in reducing bone pain, hypercalcemia, and the incidence of new pathologic fractures, whereas some commonly used drugs in patients with metastatic breast cancer (eg, aromatase inhibitors) may actually increase the risks of osteoporosis and bone lesions.^{1,38}

Spinal RT, usually delivering 30 Gy in 10 fractions to the affected vertebral bodies and those immediately above and below, is the treatment of choice in patients with localized pain not responding to systemic therapies. Good pain relief within a mean time of 35 days is usually attained in >80% of cases. The benefits of RT may be further enhanced with concomitant administration of bisphosphonates.^{1,5,8,10,39,40}

Recent developments in stereotactic radiosurgery allow the delivery of large and highly conformed target-dose radiations for the treatment of malignant vertebral body lesions, also in proximity to the spinal cord and the cauda equina, overcoming their low radiation tolerance. The total dose delivered is in the range of 8-19 Gy, and results are very promising in terms of pain control and improvement in neurologic function. Stereotactic radiosurgery requires biomechanical stability of the spine, absence of neurologic deficits, involvement of a maximum of 2 adjacent vertebral levels, and a life expectancy of >3 months.^{4;5,41}

However, because chemotherapy and RT do not rapidly restore spinal stability, surgery still preserves a significant although palliative role.

Surprisingly, data in the literature, specifically addressing results of surgical treatment of vertebral lesions in breast cancer, are still sparse.

Surgical indications usually include progressive neurologic deficits caused by significant bone, disk fragment, and/or tumor extension in the spinal canal; mechanical instability; spinal deformity; tumors that progress after maximal radiation dosages; and medically intractable pain.^{1,2,10,16,37,42}

Surgical candidates among breast cancer patients with symptomatic spine metastases have varied in different series, between 4% and 18%.^{1,7,10,33,36}

Patchell et al.¹⁷ have demonstrated in a prospective randomized trial, which included an heterogeneous series of 101 tumors (11% breast cancer), that patients affected by compressive spinal epidural metastases benefit more in terms of improved ambulation, continence, and survival after surgical treatment followed by adjuvant RT than after RT alone, reporting median survival rates of 126 days. Among them, patients with breast cancer attained better overall survival compared with other tumor histologies.^{32,36,42} Patients in the surgical group were less susceptible to infections, blood clots, and other complications of prolonged bed rest. Surgical treatment also reduced the need for corticosteroids and opioid medications. Even if bias because of selection of surgical candidates in better general condition should be acknowledged, these data were confirmed by subsequent retrospective reviews.^{2,17}

A large spectrum of surgical options, in combination with other adjuvant chemo- and radiotherapic regimens, are presently available to deal with the heterogeneous clinical conditions affecting patients with spinal metastases.

To identify which patients are the best candidates for aggressive excisional resection and which may in any case benefit from more palliative, but still surgical, treatments could be challenging.^{36,37} Different scores have been devised to aid in selecting the best adjuvant therapies.

The modified Tokuhashi score and the SINS, based on estimators of life expectancy and spine instability, although neither histologic specific nor taking in consideration pain, may also assist in decision-making in patients with breast cancer.^{1,2,15,21,22,32,36,43-45}

As for all spinal lesions in patients with cancer, excisional surgery should be considered in patients with a Tokuhashi score >12, with a predicted survival of at least 1 year, in good general conditions, and affected by solitary metastatic spinal lesions at 1-2 contiguous vertebral levels.

It requires an aggressive treatment involving vertebrectomy or somatectomy associated with posterior or lateral stabilization, which are reported to provide significant and sustained preservation of neurologic condition and improvement in pain control with decrease in VAS that lasted at least I year or even until death. No significant differences were observed between patients treated with more complex multilevel vertebrectomies compared with those treated with single-level procedures.^{1,7,10,16,32}

In our series of selected patients submitted to complex surgery, the drawbacks of a prolonged LOS and a theoretical but not confirmed, higher rate of postoperative complications, were outweigh by a significant increase of median overall survival compared with those submitted to palliative only surgery.

Less invasive techniques, such as percutaneous stabilization, vertebroplasty, and kyphoplasty (BKP) with their technical variations, have been shown to be effective alternatives for intractable pain and mechanical instability, secondary to pathologic compression vertebral fractures, in cases where the posterior vertebral wall is preserved and epidural compression is absent; with multilevel lesions which precluded a standard stabilization; and in which the patients could not tolerate for medical reasons or because of limited life expectancy prolonged and/or complex surgical procedures. Their reported advantages included reduced postoperative pain, shorter overall hospital stay, less intraoperative blood loss, and an earlier start of adjuvant therapies.^{1,22,41,46-48}

Vertebroplasties and BKPs consist of percutaneous transpedicular injections of bone cement or, more recently, purified silicon inside the injured vertebra under radioscopic guidance, and they aim to fill the anterior two-thirds of the vertebral body with the selected material, to reinforce it, and in some cases to correct its deformity. Pain control after such procedures is reported in 50%–80% of cases.

The major complications are inadvertent leakage of the filling material inside the spinal canal, with compressions of the neural structures or in the epidural plexus vessels, possibly leading to pulmonary embolism. This is a not negligible risk in metastatic vertebrae, where the bone structure is often significantly altered and the incidence of such complications in patients with cancer may reach 10%. In BKP, differently from vertebroplasty, previous dilatation of the vertebral body is attained with intravertebral inflation of a balloon, which creates a cavity apt to receive the cement with gradual pressure, reducing the risk of leakages from 11%-76% to 4.8%-39%. For this reason, we favored this latter technique in cancer patients with lytic lesions.⁴⁰

The recent Cancer Patient Fracture Evaluation randomized controlled trial and other different retrospective studies confirmed that BKP is an effective and safe treatment that rapidly reduces pain and improves function even in advanced cancer disease. Operated patients demonstrated a superior functional outcome at 1 month compared with patients who received nonsurgical management, with prompt mobilization, marked reduction in back pain, and improvement in quality of life and use of pain medications. These advantages lasted for at least 12 months.^{5,49,50}

We found BKP was also effective through an open approach, in association with a decompressive hemilaminectomy and pediculectomy, whenever it was necessary to relieve an anterolateral epidural compression or when the posterior vertebral wall was partially violated, to rapidly deal with a possible cement leakage inside the vertebral canal.

This technique has enlarged the surgical armamentarium, enabling us to include patients who were in the middle between palliative treatment and surgery.

Moreover, during a somatectomy/vertebrectomy, using cement or silicone has often proved to be useful to reinforce the adjacent vertebrae as an augmentation technique and has allowed for better accommodation of the transpedicular or lateral screws of a circumferential stabilizations.

Posterior hemilaminectomies should be only considered to relieve pure posterior compression of the spinal cord or to obtain reliable histologic biopsies.¹³

Surgical Complications, LOS, and Quality of Life

The complication rates of surgical treatment of metastatic spinal disease range from 10% to 52%. In their surgical series of 87 patients affected by breast cancer, Shehadi et al.¹ reported an overall incidence of complications of 39% (major complications reported at 26%, mainly caused by instrumentation failure). Blood losses >2500 mL and instrumentation of 5 or more spine levels were significantly associated with surgical complications. Tumor recurrence was observed in 23% of 87 patients after a median follow-up of 13 months.^{10,15,51}

In our series, the overall complications rate was 14.6%: 23% in complex surgical cases versus 10.7% in palliative surgical cases. However, this difference was not significant; the overall survival was better in the complex surgery subgroup, whereas the complicated patients survive significantly less than not complicated ones. We observed 3 cases of tumor recurrences out of 41 patients (7.3%).

As reported in other series of surgically treated patients, a large proportion of our patients maintained and even improved their ASIA grade, KPS score, and VAS score postoperatively, with preservation of these benefits throughout the follow-up period and, in many cases (90%), almost until death. All of the 20 patients with ASIA grade E before surgery did not change their ASIA grade. Among the 21 patients with neurologic deficits before surgery, 11 (52%) improved, 9 remained unchanged (43%), and only 1 (5%) further deteriorated after treatment. These data seem to indicate that also in this field of spine surgery, better postoperative results could be achieved if patients are operated on in good neurologic conditions.

A careful selection of the surgical technique, tailored to the predicted possible long-term survival of such patients, could be also essential to avoid late mechanical failures of the implanted spinal instrumentation.^{1,43}

Prognostic Factors and Overall Survival

The median overall survival after surgery for spine metastases steadily improved in the last decades from 4 months in 1993 to 21 in 2007 to a range between 26 and 36 months in 2011, reflecting the likely relevant contribution of new chemotherapies, molecular adjuvant therapies, RTs, and improved surgical techniques.^{10,15,33,36}

Attempts to identify survival prognostic factors in metastatic spine disease of breast cancer have yielded controversial results, probably because of the main limitations of our and other available studies: their retrospective nature and the bias introduced by the selection of patients for surgery.

In their review of 87 patients, reported by Sciubba and Shehadi¹, the median survival of patients after the first spinal surgery for metastases was 21 months, with an overall survival rate of 62% at 1 year, 44% at 2 years, and 33% at 3 years.

In this series, the ES positivity of the tumor was significantly associated with a better prognosis in multivariate analysis, whereas the presence of multiple vertebral lesions and even of visceral metastases did not affect survival. Metastases located in the cervical spine demonstrated a trend toward a worse post-operative overall survival compared with dorsolumbar lesions. Even if the number of metastatic vertebrae did not affect the survival in the study, it influenced surgical strategy, either regarding the surgical approach or the subsequent reconstruction. This was true also in our series where patients with multiple involvement were selected for less aggressive types of surgery, such as closed or open BKP.^{1,10,32}

In the Hill et al. series³³ of 70 patients, 21 of whom underwent surgery, a highly significant improvement in survival was observed for patients affected by spinal cord compression when they were able to walk after either decompressive or radiotherapic treatment compared with those who were not. The only other significant positive predictor of survival was an elapsed time between diagnosis of primary breast cancer and spinal cord compression, superior of 3 years. This latter observation was not confirmed in our series.

Recently Walcott et al.¹⁵ reported the results in a small group of 15 patients surgically treated for epidural spinal cord compression: no significant difference in median survival between patients groups with good or poor systemic disease control was observed. Better overall survival was reported for patients who underwent surgery without previous neurologic deficits or who improved after decompression.

Zadnik et al.,³⁶ analyzing the results of surgery between 2002 and 2011 in 43 patients, reported that the age of patients, the preoperative functional status score (KPS), the presence of visceral metastases, the spinal operated levels, and the type of surgery at single or more levels were not associated with survival differences.

On the contrary, both Chan-Seng et al.²³ and Weber et al.⁵² found in their retrospective studies on 140 and 147 patients, respectively, that the number of extraspinal organs involved by metastases was an independent negative prognostic factors of

overall survival in patients with metastatic spinal cord compression from breast cancer.

We observed only a trend toward significance in median overall survival between patients with or without visceral metastases, possibly because of the small number of patients belonging to the latter subgroup. On the other hand, we could not identify any significant differences in overall survival among patients with positive versus negative hormonal receptors, operated at single versus multiple levels, displaying a positive versus negative histology for tumors at the treated vertebrae, and with a Tokuhashi score <12 versus \geq 12.

In 38 out of the 41 patients, the median survival preserving a reasonable quality of life (KPS score \geq 60 and retained ability to ambulate independently either alone or with crutches) was 50 months (95% CI, 39–61). Because the median overall survival after the first spine surgery was also 50 months (95% CI, 35–65), this result indicates that in such a subset of patients, the surgical treatment may contribute to preserve quality of life almost until the final phase of their neoplastic disease.

To analyze the impact of quality of life, more specific tests can be used, but still the KPS score seems to retain a leading role as a measurement and prognostic instrument.³⁷

The longer overall survival in our series compared with others probably reflects the selected cohort of cases we treated, with a prevalence of patients with only bone metastases, positive hormone receptors, higher Tokuhashi scores, low incidence of tumorassociated comorbidities, the absence of significant postoperative complications, and the benefits derived from the recently introduced adjuvant targeted therapies they all received.^{42,43,53,54}

CONCLUSIONS

The treatment of symptomatic spinal metastases remains palliative and its primary aim is not to prolong survival. However, a carefully selected subset of patients affected by breast cancer and vertebral lesions to the spine may significantly benefit from surgical techniques tailored to their conditions.

Surgery is a reasonably safe and effective treatment for symptomatic spinal lesions, preventing rapid deterioration of quality of life and neurologic functions. Major excisional surgery, albeit associated with prolonged LOS and possibly higher complications rate, allowed in our series a prolonged survival compared with less aggressive type of surgery.

Percutaneous or open BKP techniques have further expanded surgical indications for palliative surgery, including patients with lower Tokuhashi scores, who may take great advantage from rapid and sustained pain relief, preservation of neurologic function, and early mobilization.

ACKNOWLEDGMENT

We thank Ms. Marzia Piccoli for editorial assistance.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 23 December 2015; accepted 12 February 2016

Citation: World Neurosurg. (2016) 90:133-146. http://dx.doi.org/10.1016/j.wneu.2016.02.065

Journal homepage: www.WORLDNEUROSURGERY.org

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