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CLINICAL ARTICLE

Prognostic Analysis of Spinal Metastasis Secondary to Lung Cancer after Surgeries: A Unicentric, Large-Cohort, Retrospective Study

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Purpose: Spinal metastases of lung cancer (SMLC) usually have high degree of malignancy and require surgical treatment. However, there are several controversies about the efficacy of surgery. This study aimed to investigate factors predicting prognosis of SMLC after surgery-based comprehensive treatment.

Methods: A cohort of 112 cases of SMLC who underwent surgical treatment between 2009 and 2020 were retrospectively reviewed and analyzed. The surgical strategies included total en-bloc spondylectomy, debulking surgery, palliative decompression, and vertebral augmentation procedures. The patients were regularly followed-up. Survival analysis was performed, as well as analysis of the patients' neurological recovery, pain relief, and improvement of Karnosky performance score (KPS). Cox regression was used to analyze influencing factors of survival time, and Kaplan–Meier method was performed in survival analysis.

Results: The cohort included 63 males and 49 females, with an average age of 60.6 ± 10.6 years. Median survival time was 16 months. A total of 86.7% of paralysis patients' neurological function recovered and 83.9% of patients with low KPS score (10–40) improved. Surgical method was significantly correlated with improvement of neurological function ($p < 0.001$) and KPS ($p < 0.001$). The mean bleeding volume was 502 ml and operative time was 170 min. The survival rates at 3, 6, 12, 24, and 36 months were 92.0%, 80.4%, 63.4%, 63.4%, and 22.6%, respectively. Postoperative Frankel grade ($p < 0.001$), postoperative KPS score ($p = 0.001$), and application of molecular targeted drugs ($p < 0.001$) were significantly correlated with survival time in univariate analysis, while application of molecular targeted drugs was an independent predictor for a longer survival by a multivariate analysis.

Conclusion: Surgery-based comprehensive treatment brought a fair outcome, with elongated survival time. Surgery can significantly improve patients' neurological function and physical performance status. Adjuvant targeted therapy is an independent positive factor for patients' survival.

Key words: Molecular targeted therapy; Overall survival period; Performance capability; Spinal metastasis of lung cancer; Surgical treatment

Introduction

Lung cancer, with its high aggressiveness and poor prognosis, is one of the main reasons of death caused by cancer. There are about 1.6 million new cases and 1.4 million deaths globally every year, and the cumulative incidence of lung cancer can reach 45%–55%.[1,2] Bone is one of the most common sites of metastases in advanced lung cancer, among which spinal metastasis is the most frequent, which occurs in about 30%–36% of lung cancer patients.[3] In recent studies, 40%–50% of lung cancer patients have bone metastases, and

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63% of bone metastases occur in the spine.[4,5] Even worse, the time from the diagnosis of lung cancer to bone metastases is only 1–2 months in some cases. A nationwide survey demonstrated that 64.3% to 64.4% of patients were found to have spinal metastases at the same time of lung cancer diagnosis.[6] The survival time of lung cancer patients is significantly reduced when developing spinal metastases. Karolinska *et al*. showed that the 1-year survival rate with and without bone metastases was 5% and 37%, respectively.[7] At least 90% patients with spinal metastases of lung cancer (SMLC) have symptoms of pain, including local pain, neuropathic pain, and axial pain. Besides, when tumor destroy more seriously and intrude into the spinal canal, it can also cause neurological injury or paralysis, pathological fracture, hypercalcemia, and other symptoms.[8]

Treatment of SMLC is usually based on comprehensive treatment, including radiotherapy, chemotherapy, molecular targeted therapy, immunotherapy, and other conservative treatments, supplemented by surgery. Surgical treatment for SMLC is usually palliative, focusing on decompression of the spinal cord and nerve roots and maintenance of spinal stability, reducing the symptoms of patients and improving the performance capability. The surgical procedure usually includes palliative decompression and local vertebral augmentation. In addition, the surgeons usually perform expanded decompression which is aimed to remove the tumor as much as possible on the basis of decompression, containing total en-bloc spondylectomy (TES), debulking surgery, and separation surgery.

There has always been a huge disagreement about the timing and efficacy of surgical treatment, in which the opinions on outcomes of surgical treatment are also different across studies. Usually patients with survival time less than 3 months are generally considered to be treated conservatively, however, more and more researchers reported that patients with short life expectancy should also be positively treated to improve the performance capability. Yao *et al*. believed that even though lung cancer patients have a low expected survival, aggressive surgery can improve neurological function and motor ability and relieve patients' symptoms.[9] In the 87 cases reported by Truong *et al*., in 2020, 32.2% of patients survived more than 6 months, 16.1% survived more than 12 months, and 98.4% of patients with low Tokuhashi score (0–8) regained walking ability.[10]

Thus, the aim of this study was to evaluate the effects of surgery on the survival time and performance capability in patients with SMLC. Furthermore, it can provide evidence for surgeons when making surgical decisions and how they can choose the appropriate operation method and operation time.

Methods

Inclusion and Exclusion Criteria

The inclusion criteria were as follows:

i. Diagnosis of SMLC by pathological examination.
ii. Undergoing surgical treatment in our center.
iii. Being regularly followed-up (≥1 year)

The exclusion criteria were as follows:

i. Lack of pathological diagnosis;
ii. History of surgery or radiation treatment for SMLC in other hospitals;
iii. History of other malignancies except from lung cancer.

Ethical Approval

This study was approved by the ethics committee of Peking University Third Hospital's institutional review board (NO. M2021085). Written informed consent was obtained from all patients whose specimens and clinical information were used for this study.

Selection of the Participants and Observation Assessment

There were 132 patients with SMLC who underwent surgical treatment in the orthopaedic department of Peking University Third Hospital from 2009 to 2020, in which 112 cases were retrospectively followed up and the other 20 cases (15%) were excluded due to loss of follow-up. We reviewed demographic profile, tumor information (segments, pathology, metastases, and so on), treatment method, and performance capability, which included general status, neurological function, pain, and ambulatory status assessment preoperative, postoperative, and during follow-up. General status was evaluated by Karnofsky's performance scores (KPS), with 10–40 points as poor, 50–70 points as medium, and 80–100 points as good. Neurological function and pain assessment were separately evaluated by Frankel grades and visual analog scale (VAS). During the follow-up period, KPS, Frankel grades, VAS, and ambulatory status were recorded as the final postoperative performance capability. Survival time and survival status were also recorded. Surgical indications included intractable pain, progressive neurological dysfunction, and spinal instability.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics (version 20.0; IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Continuous variables were manifested as the mean and standard deviation and were compared with Student's t-test. Categorical variables were presented as frequencies and Pearson's χ^2 tests were used for group comparison. The influencing factors of survival time were analyzed by univariate and multivariate Cox regression. The Kaplan–Meier method was used to calculate and analyze postoperative survival time. Statistical significance was defined at a p-value of <0.05 based on two-tailed tests.

Results

Demographic Characteristics

The cohort included 63 males and 49 females with an average age of 60.6 ± 10.6 years (range 29–80 years [Table 1]).

Thirty patients had a history of lung cancer before spinal metastases, and the median interval between primary lesion and spinal metastasis was 30.5 months. While in 82 cases, spinal metastases were found at the same time as pulmonary primary lesions. Thirty-six patients had history of treatment for pulmonary primary lesion before spinal surgery, including surgical resection, molecular targeted therapy, radiotherapy, chemotherapy, interventional therapy, and traditional Chinese medicine.

Preoperative Clinical Symptoms

One hundred and eight patients had symptoms of pain and lasted an average of 4.9 months, including 31 cases (28.7%) with axial pain, 28 cases (25.9%) with neurological pain only, and 49 cases (45.4%) accompanied with neurological dysfunction (Table 1). For neurological symptoms, 14 cases (12.5%) had complete loss of motor function, in which four cases were Frankel A, and 10 cases were Frankel B. Fifty-nine (52.7%) patients had incomplete motor dysfunction and limb weakness, in which 16 cases were Frankel C and 43 cases were Frankel D. Besides, 39 patients were Frankel E with normal neurological function (Table 2). Thirty-two patients (28.6%) were unable to walk and 35 cases (31.3%) had acute neurological deterioration within 14 days. Sphincter dysfunction was found in 21 patients. Preoperative KPS scores were poor (10–40 points) in 31 cases (27.7%), moderate (50–70 points) in 71 cases (63.4%), and good (80–100) in 10 cases (8.9% [Table 2]).

TABLE 1 Demographic and clinical characteristics (N = 112)

Characteristic	Value
Gender (n, %)	
Male	63 (56.2)
Female	49 (43.8)
Age (years)	60.6
Preoperative pain (n, %)	108 (96.4)
Axial pain	31 (28.7)
Neuralgia	28 (25.9)
Neurological dysfunction	49 (45.4)
Tumor pathological type (n, %)	
Adenocarcinoma	78 (69.6)
Squamous cell carcinoma	19 (17.0)
Adenosquamous carcinoma	2 (1.8)
Sarcomatoid carcinoma	3 (2.7)
Small cell lung cancer	8 (7.1)
Large cell lung cancer	1 (0.9)
Carcinoid	1 (0.9)
Gene mutation (n, %)	
EGFR	42 (37.5)
ALK	3 (2.7)
Metastase segments (n, %)	
Single-segment	36 (32.1)
Multi-segment	76 (76.9)
Destruction type (n, %)	
Osteolytic destruction	98 (87.5)
Steogenic destruction	12 (10.7)
Mixed destruction	2 (1.8)
Visceral metastases (n, %)	26 (23.2)
Surgical method	
Total en-bloc spondylectomy	2 (1.8)
Debulking surgery	57 (50.9)
Palliative decompression	45 (40.2)
Percutaneous vertebroplasty	8 (1.5)
Mean operative bleeding volume (ml)	551
Mean operative time (min)	175
Postoperative adjuvant therapy (n, %)	
Radiotherapy	53 (47.3)
Chemotherapy	42 (37.5)
Molecular targeted therapy	45 (40.2)
Immunotherapy	5 (4.5)

Tumor Characteristics

Adenocarcinoma was the main pathological type, which was found in 78 cases (69.6%). Besides, there were 19 cases of squamous cell carcinoma (17.0%), two cases of adenosquamous carcinoma (1.8%), three cases of sarcomatoid carcinoma (2.7%), eight cases of small cell lung cancer (7.1%), one case of lung carcinoid (0.9%), and one case of large cell lung cancer (0.9% [Table 1]). Mutations were found in 45 cases, including 42 EGFR mutations (37.5%) and three ALK mutations (2.7%). The tumors were mainly multi-segmental metastases (67.9%), and thoracic vertebra metastases were most common (56.3%). The lesions were mainly osteolytic destruction in 98 cases (87.5%), while 12 cases were osteoblastic destruction, and two cases were mixed destruction (Table 1). Sixty-one cases (56.3%) were with pathological fracture. There were 63 cases with intrapulmonary metastases and 26 cases were with visceral metastases.

Treatment

There were two patients (1.8%) who underwent TES and 57 (50.9%) who underwent debulking surgery, in which 33 cases (29.5%) were treated with separation surgery supplemented by postoperative radiotherapy. Besides, 53 cases underwent palliative surgery, including 45 cases (40.2%) of palliative decompression and eight cases (4.5%) of percutaneous vertebroplasty (PVP). Among all patients, the mean

TABLE 2 Comparison of preoperative and postoperative neurological function and performance capability

	Preoperative	Postoperative
VAS score (n, %)		
No pain (0 score)	3 (2.7)	77 (68.7)
Mild pain (1–3 score)	6 (5.4)	21 (18.8)
Moderate (4–6 score)	45 (40.2)	12 (10.7)
Severe pain (7–10 score)	58 (51.7)	2 (1.8)
Frankel grades (n, %)		
Frankel A	4 (3.6)	0 (0.0)
Frankel B	10 (8.9)	4 (3.6)
Frankel C	16 (14.3)	8 (7.1)
Frankel D	43 (38.4)	20 (17.9)
Frankel E	39 (34.8)	80 (71.4)
KPS score (n, %)		
Poor (10–40 points)	31 (27.7)	8 (7.1)
Moderate (50–70 points)	71 (63.4)	19 (17.0)
Good (80–100 points)	10 (8.9)	85 (75.9)

operative bleeding volume was 551ml and the mean operative time was 175 min. Fifty-three cases (47.3%) were treated with radiotherapy, 42 cases (37.5%) with chemotherapy, 45 cases (40.2%) with postoperative molecular targeted therapy, and five cases (4.5%) with immunotherapy (Table 1).

Complications

Thirty-four cases of complications were found in 25 patients (22.3%), in which 19 were with one complication and six were with two or more. Among the complications, 24 were mild complications and 10 were severe complications. There was one case of deep vein thrombosis in lower limbs and two cases of intermuscular vein thrombosis. One case was with gastric ulcer and another case with intestinal obstruction. There were seven cases with pulmonary dysfunction (two cases with pulmonary embolism, two cases with transient hypoxia, two cases with hydrothorax, and one case with respiratory failure) and one case with atrial fibrillation. Postoperative muscle strength decreased in six cases and all patients recovered to varying degrees within 1 to 2 weeks after surgery. Delayed hematoma was found in one case, while incision disunion and wound fat liquefaction in two cases. Furthermore, there were cerebrospinal fluid leakage in three cases, injury of superior laryngeal and recurrent laryngeal nerve in one case, and respiratory muscle fatigue during operation in one case.

Postoperative Performance Capability

There was no pain (VAS score 0) in 77 cases (68.7%), mild pain (VAS score 1–3) in 21 cases (18.8%), moderate pain (VAS score 4–6) in 12 cases (10.7%), and severe pain (VAS score 7–10) in two cases (1.8% [Table 2]). The postoperative VAS scores of 105 cases were lower than preoperative. After operation, there were four cases (6.3%) of complete paralysis (Frankel A and B), 28 cases (25.0%) of incomplete paralysis (Frankel C and D), and 80 cases (71.4%) of normal neurological function (Frankel E). The neurological function of 93 patients improved or remained normal after operation, 14 patients (Frankel D 11 cases, Frankel C two cases, Frankel B one case) had no obvious changes, and five patients had decreased neurological function. Postoperative KPS scores were poor in eight cases (7.1%), moderate in 19 cases (17.0%), and good in 85 cases (75.9% [Table 2]). Besides, both the improvement of postoperative Frankel grades ($p < 0.001$) and KPS score ($p < 0.001$) were significantly correlated with the surgical method. Compared with palliative surgery (palliative decompression and PVP), complete decompression (TES and debulking surgery) significantly improved postoperative neurological function and performance capability (Table 3).

Survival Time Analysis

The median follow-up period was 47.4 months (range 13–142 months). To date, 27 patients survived (24.1%) and 85 patients died (75.9%), in which 83 cases died due to tumor progression and the other two cases died of sudden dyspnea and cardiovascular events. The median survival was 16 months (range 1–123 months). The survival rates at 3, 6, 12, 24, and 36 months postoperative were respectively 92.0%, 80.4%, 63.4%, 63.4%, and 22.6% (Figure 1).

In univariate analysis of survival time, postoperative Frankel grade ($p < 0.001$), postoperative KPS score ($p = 0.001$) and application of molecular targeted drugs ($p < 0.001$) were significantly correlated with survival time. In the multivariate analysis of these factors in survival time, only application of molecular targeted drugs ($p = 0.005$) was associated with survival time (Table 4).

Patients were separated into molecular targeted treatment group (45 cases) and non-molecular targeted treatment group (67 cases). The median survival time of molecular targeted treatment group was 39 months (range 4–64 months), while 11 months (range 1–123 months) in non-molecular targeted treatment group ($p < 0.001$). The survival rates of molecular targeted treatment group at 3, 6, 12, 24, and 36 months were 95.6%, 93.3%, 84.3%, 62.4%, 53.7%, respectively, while in non-molecular targeted treatment group they were separately 76.1%, 58.2%, 31.3%, 13.1%, 7.5% (Figure 2A).

For 30 cases with paralysis preoperative (Frankel A, B and C), 26 patients' neurological function recovered after

TABLE 3 Effects of surgical methods on postoperative neurological function and performance capability

	p	95%CI
Improvement of Frankel grades	<0.001*	0.481–3.472
Improvement of KPS score	<0.001*	0.565–10.049

The correlation analysis was compared with complete decompression and palliative surgery. Complete decompression included debulking surgery, while palliative surgery included palliative decompression and PVP.

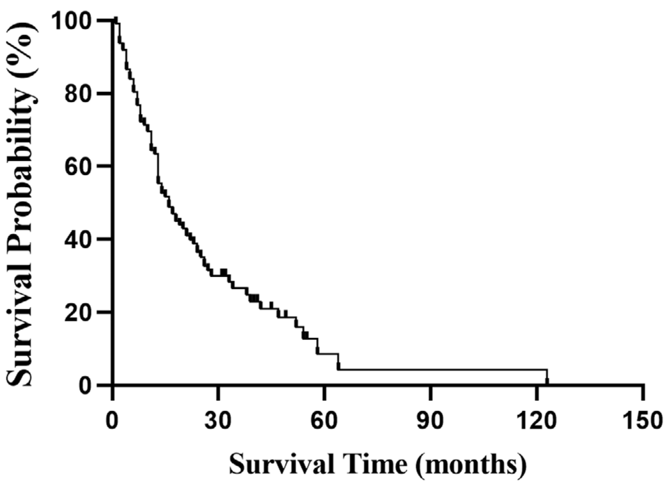

Fig. 1 Kaplan–Meier survival curve of patients with spinal metastasis of lung cancer (N = 112)

surgery while four patients' symptoms did not improve. Median survival time was 28 months (range 2–26 months) in the recovered group and 16 months (range 2–13 months) in the non-recovered group (p = 0.0002 [Figure 2B]). Furthermore, for 31 cases with poor KPS scores (10–40 points), 26 patients (83.9%) improved after surgery, and the mean

TABLE 4 Regression analysis of influencing factors of survival time

	Univariate regression analysis			Multivariate regression analysis		
	aHR	CI	*p*	aHR	CI	*p*
Preoperative Frankel grades	1.010	0.833–1.225	0.921			
Postoperative Frankel grades	0.512	0.397–0.662	<0.001*	0.737	0.405–1.343	0.319
Preoperative KPS score	1.000	0.988–1.013	0.945			
Postoperative KPS score	0.974	0.964–0.984	<0.001*	0.991	0.968–1.015	0.478
Radiotherapy (Yes *vs* No)	0.661	0.429–1.019	0.061			
Molecular targeted therapy (Yes *vs* No)	0.284	0.175–0.463	<0.001*	0.342	0.206–0.567	<0.001*
Pathological type (Non-small cell lung cancer *vs* Small cell lung cancer)	0.618	0.283–1.349	0.227			
Surgical methods	1.049	0.646–1.701	0.847			

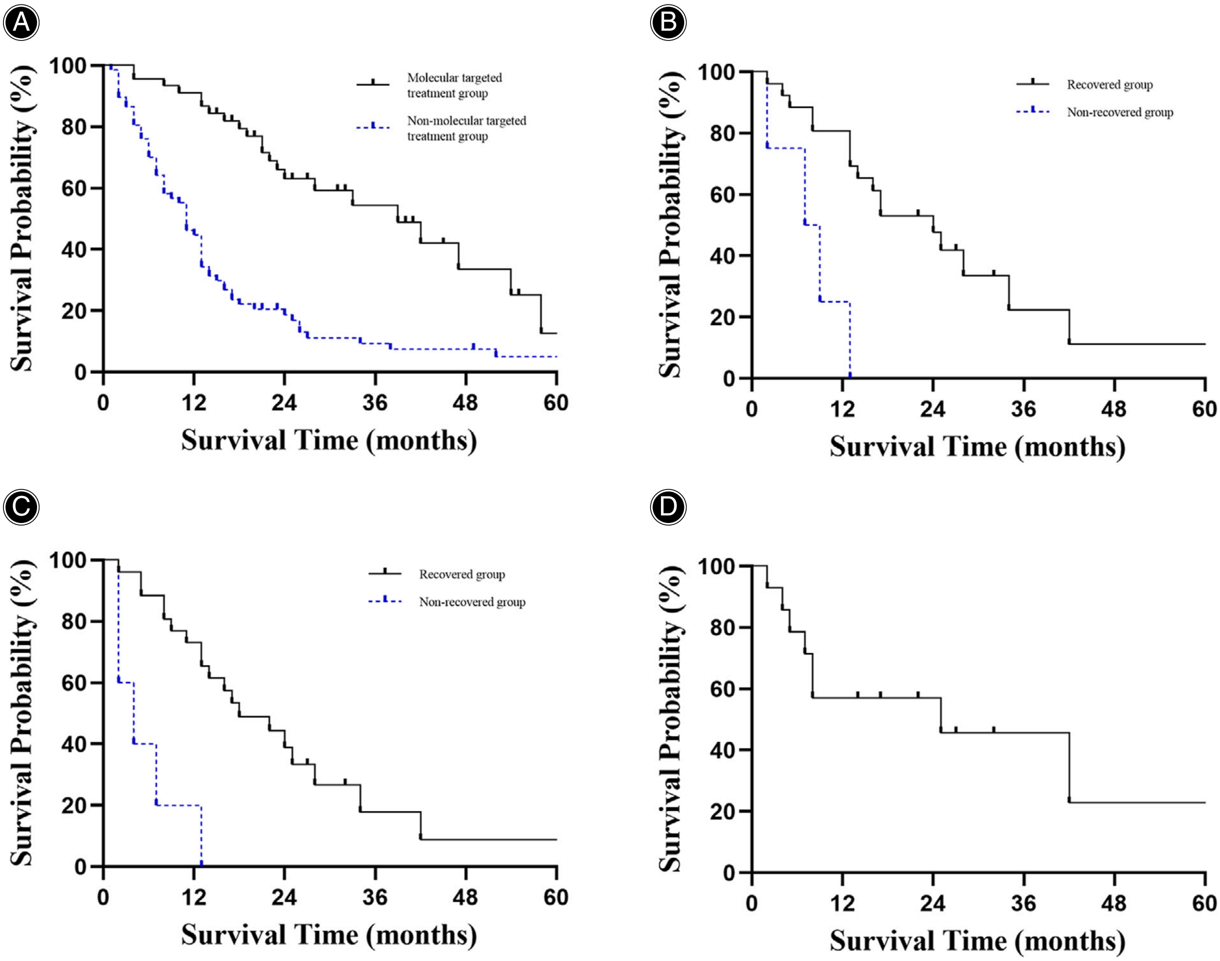

Fig. 2 Survival curve of patients in different groups. (A) Survival curve of patients in molecular targeted treatment group and non-molecular targeted treatment group. (B) Survival curve for patients with preoperative paralysis in recovered group and non-recovered group. (C) Survival curve for patients with poor KPS preoperative scores (10–40 points) in recovered group and non-recovered group. (D). Survival curve for patients with complete loss of motor function (Frankel A and Frankel B)

KPS score increased by 120.4%. Median survival time was 16 months (range 2–64 months). The survival rates at 3, 6, 12, 24, and 36 months were 80.6%, 71.0%, 51.3%, 27.4%, 14.9%, respectively. Twenty-six cases improved and five cases unchanged or worsened KPS postoperatively, in which median survival time was 18 months (range 2–64 months) in the recovered group and 4 months (range 2–13 months) in the latter group ($p < 0.001$ [Figure 2C]).

Furthermore, in 14 cases with complete loss of motor function (Frankel A and B), median survival time was 25 months (range 2–64 months), and eight patients underwent molecular targeted therapy. The survival rates at 3, 6, 12, 24, and 36 months were 78.6%, 57.1%, 57.1%, 45.7%, 45.7%, respectively (Figure 2D).

Discussion

Among all patients, the median survival time was 16 months which were longer than in previous studies. They achieved perfect improvement of performance capability after surgery in pain, neurological function and general status. Complete decompression could better improve postoperative neurological function and performance capability than palliative surgery. Postoperative Frankel grade, postoperative KPS score and application of molecular targeted drugs could significantly influence survival time. For patients with poor neurological function and general status, surgical treatment resulted in good survival, and the recovery of performance capability was significantly associated with survival time.

Lung cancer is regarded as a moderate-to-high malignancy and metastasis to the spine represents the end stage of the disease. Conventionally, physicians tend to adopt anti-tumor drugs, radiation therapy, and other conservative modalities instead of surgical intervention to SMLC, due to very limited life expectancy of the patients. Surgery is, however, needed in some clinical scenarios, for example severe, drug-failed local pain and progressive neurological dysfunction. There are several articles to report the surgical outcomes of SMLC, which mostly demonstrated favorable results. In this study, we present a retrospective review of our SMLC case series, which contains the largest sample size ever reported on surgery of SMLC. Herein, we believe some results of this study are of great interest and reference to the peers in this field.

Treatment

For all the cases in this cohort, surgical decision was made following the advice of our institutional multidisciplinary treatment (MDT) team for spinal metastasis. There are three indications for surgery in our center, namely severe yet drug-ineffective local pain, progressive neurological dysfunction and emerging or latent spinal instability. Symptomatically, SMLC manifested no pathognomonic characteristics for other spinal metastases. Pain and neurological deficits are the most common presentations before the surgery, with ratios of 96.4% and 45.4%, respectively (Table 1). Notably, primary lung cancer was not found in 73.2% (82/112) cases before symptomatic spinal metastasis, and this phenomenon poses a hard question about the orders of treatment to primary lesions or metastatic lesions. In our series, we made a reasonable choice to deal with symptomatic metastatic lesions firstly, in order to relieve the pain, decompress the cord, and restore spinal stability. Proper and effective local lesion management also leads to a safe and sufficient conduct of anti-tumor therapies. A total of 31.3% of the cases suffered acute deterioration of neurological function, which indicates emergent neurological decompression and leaves insufficient time for a careful whole-body screening and surgical preparation. As for the pathological examination, non-small cell lung cancer (NSCLC) was predominant for spinal metastasis, within which adenocarcinoma was the most common type, in up to 70% of the cases.

As we know, overall survival of SMLC is quite limited, which is presumably half to 1 year after the diagnosis, according to some well-established Tomita's and modified Tokuhashi's prognosis-predicting systems. Thus, we must carefully weigh up the risk *versus* effectiveness of a specific surgical procedure; we must clearly understand the goals of surgery. In our cohort, 44.7% of the patients underwent neurological decompression with limited tumor mass excision or vertebral reinforcement therapy only. By adopting these procedures, the patients received a lowly invasive surgery, which saved the time for the recovery of patients' physical conditions and made it possible for early start of adjuvant therapies. Previous articles demonstrated that laminectomy decompression with or without fixation had an immediate and apparent effect on reducing pain and improving neurological dysfunction. Lei *et al.*[11] reviewed a cohort of 73 cases of metastatic spinal cord compression (MSCC) who underwent decompressive surgery. They found 51.5% of the unambulatory patients regained walking ability after the surgery. In recent years, separation surgery has gained wide popularity and acceptance. The basic concept of separation surgery is to accomplish circumferential decompression of neurological elements, to spare a safe space for the delivery of high radiation dose for the remaining tumor lesion. Literally, separation surgery is more invasive than laminectomy decompression only, and may have an elevated risk of postoperative complications.[12] However, combined with postoperative SBRT, this procedure brings satisfying local tumor control. In their article on separation surgery, Laufer and colleagues reviewed 186 patients with metastatic epidural spinal cord compression who underwent separation surgery combined with postoperative hypofractionated SBRT, and they concluded this treatment manner is safe and effective for durable locoregional tumor control no matter what level of tumor histology-specific radiosensitivity.[13] Alghamdi *et al.*[14] discussed that separation surgery, followed by SBRT, can downgrade preoperative epidural disease and provide better local control. In another article, we described the general practice of separation surgery and the delivery of postoperative SBRT and concluded that a moderate resection of ventral tumor mass provided a comparable therapeutic outcome.[15] Furthermore, there are 33 cases in this study treated with separation surgery combined with postoperative radiotherapy. These patients showed a longer locoregional progression-free survival than the others.

Complications

In our case series, a high incidence of postoperative complications was noted, around 23.2% of all the cases. Previous studies reported complication rates after surgeries for spinal metastasis varied from 10% to 66.7%.[16] Wound healing problems tend to be a very common complication, with rates of 2.5% to 16% in different reports, according to a systematic review by Bakar and colleagues.[17] There are many factors associated with the risk of postoperative complications, such as patients' physical conditions, age, co-existing diseases, and surgical procedures. In Lee's article, they found that the occurrence of complications was relevant with surgical procedures and reminded that debulking surgery had a higher risk compared with en-bloc resection and palliative surgeries.[12] Different procedures are presumably accompanied with different extents of blood loss, and heavy bleeding often arouses some severe vascular events. In our cohort, the occurrence of vascular events is not un-neglectable, including deep vein thrombosis, pulmonary embolism, and atrial fibrillation. In fact, interoperative blood loss was well-prohibited, compared with many other reports.[18] Generally, SMLC is a hypo-vascular lesion and preoperative embolism of tumor-feeding vessels did not necessarily decrease intraoperative blood loss.[19] Noticeably, there are six cases of neurological deterioration in our patients, a rate up to 5.4%. Based on published articles, the incidence of neurological complications ranges from 0.6% to 14.5%.[16] There are a lot of factors associated with occurrence of neurological deterioration, for example direct injury, disturbance of blood perfusion, hematoma, infection, cerebrospinal fluid leakage, and cement leaking. Besides, different surgical procedures represent different risk of neurological complications.[20] In our cohort, postoperative neurological deterioration was mostly developed in patients with expanded tumor resection; however, all these patients eventually witnessed neurological recovery quickly after the surgery. Therefore, we shall balance the benefit and cost for the SMLC patients when scheming surgical plans.

Survival Analysis

The median survival time of our patients was 16 months, and this result is encouraging. There are many factors affecting survival time of SMLC, including performance status, number of vertebrae involved, neurological dysfunction and recovery, visceral metastases, time developing motor deficit, types of surgery, and adjuvant therapies.[5,21] In comparison studies, we gain controversial results regarding surgical effect on survival time. Tang *et al.*[22] found that surgical group had a longer survival than non-surgical group, after reviewing outcomes of 133 cases of non-small-cell lung cancer, whereas Amelot *et al.*[23] found that surgery did not pose significant effect on survival. Even worse, some studies reported shorter survival period in surgical group than non-surgical group, according to a systematic review by Armstrong *et al.*[24] Different surgical procedures may have different outcomes. Murakami *et al.*[25] reported that total en-bloc spondylectomy provided favorable outcomes for some cases with controllable primary lung cancer, localized spinal lesions, and no visceral metastasis. Xu *et al.*[26] reported that massive tumor debulking also provided a satisfying outcome even for those with failed locoregional radiotherapy. However, in the present study, we did not find significance between surgical procedures and survival time (Table 4).

Apart from surgical procedures, this study also analyzed survival time, and found that postoperative performance capability (KPS scores), neurological status (Frankel grades), and adjuvant therapies (targeted therapy) were independent predicting factors of SMLC (Table 4). Besides, in the survival curves for patients with preoperative paralysis and poor KPS scores, the recovered group had significantly higher survival time than the non-recovered group, which suggested that improved neurological function and performance were associated with longer survival time (Figure 2B,C). Preoperative neurological function and performance capability was not an indicator of outcome, and surgery was significant even in patients with poor preoperative status. A good KPS after the operation usually gives a better chance for early start of adjuvant therapies, which heralds better control of local and systematic tumor lesions.[24,27] Thus, an elongated survival period was observed among patients with better performance status.[5,21,28] Previous articles did not receive wide consensus about the effect of neurological recovery on survival.[5,21,29–31] Chen *et al.*[21] discussed that postoperative ambulatory status, improvement of ambulatory status after surgery, together with preoperative performance status had significant effect on survival. According to our study, we believed that a good recovery of neurological function, namely a better Frankel, after the operation is very likely to bring a longer survival. Even in patients with complete loss of neurological function, surgical treatment can still achieve a median survival time of 25 months (Figure 2D). After the operation, most patients (83.0%) in our cohort remained or regained neurological improvement, which eventually enjoyed a better performance capability and longer survival. Even in patients with poor preoperative status, surgery is of great significance.

Compared with conventional chemotherapeutic drugs and regimen, advancement of anti-tumor drugs has been mainly seen in the aspects and target therapy and immunotherapy. Targeted drugs can exactly act on these specific mutations and diminish tumor cells. Dohzono *et al.*[32] compared the median survival time of SMLC patients receiving EGFR tyrosine kinase inhibitors (EGFR-TKIs) with those without EGFR-TKIs and found the former enjoyed a longer overall survival period (21.4 months *vs* 6.1 months). In the recent years, application of some immunotherapeutic drugs has proven to be effective.[33] Borghaei *et al.*[34] found that the median survival period of PDL1(+) patients, who received specific targeted blockers, was longer than that of PD-L1(−) patients (17.7 months *vs* 10.5 months). Thus, as shown in our study, a sensitive targeted therapy after the operation posed as an independent predictor for a longer survival (Table 4, Figure 2A).

Strengths and Limitations

Overall, the findings of this study, especially the results of prognosis analysis, well addressed the value of surgery-based treatment strategy for advanced SMLC, and our study will provide solid evidence for our peers in the future. However, there were several limitations to this study. First, the sample size was a little insufficient and it still needs to be further verified in large clinical samples. Secondly, the level of evidence in retrospective studies was still slightly insufficient and some data were missing, which requires targeted prospective studies in the future.

Conclusion

In conclusion, an appropriate and timely surgical intervention for SMLC may provide a good local tumor control, improve patients' performance capability and neurological function. Currently, we do not have adequate evidence to support some specific surgical procedures, whereas the main goals of surgery shall be kept in mind: to fully decompress the neurological elements, restore spinal stability, and facilitate subsequent adjuvant therapies. Recovery of neurological function and elevated performance status after the operation can predict a longer survival. Besides, administration of target therapy is also associated with longer survival. In the comprehensive therapy of SMLC, surgery played an important role in improvement of patients' survival time and performance status, even for patients with poor preoperative status.

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Conflicts of Interest

The authors have no relevant financial or non-financial interests to disclose.

Author's Contribution

Shuheng Zhai and Panan Hu are shared first authors. Feng Wei and Yan Li contributed to the study conception and design. Material preparation, data collection and analysis were performed by Shuheng Zhai, Ben Wang, Xiao Liu, Hua Zhou, Zhongjun Liu, and Zihe Li. The first draft of the manuscript was written by Shuheng Zhai and Panpan Hu. Feng Wei, Yan Li, and Xiaoguang Liu revised the manuscript.

Availability of Data and Material

Yes.

Code Availability

Yes.

Ethics Approval

This study was approved by the Ethics Committee of Peking University Third Hospital (NO. M2021085).

Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

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