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Survival Rate and Neurological Outcome after Operation for Advanced Spinal Metastasis (Tomita's Classification ≥ Type 4)

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Purpose: We investigated whether primary malignancy entities and the extent of tumor resection have an effect on the survival rate and neurological improvement in patients with spinal metastases that extend beyond the vertebral compartment (Tomita's classification ≥ type 4). **Materials and Methods:** We retrospectively reviewed 87 patients with advanced spinal metastasis who underwent surgery. They were divided into groups 1 and 2 according to whether they responded to adjuvant therapy or not, respectively. They were subdivided according to the extent of tumor resection: group 1, gross total resection (G1GT); group 1, subtotal resection (G1ST); group 2, gross total resection (G2GT); and group 2, subtotal resection (G2ST). The origin of the tumor, survival rate, extent of resection, and neurological improvement were analyzed. **Results:** Group 1 had a better survival rate than group 2. The G1GT subgroup showed a better prognosis than the G1ST subgroup. In group 2, the extent of tumor resection (G2GT vs. G2ST) did not affect survival rate. In all subgroups, neurological status improved one month after surgery, however, the G2ST subgroup had worsened at the last follow-up. There was no local recurrence at the last follow-up in the G1GT subgroup. Four out of 13 patients in the G2GT subgroup showed a local recurrence of spinal tumors and progressive worsening of neurological status. **Conclusion:** In patients with spinal metastases (Tomita's classification ≥ type 4), individuals who underwent gross total resection of tumors that responded to adjuvant therapy showed a higher survival rate than those who underwent subtotal resection. For tumors not responding to adjuvant therapy, we suggest palliative surgical decompression.

Key Words : Bone neoplasm, decision making, metastasis, prognosis

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INTRODUCTION

The spine is the most common site for skeletal metastasis in patients with malignancy.[1-3] Approximately 30-70% of patients with an advanced malignancy have an evidence of spinal metastasis.[4-6] Surgical treatment of spinal metastases, particularly when the tumor extends beyond the anatomical barrier of the spine, remains a source of debate.[4,7,8] Many clinicians consider radiation therapy as the initial choice of treatment for spinal metastases of malignant tumors;[9,10] however, surgical intervention for spinal metastatic tumors is still indicated for patients with intractable pain that is unresponsive to conservative care, signs of neurological compromise, spinal instability observed on radiological evaluation, and for patients who do not respond to radiation therapy and/or chemotherapy.[2] Moreover, total resection of complicated metastatic spinal tumors is possible using recently developed surgical techniques, such as total en bloc spodylectomy.[8,11]

The goals of surgical intervention are to prolong the survival period and improve

the quality of life of patients, with minimal surgical complications. Therefore, prognostic factors for spinal metastasis need to be well established in order to reach an appropriate decision on treatment modalities. In general, the survival rate of malignant tumors is largely dependent on the histology of the primary tumor and on the presence of visceral or bone metastases, which include spine metastasis.[12,13] According to preoperative scoring systems, which serve to determine the surgical strategy for spinal metastases, rapidly growing primary tumors, visceral metastases, and multiple bone metastases are poor preoperative prognostic factors.[12,13]

Tomita, et al.[11,14] devised a surgical classification of spinal tumors in which intracompartmental, extracompartmental, and multiple lesions are classified according to tumor location inside or outside the vertebral anatomical barrier. Extracompartmental lesions include metastatic tumors that grow into the spinal canal (type 4), extend outside the vertebral body (type 5), and finally spread to the adjacent vertebra(e) (type 6). Multiple-skip spinal metastases represent type 7. In terms of surgical prognostic factors, excellent results have been reported for aggressive total en bloc spondylectomy of intracompartmental tumors;[8,11,13] however, few prognostic factors associated with surgical resection are known for spinal metastases that extend beyond the anatomical barriers and compartment (Tomita's classification ≥ type 4).

The aim of this study was to evaluate whether the extent of tumor resection in different primary tumors has an effect on the survival rate and neurological outcomes in patients with advanced spinal metastasis (Tomita's classification ≥ type 4).

MATERIALS AND METHODS

Patients

This study was based on a retrospective review of 87 patients (male-to-female ratio, 50 : 37) who had advanced spinal metastasis that extended beyond the anatomical barrier (Tomita's classification ≥ type 4) and who underwent surgical intervention in our institution between August 1997 and February 2008. The mean age of the patients was 57 years (range, 27-76). The average clinical and radiological follow-up period was 24.5 months (range, 1-75 months) (Table 1).

Surgery was performed in patients who had six months or more of life expectancy, as predicted by oncologists, and who had progressive neurological deficit before, during, or after radiation therapy, and who had intractable pain unresponsive to conservative treatment, and/or spinal instability or vertebral collapse. Some patients were under radio- and/or chemotherapy. If the neurological status or spinal stability of the patient worsened during adjuvant therapy, we considered surgical tumor resection and stabilization of the spinal column. The adjuvant therapy

Table 1. Characteristics of Patients with Spinal Metastases

	Group 1	Group 2	Total
No. of patients	36	51	87
Male-to-female ratio	14 : 22	36 : 15	50 : 37
Mean age (yrs)	54.0 (12 - 75)	55.7 (16 - 79)	55 (12 - 79)
Mean follow-up (months)	28.6 (2 - 75)	9.1 (1 - 50)	17.6 (1 - 75)
Spinal location			
Cervical	4	11	15
Thoracic	24	29	53
Lumbar	7	11	18
Sacrum	1	0	1
Tomita's classification			
Type 4	9	7	16
Type 5	9	8	17
Type 6	7	16	23
Type 7	11	20	31
Extent of tumor resection			
Gross total	(G1GT, 15)	(G2GT, 13)	28
Subtotal	(G1ST, 21)	(G2ST, 38)	59

G1GT, gross total resection in group 1; G1ST, subtotal resection in group 1; G2GT, gross total resection in group 2; G2ST, subtotal resection in group 2.

was resumed after confirmation of the complete healing of the surgical wound. Patients who were followed-up for more than one year after the operation and who had a definite primary malignancy lesion were included in this study. Patients who died within one year of the operation were also included.

For tumor grading using Tomita's classification, we used bone scintigraphy, preoperative magnetic resonance imaging (MRI) of the entire spine, and computed tomography (CT) of the chest, abdomen, and brain. Exclusion criteria for the study were as follows: spinal metastasis with unknown primary origin, a follow-up period shorter than one year, tumor grade less than type 4 (Tomita's classification), and patients who underwent only biopsy or vertebroplasty.

Grouping of the patients

The patients were divided into two groups according to the characteristic of the primary malignant tumor:[11,15-18] group 1 included tumors known to respond to adjuvant chemotherapy, radiotherapy, or hormonal therapy (thyroid cancer, breast cancer, prostate cancer, and hematopoietic malignancy); group 2 comprised tumors known not to respond well to adjuvant therapy (lung cancer, hepatocellular carcinoma, pancreas cancer, renal cell cancer, sarcoma, and gastrointestinal cancer).

Groups 1 and 2 were further divided into two subgroups according to the extent of tumor resection (gross total vs. subtotal), which was analyzed using radiological studies and operation records. Gross total resection meant that no tumor mass remained attached to the surrounding normal tissues via thorough debulking and removal of the marginal barriers or total en bloc spondylectomy via a posterior-only or anterior-posterior combined approach. For subtotal resection, laminectomy or internal decompression with/without instrumentation was performed. Patients with remaining tumor mass at the operated site or at other bone sites (including vertebrae) were classified in the subtotal resection group. As a result of patient grouping according to extent of surgical resection, four subgroups were obtained: group 1, gross total resection (G1GT); group 1, subtotal resection (G1ST); group 2, gross total resection (G2GT); and group 2, subtotal resection (G2ST) (Table 1 and 2).

Evaluation of survival rates and neurological status

We analyzed survival periods, grade of metastatic spinal tumor (using Tomita's classification), primary tumor entities, extent of tumor resection, and neurological outcomes. The survival period after operation was calculated to the last date of the follow-up in the patients who were still alive, or to the date of expiration. Statistical analysis of the survival period was performed using the Kaplan-Meier method and the log-rank test was used for statistical comparisons. Significance was achieved if the probability was lower than 5% ($p < 0.05$).

The neurological outcome was graded before and after surgery using Frankel's grade system.[19] We converted Frankel's grades A, B, C, D, and E into Frankel's points 1, 2, 3, 4, and 5. To compare neurological improvement among the four subgroups, the sum of Frankel's points in each subgroup was expressed as a percentage of the sum of full points: $100 \times \Sigma$ (patients' Frankel points)$/5 \times$ (number of patients). The neurological status of each subgroup was estimated and compared at the preoperative stage, at one month after surgery, and at last follow-up. Statistical analysis of the neurological outcome was performed using the paired t test. Significance was achieved if the probability was lower than 5% ($p < 0.05$).

RESULTS

Characteristics of patients in groups 1 and 2

Patient characteristics are listed in Table 1. Groups 1 and 2 comprised 36 and 51 patients, respectively. The most frequent site of spinal metastasis was the thoracic spine (67% of patients in group 1 and 57% of patients in group 2), followed by the lumbar and cervical spine.

Among the 87 patients, 56 individuals had an isolated spinal metastasis (Tomita classification types 4, 5, or 6), whereas 31 patients had multiple metastases (type 7). In terms of multiple bone metastases, 39% of patients in

Table 2. Tomita's Classification according to the Extent of Tumor Resection

Tomita's classification	G1GT	G1ST	G2GT	G2ST	Gross total resection (%)
Type 4	8	1	5	2	81
Type 5	5	4	3	5	47
Type 6	2	5	5	11	30
Type 7	0	11	0	20	0
Total	15	21	13	38	32

G1GT, gross total resection in group 1; G1ST, subtotal resection in group 1; G2GT, gross total resection in group 2; G2ST, subtotal resection in group 2.

group 2 were type 7 and 31% of patients in group 1 were type 7.

Gross total resection of tumors was achieved in 28 patients (32%). Gross total resection of spinal tumors was performed more frequently in group 1 than in group 2 (42% vs. 25%). In terms of Tomita's classification, the ratio of gross total resection was 81, 47, and 30% for Tomita's type 4, 5, and 6, respectively (Table 2).

Tumor origin and pathological diagnosis

Among the 36 patients included in group 1, the most common origin of primary tumors was the bone marrow (12 cases) and breast tissues (12 cases), followed by the thyroid (9 cases) and the prostate (3 cases). Among the 51 patients included in group 2, the lung (12 cases) was the most common primary tumor site, followed by the liver (8 cases) and the kidney (7 cases) (Table 3). Thyroid cancer cases showed the highest one-year survival rate, followed by cancers of the breast and of the bone marrow. In contrast, lung cancer patients had the worst one-year survival rate (17%), followed by liver, colon, and kidney cancers. The most common overall pathologic cell types were adenocarcinoma (23 cases), followed by ductal cell carcinoma (12 cases), plasmacytoma (8 cases), hepatocellular carcinoma (8 cases), and squamous cell carcinoma (7 cases).

Table 3. Origin of Primary Tumors

Origin of tumor	No. of cases	1-year survival rate (%)
Group 1		
Bone marrow	12	75
Breast	12	83
Thyroid	9	100
Prostate	3	N/A
Group 2		
Lung	12	17
Liver	8	25
Kidney	7	43
Colon	6	30
Rectal	3	N/A
Pancreas	2	N/A
Stomach	2	N/A
Cervix	2	N/A
Nasoparhynx	2	N/A
Uterus	1	N/A
Ovary	1	N/A
Parotid gland	1	N/A
Ethmoid sinus	1	N/A
Skin	1	N/A
Orbit	1	N/A
Chondrosarcoma	1	N/A
Total	87	

N/A indicates nonavailable survival rate because of the small sample size.

Survival rates

Patients in group 1 had a better survival rate than patients in group 2 (p = 0.009) (Fig. 1). The mean survival period was 28.6 months (range, 2-75) for group 1 and 9.1 months (range, 1-50) for group 2. In group 1, 5 out of 36 patients

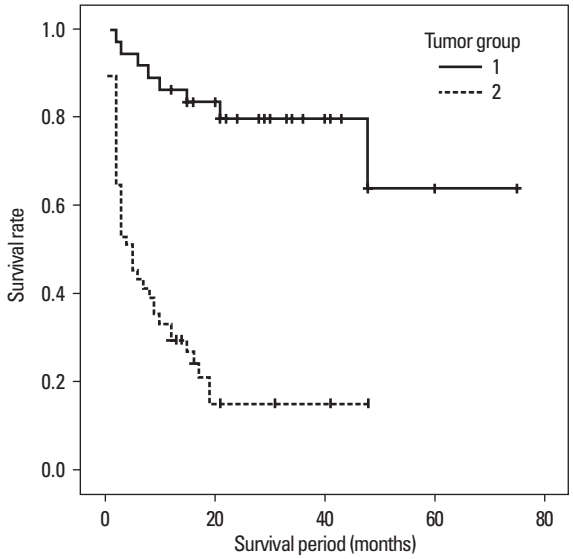

Fig. 1. Comparison of the postoperative survival rate between groups 1 and 2. Kaplan-Meier survival curves of patients with spinal metastases in group 1 (breast cancer, thyroid cancer, hematopoietic malignancy, and prostate cancer) and group 2 (lung cancer, hepatocellular cancer, renal cell cancer, colon cancer, pancreas cancer, rectal cancer, etc) showed a significantly higher survival rate for patients in group 1 (p<0.01).

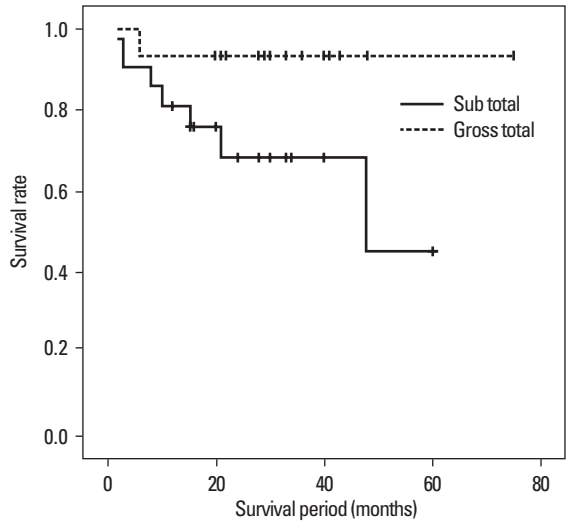

Fig. 2. Comparison of the postoperative survival rate between gross total resection and subtotal resection subgroups of group 1. Kaplan-Meier survival curves revealed a significantly higher survival rate for patients who received gross total resection of tumor when compared with subtotal resection (p = 0.049).

had died within one year after the operation (one-year survival rate = 86.2%); however, 28 patients were alive at the last follow-up. In group 2, 34 out of 51 patients died within one year after the operation (one-year survival rate = 33.3%) and only 13 patients were alive at the last follow-up. The average follow-up period for patients in groups 1 and 2 who died was 27.1 and 7.8 months, respectively.

The analysis of the survival rate according to the extent of tumor resection revealed that one patient expired six months after the operation and the remaining 14 patients in the G1GT subgroup were alive at the last follow-up. In contrast, 7 out of 21 patients in the G1ST subgroup, expired and 14 patients were alive at the last follow-up. Therefore, the G1GT subgroup showed a significantly better survival rate (p = 0.049) when compared with the G1ST subgroup (Figs. 2 and 3). The mean survival period was 36.5 months (range, 2-75) for the G1GT subgroup and 28.3 months (range, 1-60) for the G1ST subgroup. In group 2, the extent of tumor resection (G2GT vs. G2ST) did not affect the survival rate of patients (p = 0.115) (Fig. 4).

Forty-six patients died before the last follow-up: 8 patients (22.2%) in group 1 and 38 patients (74.5%) in group 2. The most common causes of death were major organ metastasis and failure, especially pulmonary and hepatic failure. Six patients expired because of septic shock and one patient expired because of intracerebral hemorrhage. There were no significant differences in the cause of death between groups 1 and 2.

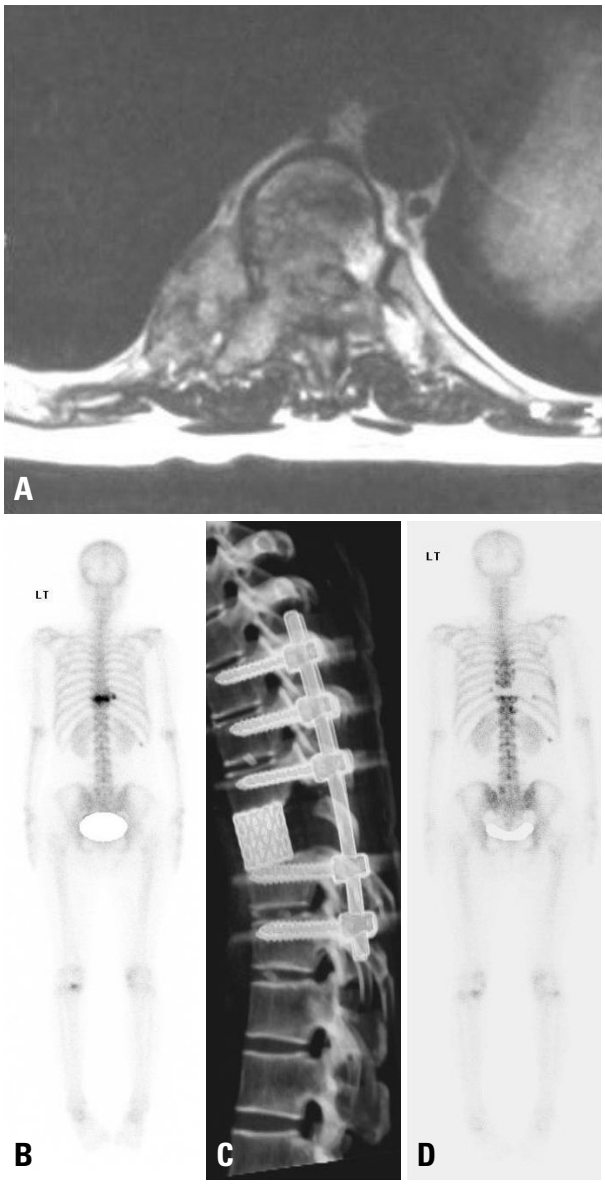

Fig. 3. Illustration of a case of metastatic thyroid cancer involving the T9 vertebra. A 53-year-old female patient, who had severe back pain and paraparesis, underwent gross total resection of the tumor using an anterior and posterior combined approach and instrumentation. (A) T1-weighted MR axial image shows metastatic spinal tumor extended to the right paraspinal space (Tomita's classification type 5). (B) Preoperative bone scintigraphy image shows single metastatic lesion on T9. (C) Postoperative X-ray image shows posterior pedicle screw fixation after total T9 spondylectomy. The mesh cage was filled with polymethylmethacrylate. (D) Bone scintigraphy image taken 39 months after surgery shows resected T9 vertebra and ribs without recurrent lesion.

Neurological improvement and local recurrence after gross total resection

In the G1GT subgroup, preoperative neurological status was 89% of full points, which significantly improved to 98% one month after the operation and to 99% at the time of last follow-up (p = 0.008). There was no significant difference in neurological status between one month after the operation and the last follow-up. In the G1ST subgroup, the neurological status at one month after the operation improved slightly from 76 to 80% (p = 0.961), but worsened to 76% at the time of the last follow-up. In the G2GT

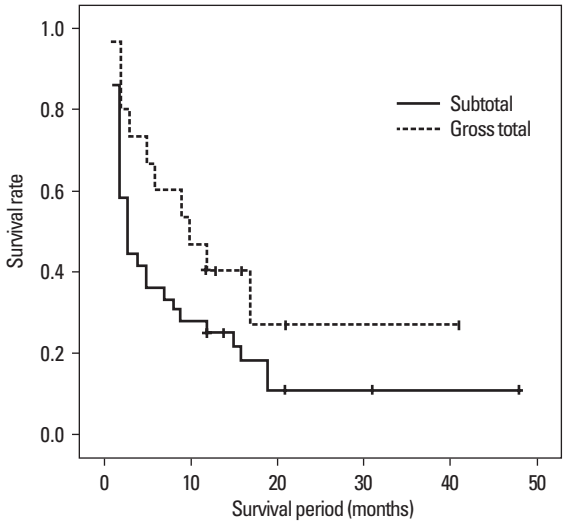

Fig. 4. Comparison of postoperative survival rate between gross total resection and subtotal resection subgroups of group 2. Kaplan-Meier survival curves show absence of statistical differences between patients who received gross total and subtotal resection of tumor (p = 0.115).

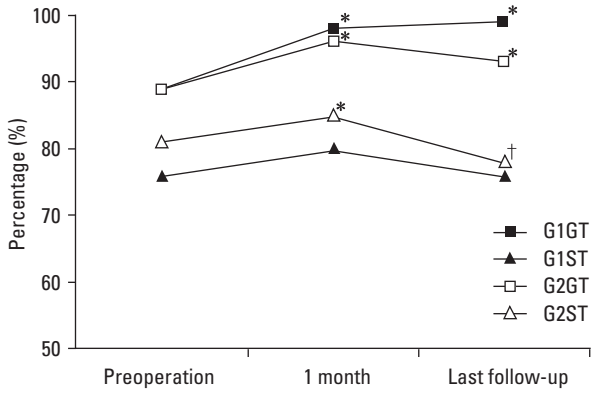

Fig. 5. Neurological grade assessed by conversion of Frankel's grade system to a point system. The neurological status of the G1GT and G2GT subgroups was significantly improved one month after surgery and at the last follow-up. In contrast, the G1ST and G2ST subgroups improved shortly after surgery but worsened at the time of last follow-up; in particular, the neurological status of the G2ST subgroup became even worse than at the preoperative stage. *Significantly improved neurological status when compared with the preoperative stage ($p < 0.05$). † Significantly worsened neurological status when compared with the preoperative stage ($p < 0.05$).

subgroup, the neurological status improved significantly from 89% preoperatively to 96% one month after the operation ($p = 0.019$), but worsened to 93% at the last follow-up; however, there was a significant improvement in neurological status between the preoperative time point and the time of last follow-up ($p = 0.041$). In the G2ST subgroup, the neurological status improved from 81% to 85% ($p = 0.048$) at one month after the operation, but worsened to 78% at the time of last follow-up, which was even worse than the preoperative neurological status (Fig. 5).

Three of the 15 patients in the G1GT subgroup showed a remote recurrence of spinal metastasis, which was removed by secondary operation. There was no local recurrence in the G1GT subgroup at the last follow-up. Four of the 13 patients in the G2GT subgroup had a local recurrence of spinal tumor and progressive worsening of neurological status.

DISCUSSION

In the 1980s, patients with spinal metastases were considered to be in the terminal stage of disease, as about half of them died within six months of spinal surgery.[20] Recently, however, the survival rate of malignant spinal metastases has rapidly improved because of early detection of metastases and multimodality treatment, which includes the development of surgical techniques. Life expectancy, the general condition of a patient, the characteristics of the primary tumor, and the resectability of metastatic tumor masses should be considered in the surgical treatment of advanced metastatic spinal tumors. The prognostic parameters suggested for metastatic spine tumors include the general condition of the patient, number of spinal and extraspinal metastases, primary site of the cancer, visceral metastasis, and severity of spinal cord palsy.[11-13,21] Among them, the presence of spinal tumor metastasis and spinal cord palsy are controllable surgical factors, if efficient total resection of the tumor mass can be achieved.

Our present results showed that the survival rate in cases with advanced spinal metastasis was affected largely by the pathological characteristics of the primary tumors. Before and/or after spinal tumor surgery, the primary tumor was managed medically or surgically by each responsible department. Some patients died because of major organ metastasis, even though there was no recurrence at the site of spinal surgery. It seems that 100% of thyroid cancer patients survived at the last follow-up because curative tumor resection was possible in most cases. We think that complete control of the primary tumor is as important for long-term survival as the pathological type of the tumor. Previous studies addressing the survivability of patients showed a favorable prognosis for cases with spinal metastases,[11,13,22,23] myeloma, breast, thyroid, and prostate cancers, while patients with cancers of the lung, liver, and gastrointestinal tract had poor prognosis. Visceral metastases at the time of the first surgical treatment of a bony metastasis are significantly correlated with survival time,[24,25] and, as shown in this study, major organ failure is the most common cause of death. Cancers of the lung and liver, which were classified as tumors not responding well to adjuvant therapy (group 2) in this study, are the most common metastatic spinal tumors, and the primary sites themselves represent the beginning of major visceral organ failure. In renal cell cancer, the prognosis ranges from favorable to poor.[13,22,26] In the case of intracompartmental metastasis, a long survival time would be expected after total en bloc spondylectomy.[11,13] As all the cases in our series were extracompartmental spinal metastasis, renal cell cancer (Tomita's classification ≥ type 4) was classified as group 2. Nevertheless, the renal cell cancer cases analyzed here exhibited a better survival rate when compared with lung, liver, or colon cancer cases. Our results seem to indicate that the characteristics and controllability of the primary tumor are of vital importance in the decision-making process regarding the goal of the surgery (i.e., gross total removal or palliative decompression). Overtreatment of the patients by aggressive resection to obtain minimal surgical benefits must be avoided; however, aggressive total tumor resection should be a surgical goal for patients who have spinal metastasis from a favorable primary tumor, even if the metastasis extends beyond the vertebral compartment.

Although cases of spinal metastasis from low-grade malignant tumors show a higher survival rate after surgery, surgeons may be conflicted as to whether total removal or subtotal resection of the tumor should be performed. As surgery-related complications, which include wound infection, excessive blood loss, neurological deterioration, and death, can occur,[2] aggressive surgical intervention remains debatable. Because the tumor mass extended beyond the barriers in our series, it was difficult to remove the whole mass en bloc and had to be removed frequently in multiple pieces. During the initial periods of this study, subtotal resection was more frequent than gross total resection. In the G1GT subgroup, total en bloc resection was possible only in 5 of 15 patients (33.3%). In the remaining 10 patients (66.7%), the tumor mass was removed by dividing it into several pieces or by debulking the main mass followed by thorough marginal resection, because of the large tumor size and irregular margin of invasion. In the group 1 tumors, though the cases of total en bloc spondylectomy and thorough debulking with marginal resection were mixed in the G1GT subgroup, the fact that gross total removal of metastatic tumors yielded a higher survival rate and better neurological outcomes when compared with subtotal removal seems to be meaningful. Considering the higher survival rate without local recurrence after surgery in the G1GT subgroup when compared with the G1ST subgroup, total resection should be the goal of surgery for group 1 tumors. Tomita, et al.[13] reported similar results: 28 patients treated with wide or wide-marginal excision lived longer than 13 patients treated with intralesional excision-the mean survival period was 38.2 vs. 21.5 months, respectively; however, in their series, some fast- and slow-growing tumors were mixed in each group of surgical excision and the extent of tumor invasion (intracompartmental vs. extracompartmental) was not clearly differentiated. For gross total resection, we used the surgical techniques of posterior or anterior-posterior combined approach. Sometimes we needed to perform en bloc resection of the ribs attached to the tumor mass followed by reconstruction of the chest wall (Fig. 3). Collaborations with other surgical departments and/or preoperative angiography with selective embolization were mandatory considerations to achieve successful surgeries.

The analysis of the survival rate of group 2 patients according to the extent of surgical resection revealed that it was not significantly different between the gross total and subtotal resection groups. We suggest that minimal surgery consisting of the decompressive debulking technique followed by radiotherapy and/or chemotherapy may be the best choice to treat patients with highly malignant metastatic spinal tumors that extend beyond the anatomical barrier. Our results do not imply that conservative medical care or radiation therapy alone is better than surgery in rapidly growing group 2 spinal metastasis. Despite the low survival rate of patients with highly malignant spinal metastatic tumors, surgical treatment is still worthy of consideration, as it reduces the intractable pain and leads to neurological improvement. In this study, patients showed improved neurological status shortly after surgery when compared with the preoperative status. Patchell, et al.[27] reported that direct decompressive surgical resection followed by radiotherapy has a superior outcome in improving the neurological deficit when compared with radiotherapy alone for patients with spinal metastatic cancer that compresses the spinal cord. Our study also showed superior neurological improvement in the G2GT subgroup compared to that of the G2ST subgroup. Therefore, gross total resection would be preferable in selected cases, such as Tomita's classification type 4 or 5. The general condition of the patient (to endure heavy spinal surgery), less invasiveness into surrounding tissue, and long life expectancy in group 2 tumors are essential factors that should be considered before deciding for gross total resection.

In summary, our results suggest that gross total resection of spinal metastatic tumors should be the goal of surgery when primary tumors respond well to adjuvant therapy. Even in cases where the tumor mass extends beyond the anatomical barrier (Tomita's classification ≥ type 4), gross total resection of the tumor mass yields better survival rates and neurological outcomes when compared with subtotal resection of the tumor. However, in the case of tumors that do not respond to adjuvant therapy, we suggest that the surgical intervention of choice should be palliative decompression of the spinal cord.

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