Factors Associated with Life Expectancy in Patients with Metastatic Spine Disease from Adenocarcinoma of the Lung

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Global Spine J 2015;5:417–424.

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Abstract

Study Design Retrospective study.

Objective Our objective was to identify preoperative prognostic factors associated with survival in patients with spinal metastasis from lung carcinoma.

Methods A retrospective analysis of 26 patients diagnosed with lung carcinoma metastatic to the spinal column was performed to determine factors associated with survival. We used 3 months survival as the clinical cutoff for whether surgical intervention should be performed. We analyzed patients who survived less than 3 months compared with those who survived more than 3 months. Demographic, preoperative, operative, and postoperative factors including functional scores were collected for analysis.

Results The median survival for all patients in our study was 3.5 months. We found a statistically significant difference between the group that survived less than 3 months and the group that survived greater than 3 months in terms of extrathoracic metastasis, visceral metastasis, and average postoperative modified Rankin score.

Conclusion Determining which patients with lung cancer spinal metastases will benefit from surgical intervention is often dictated by the patient's predicted life expectancy. Factors associated with poorer prognosis include age, functional status, visceral metastases, and extrathoracic metastases. Although the prognosis for patients with lung cancer spinal metastases is poor, some patients may experience long-term benefit from surgical intervention.

Keywords

- prognostic factors
- life expectancy
- metastasis
- spine
- surgery
- tumor
- lung cancer
- adenocarcinoma

Introduction

Lung cancer is considered the most common cancer worldwide, with estimates of 1.6 million new cancers diagnosed each year. It is also the leading cause of cancer-related deaths, accounting for an estimated 1.4 million deaths per year.[1] Some studies estimate that 30 to 70% of the patients who die from cancer have spinal metastases at autopsy, and roughly 14% of these patients will have a symptomatic lesion over their disease course.[2,3] Moreover, in the United States it is estimated that there are more than 20,000 cases of metastatic epidural spinal cord compression diagnosed per year.[2,3] The mean survival for patients with breast, renal, or prostate cancer that has spread to distant organs is estimated to average from 1 to 2 years, whereas the mean survival time for patients diagnosed with lung cancer that has spread to

received November 17, 2014
accepted after revision March 16, 2015
published online June 5, 2015

DOI http://dx.doi.org/10.1055/s-0035-1554778.
ISSN 2192-5682.

distant organs is only 6 months.[4] Lung cancer has a propensity to metastasize to bone resulting in skeletal complications that include bony destruction causing instability, pathologic fractures, pain, and spinal cord compression.[5–7] Each of these skeletal complications can decrease the quality of life, can cause significant morbidity, and is associated with increased mortality for patients.[7,8] For the patients with non–small cell lung cancer (NSCLC), the spinal column is the most common site of bone metastasis. Some studies demonstrate that 30% of patients with NSCLC develop skeletal metastasis over their clinical course, and 50% of these metastases are in the spinal column.[9]

The surgical treatment of spinal metastases is often dictated by the systemic burden and life expectancy. Some studies advocate a life expectancy greater than 3 months as the cutoff for surgical intervention.[2,4,10] For patients with a life expectancy less than 3 months, less invasive interventions such as kyphoplasty, vertebroplasty, and/or radiotherapy are advocated irrespective of whether the patient has a neurologic deficit.[2] Most commonly, the opinion of the clinicians managing the primary lesion is given priority in determining the life expectancy of patients diagnosed with spinal metastases. Nonetheless, this opinion can be inaccurate even when the estimations of clinicians from other departments are included in preoperative determination of the overall survival.[11]

The majority of studies to date have attempted to identify the prognostic factors that predict postoperative surgical outcomes through the assessment of preoperative demographic, radiologic, and functional status and/or adjuvant therapy variables. Despite these assessments, the majority of the studies contain a heterogeneous composition of patients with multiple different tumor subtypes. Studies that assess prognostic factors associated with specific tumor subtypes are needed to make better predictions of the optimal surgical candidate and moreover the specific interventions that will be ideal for a given patient. We performed a retrospective analysis of patients diagnosed with NSCLC metastasis to the spine stratified by survival either greater than or less than 3 months to determine variables that were associated with prolonged survival. Our objective was to identify preoperative prognostic factors associated with survival greater than or less than 3 months in patients with spinal metastasis from lung carcinoma.

Methods

We performed a retrospective analysis of 26 patients diagnosed with lung carcinoma metastatic to the spinal column at a single institution from the years 2002 to 2011. The surgical indications included pain, neurologic deficit, and/or mechanical instability. Only patients who had an estimated life expectancy greater than 3 months, as determined by the clinical assessment of their medical oncologist, were deemed potential candidates for surgical intervention. Using the clinical cutoff for whether surgical intervention should be employed of 3 months, patients were stratified into two groups for analysis: patients who survived less than 3 months and patients who survived more than 3 months.

We collected patient information including demographics, preoperative neurologic condition, functional status, primary disease location, systemic disease burden, other treatments, intraoperative and postoperative data on neurologic status, number of vertebral bodies removed, estimated blood loss, perioperative blood transfusions, crystalloid replacement, and complications stratified by neurologic, hematologic, respiratory, gastrointestinal, infectious, wound dehiscence, and hardware failure. Length of stay and overall survival were also calculated in each group. Magnetic resonance imaging was also used to determine extension of vertebral lesion into the ventral, lateral or paraspinal area.

Karnofsky Performance Score (KPS) and modified Rankin score were determined for each patient preoperatively and postoperatively based on the patient records. The modified Rankin score is calculated based on the following criteria: 0 = no symptoms; 1 = no significant disability, able to carry out all usual activities, despite some symptoms; 2 = slight disability, requires some help, but walks unassisted; 3 = moderate disability, requires some help, but able to walk unassisted; 4 = moderately severe disability, unable to attend to own bodily needs without assistance, and unable to walk unassisted; 5 = severe disability, requires constant nursing care and attention, bedridden, incontinent; 6 = dead. Statistical analysis was performed using GraphPad Prism (La Jolla, California, United States) software. Results are described as mean ± standard error unless otherwise specified. The university's Institutional Review Board (IRB Protocol # NA_00067508) approved this study.

Results

Using the clinical cutoff of 3 months' survival for whether surgical intervention should be employed, patients with a diagnosis of lung adenocarcinoma spinal metastasis were stratified into those who survived less than 3 months and those who survived more than 3 months. The difference in survival between patients who survived less than 3 months compared with those who survived more than 3 months was statistically significant according to the log rank (Mantel–Cox) test ($p < 0.0001$). The median survival for the entire group was 3.5 months (►**Fig. 1**). The median survival

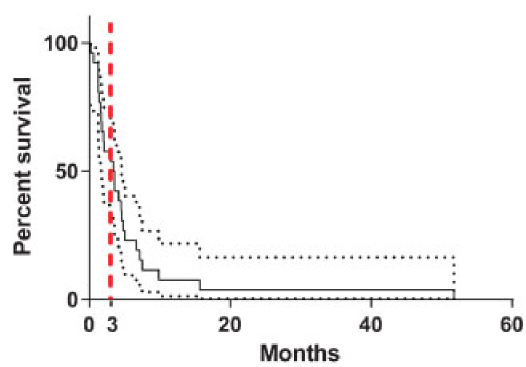

Fig. 1 Survival of patients diagnosed with lung cancer spinal metastasis who underwent surgical intervention. Red vertical dashed line denotes survival at 3 months, and dotted line is the confidence interval. Median survival, 3.5 months.

for patients diagnosed with lung carcinoma spinal metastasis was 1.5 months in the group that survived less than 3 months compared with 4.9 months in the group that survived more than 3 months, with mean survivals of 1.525 ± 0.2064 and 9.471 ± 3.373, respectively ($p = 0.04$). Twelve patients (46%) survived less than 3 months, and 14 (54%) patients survived more than 3 months. There were 7 males (58%) and 5 females (42%) in the group that survived less than 3 months and 7 males (50%) and 7 females (50%) in the group that survived more than 3 months. The average age at surgery was 71.83 ± 2.272 for patients who survived less than 3 months and 62.07 ± 2.286 for patients who survived more than 3 months ($p = 0.0061$). The time from presenting symptoms to surgical treatment of the spinal metastasis was 24.58 ± 7.263 in the group that survived less than 3 months and 68.50 ± 18.36 in the group that survived more than 3 months (►**Table 1** and ►**Fig. 2**).

Extension of the disease (paraspinal, ventral, or lateral) relative to the affected vertebral level was also analyzed. In the group that survived less than 3 months, 3 patients had paraspinal extension, 2 patients had ventral extension, and no patient had lateral extension. In comparison, in the group that survived more than 3 months, 6 patients had paraspinal extension, 8 patients had ventral extension, and 1 patient had lateral extension (►**Table 1**). There was a statistically significant difference between the two groups in terms of ventral extension ($p = 0.05$). There was a statistically significant difference in extrathoracic metastasis between groups, which occurred in 6 (50%) patients in the group that survived less than 3 months compared with 1 (7%) in the group that survived more than 3 months ($p = 0.0261$). We also found

Table 1 Preoperative demographics

Baseline characteristics	Survival $<$ 3 mo ($n = 12$)	Survival $>$ 3 mo ($n = 14$)	p Value
Demographics			
Age at surgery	71.8	62.1	0.0061*
No. of males	7	7	0.7127
Smoking history	9	8	0.4291
Comorbidities	40	36	>0.9999
Adenocarcinoma pathology	6	7	>0.9999
Radiologic features			
Extrathoracic spinal level	6	1	0.0261*
Extension paraspinal	3	6	0.4291
Extension ventral	2	8	0.05*
Extension lateral	0	1	>0.9999
Pathologic fracture	9	8	0.4291
Distant metastases			
Other spinal metastases	3	4	>0.9999
Extravertebral bony metastases	2	3	>0.9999
Visceral metastases	8	3	0.0447*
Brain metastases	4	4	>0.9999
Presenting symptoms			
Motor weakness	8	8	0.7015
Paresthesias	4	6	0.7015
Gait impairment	7	6	0.6951
Pain	10	13	0.5800
Incontinence	1	1	>0.9999
Adjuvant preoperative treatments			
Preoperative chemotherapy	6	8	>0.9999
Preoperative embo	0	1	>0.9999
Preoperative XRT to spine	2	5	0.3913
Preoperative XRT to primary	6	7	>0.9999

Abbreviations: embo, embolization; XRT, radiation therapy.
*$p < 0.05$ indicates statistical significance.

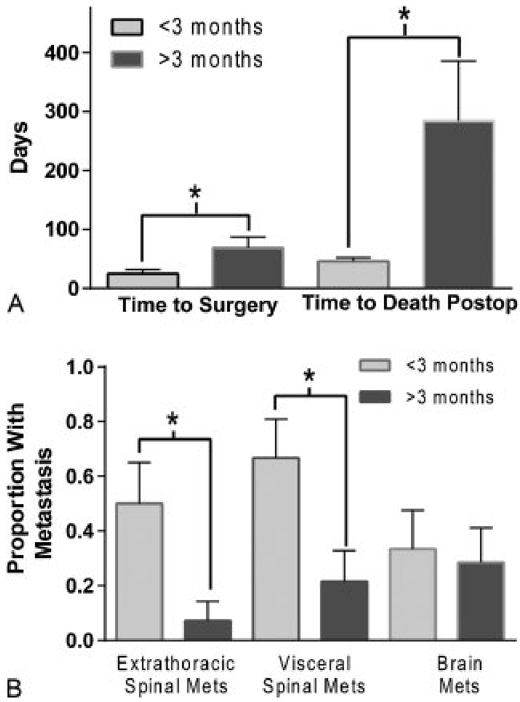

Fig. 2 Time to surgery from presenting symptom, time to death from surgery, and spinal metastasis site stratified by survival less than 3 months or greater than 3 months. There was a statistically significant difference with increased time to surgery ($p = 0.0472$) and increased survival time ($p = 0.0400$) when the group that survived less than 3 months was compared with the group that survived more than 3 months. The proportion of patients with either extrathoracic vertebral metastasis, visceral metastasis, or brain metastasis was stratified by survival less than 3 months or greater than 3 months. There was a statistically significant difference with extrathoracic vertebral metastasis ($p = 0.0261$) and visceral metastasis ($p = 0.0447$) when the group that survived less than 3 months was compared with the group that survived more than 3 months. No significant difference was seen between brain metastasis in the two groups. $^{*}p < 0.05$ indicates statistical significance.

a statistically significant difference in visceral metastasis between groups, which occurred in 8 (67%) patients in the group that survived less than 3 months compared with 3 (21%) in the group that survived more than 3 months ($p = 0.0447$; ►**Fig. 2**). There were 5 (42%) patients with a baseline KPS > 70 and 7 (58%) patients with a baseline KPS < 70 in the group that survived less than 3 months and 8 (57%) patients with a baseline KPS > 70 and 6 (43%) patients with a baseline KPS < 70 in the group that survived less than 3 months. The average baseline modified Rankin score was 2.75 ± 0.411 in the group that survived less than 3 months and 2.36 ± 0.372 in the group that survived more than 3 months (►**Table 2**).

Fourteen surgeries were performed in the group that survived less than 3 months and 17 in the group that survived more than 3 months. One patient in the group that survived less than 3 months had a staged operation, whereas 2 patients in the group that survived more than 3 months had staged operations. Five patients underwent anterior-only procedures, six patients underwent posterior-only procedures, and one patient underwent a combined approach in the group that survived less than 3 months. In the group that survived more than 3 months, 4 patients underwent anterior-only procedures, 9 patients underwent posterior-only procedures, and 1 patient underwent a combined approach. The procedures performed during both combined approaches included anterior corpectomy and reconstruction, and posterior decompressive laminectomy and fusion. The average number of instrumented levels was 5.50 in the group that survived less than 3 months and 5.71 in the group that survived more than 3 months. We found that the 3 longest survivors in our series underwent en bloc resection with an average survival of 25.8 months (range 9.9 to 51.8 months; ►**Table 3**).

Table 2 Preoperative and postoperative functional status

Functional status	Survival < 3 mo ($n = 12$)	Survival > 3 mo ($n = 14$)	p Value
Baseline mRS	2.75	2.36	0.4845
Baseline KPS > 70	5	8	0.6951
Baseline KPS > 40	4	6	0.7015
Baseline KPS < 40	3	0	0.0846
KPS < 70	7	6	0.6951
Postoperative mRS	4.17	2.62	0.0236*
Postoperative mRS > 4	7	1	0.0093*
Postoperative KPS > 70	2	7	0.1100
Postoperative KPS 40–70	2	6	0.2164
Postoperative KPS < 40	8	1	0.0029*
Postoperative KPS < 70	10	7	0.1032

Abbreviations: KPS, Karnofsky Performance Score; mRS, modified Rankin scores.
$^{*}p < 0.05$ indicates statistical significance.

When postoperative functional status was assessed, the average postoperative modified Rankin score was 4.167 ± 0.4234 in the group that survived less than 3 months and 2.615 ± 0.4742 in the group that survived more than 3 months ($p = 0.0236$; ►**Fig. 3**). In terms of KPS, there were 2 (17%) patients with a postoperative KPS > 70 and 12 (83%) patients with a baseline KPS < 70 in the group that survived less than 3 months and 7 (50%) patients with a baseline KPS > 70 in the group that survived more than 3 months, which approached statistical significance ($p = 0.1032$; ►**Fig. 3**). For patients with a postoperative KPS < 40, there were 8 (67%) patients in the group that survived less than 3 months and only 1 (7%) patient in the group that survived more than 3 months ($p = 0.0029$; ►**Table 2**).

For postoperative adjuvant therapies, 3 (25%) patients underwent postoperative radiotherapy in the group that survived less than 3 months compared with 6 (43%) in the group that survived more than 3 months, which was not significant. No patients underwent postoperative chemotherapy in the group that survived less than 3 months compared with 10 (71%) patients in the group that survived more than 3 months, which was statistically significant ($p < 0.001$) and

Table 3 Perioperative factors

Factors	Survival < 3 mo (n = 12)	Survival > 3 mo (n = 14)	p Value
Intraoperative factors			
Staged	1	2	>0.9999
Total no. of spinal surgeries	14	17	–
Approach			
Anterior only (fusion + corpectomy)	5	4	–
Posterior only	6	9	–
Decompressive laminectomy only	2	0	
Decompressive laminectomy + fusion	2	3	–
Decompressive laminectomy + fusion + vertebrectomy	2	6	–
Combined	1	1	–
No. of levels instrumented	5.50	5.71	0.8808
En bloc	0	3	0.2246
Postoperative factors			
Time to death from surgery (mo)	1.53	9.47	0.0400*
Length of stay	18.50	14.57	0.4745
Discharge to rehab	8	8	0.7015
Total complications	13	7	0.2002
Postoperative XRT to spine	3	6	0.4291
Postoperative chemotherapy	0	10	<0.0002*
Postoperative embo	0	0	>0.9999
Hardware failure within 6 wk	0	0	>0.9999
Revision required	1	1	>0.9999

Abbreviations: embo, embolization; XRT, radiation therapy.
*$p < 0.05$ indicates statistical significance.

most likely reflects the subset of patients who survived long enough to receive chemotherapy. There were 13 complications in the group that survived less than 3 months compared with 7 complications in the group that survived more than 3 months, which was not statistically significant ($p = 0.2002$); complications included deep vein thromboses, pulmonary embolism, pneumonias, wound infections, wound dehiscence, and cerebrospinal fluid fistulae. There was one hardware revision in each group: In the group that survived greater than 3 months, a T4 pedicle screw that broke out laterally, close to the aortic arch. In the group that survived less than 3 months, one patient with recurrence of tumor and severe cord compression lost the ability to walk for 2 to 3 days prior to surgery (►**Table 3**).

Discussion

Recent advances in molecular biology, genomics, and surgical resection have demonstrated that NSCLC is comprised of multiple tumor subtypes with specific genetic alterations that determine the growth characteristics, treatment paradigms, and prognosis.[12,13] The armamentarium of pharmacologic inhibitors, which include epidermal growth factor inhibitors and anaplastic lymphoma kinase fusion oncogene inhibitors, combined with an increased understanding of the genetic background of NSCLC, has resulted in more patients living with lung cancer, and this number is expected to increase in the upcoming years. With the increased prevalence of lung cancer and better treatments to control systemic disease and local recurrence, the incidence of patients developing spinal metastases is also expected to increase.[3] With the increased prevalence of patients diagnosed with lung cancer spinal metastasis, surgeons will be confronted with the challenge of determining which patients will benefit from surgical intervention to improve functional status, reverse neurologic deficit, alleviate pain, or improve quality of life.[4] Our objective in this study is to identify factors that are associated with survival loner than 3 months in patients with spinal metastasis from lung carcinoma. We identified the presence of extrathoracic metastasis, visceral metastasis, and ventral extension of the tumor as factors associated with patients living less than 3 months. A preoperative and postoperative KPS less than 40 was associated with survival less than 3 months. Other scores of functional status, such as modified Rankin score, demonstrated that higher scores were associated with less than 3-month survival as well.

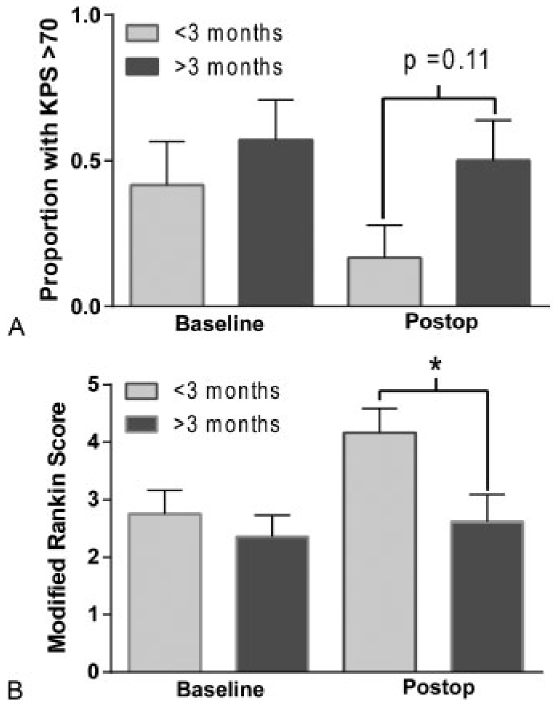

Fig. 3 Functional outcome stratified by survival less than 3 months or greater than 3 months. There was a difference in the proportion of patients with a postoperative Karnofsky Performance Score (KPS) > 70 ($p = 0.10$) that approached significance and no significant difference in the proportion of patients with a baseline KPS > 70 when the group that survived less than 3 months was compared with the group that survived more than 3 months. There was a statistically significant difference in the postoperative modified Rankin scores ($p = 0.0236$) and no significant difference in the baseline modified Rankin scores when the group that survived less than 3 months was compared with the group that survived more than 3 months. $^{*}p < 0.05$ indicates statistical significance.

A variety of studies have identified factors that predict postoperative surgical outcomes and/or prolonged or shortened survival utilizing a heterogeneous group of tumor subtypes. Studies have cited several favorable prognostic factors associated with metastatic spine disease including 0 to 2 ECOG (Eastern Cooperative Oncology Group) Scale of Performance Status, higher KPS, female gender, primary histologic diagnosis of adenocarcinoma, absence of appendicular metastases, lack of pathologic fracture, use of adjuvant chemoradiation, preoperative ambulation, and slower preoperative primary tumor growth rate.[14–19] In contrast, previously discovered negative prognostic factors include pathologic fracture in extraspinal metastases, complete pathologic vertebral fracture, primary histologic diagnosis of small cell lung carcinoma, absence of adjuvant chemoradiation, visceral metastases, and greater number of spinal segments affected by metastatic lesions.[17,20–22] In 2005, Tokuhashi et al proposed a scoring system to evaluate prognosis and potential treatment strategies, relegating lung cancer to the poor prognosis group and thus better suited to palliative or conservative treatments.[23] Weigel et al also performed a retrospective analysis of 76 patients and concluded that survival was worse in the patients with lung cancer in comparison with other tumor subtypes.[24] Some authors contend that these studies may indicate that patients with lung cancer should be discussed separately from other cancer subtypes.[25] With this consideration in mind, Fukuhara and colleagues performed a retrospective analysis of patients with metastatic lung cancer to the spine and identified 13 patients with a median postoperative survival of 5 months (range: 1 to 25 months). The authors also demonstrated that good postoperative performance was associated with better median postoperative survival.[25] In our study, patients showed no significant difference in baseline KPS or modified Rankin scores preoperatively; however, there was a significant difference, with better scores (i.e., higher KPS and lower modified Rankin scores) in the group with survival greater than 3 months. Our findings support the claim that improvement and/or maintenance of functional status is associated with improved survival.

Improvements in adjuvant treatment modalities, including chemotherapy, radiotherapy, small molecule inhibitors, and immunotherapies, have resulted in increased control of systemic disease and longer life expectancies for patients diagnosed with lung cancer spinal metastases.[4] Although there was no significant difference with respect to brain metastases, we found that the group that survived less than 3 months had a higher proportion of patients with visceral metastasis compared with the group that survived more than 3 months; the difference was statistically significant ($p = 0.0447$). Similar to other studies, control of the systemic disease was a good prognostic factor.[23] In our series, 10 patients underwent postoperative chemotherapy in the group that survived more than 3 months in comparison with no patients who survived less than 3 months. These findings are likely associated with the better overall functional outcomes in the patients who survived more than 3 months and their ability to undergo postoperative chemotherapy (better nutritional status and higher KPS, among other factors). Although postoperative chemotherapy may also play an important role in the overall survival of patients with spinal metastasis secondary to lung adenocarcinoma, the lack of postoperative chemotherapy in patients who lived less than 3 months is not likely to have played a significant role in our study. This observation is based on the fact that these patients had a median survival of only 1.5 months after surgery, and they did survive long enough to be considered appropriate candidates for adjuvant chemotherapy.

Cetin et al evaluated the incidence of bone metastasis and skeletal-related events (spinal cord compression, fracture, bone surgery, radiation) in patients with lung cancer, demonstrating a 1-year survival of 37.4% for patients with no bone metastasis, 12.1% for patients with bone metastasis and no skeletal-related events, and 5.1% for patients with both bone metastasis and skeletal-related events.[7] We found a significant difference between both groups with 6 (50%) patients who survived less than 3 months having extrathoracic metastasis compared with 1 (7%) who survived more than 3 months ($p = 0.0261$). The presence of extrathoracic metastases may indicate the presence of more disseminated disease; however, larger studies determining the natural history of the disease progression would be needed to determine whether this observation is in fact the case.

The complication rates associated with different surgical approaches must be weighed against the benefits of providing better local recurrence control, increased quality of life, and ultimately increased overall survival. The determination of the ideal surgical intervention should avoid shortening the patients' life or lowering their quality of life relative to the natural history of their associated disease.[26,27] Lee et al assessed surgical outcomes, complications, and mortality in patients with spinal metastases from multiple tumor subtypes who underwent either en bloc resection, tumor debulking, or palliative surgery. Twenty-one percent of their cases were lung cancer (42 cases) and 15 of these patients underwent en bloc resection. They demonstrated that patients who underwent en bloc resection had the longest mean survival postoperatively, but they did not analyze the subgroup of patients with lung cancer.[27] Similarly, Ratasvuori et al demonstrated that en bloc resection for solitary bone metastases (any skeletal metastasis) resulted in a significant improvement in overall postoperative survival rate for all tumor subtypes when compared with other surgical strategies.[28] Interestingly, we found that the three longest survivors in our series underwent en bloc resection with an average survival of 25.8 months (range 9.9 to 51.8 months). Weighing the increased survival seen in the patients undergoing en bloc resection against the complications in this group of three patients, one patient had three complications, whereas the remaining two patients had none. These findings suggest that in appropriate circumstances en bloc resection could be considered an appropriate treatment option; however, larger studies will be needed to substantiate this claim.

Our study was limited by the relatively small number of patients and lack of a control group of nonsurgically treated patients with lung cancer spinal metastasis and/or patients treated with radiotherapy. Furthermore, we are only able to make associations as a retrospective study. Larger multicenter prospective randomized trials focused on individual tumor subtypes will be needed to make more formidable conclusions that will influence the current treatment paradigms for this disease.

Conclusion

The determination of which patients with lung cancer spinal metastases will benefit from surgical intervention is a multifactorial process that is often dictated by the patient's predicted life expectancy. Several factors associated with poorer prognosis include age, functional status, visceral metastases, and extrathoracic metastases. Although the prognosis for patients with lung cancer spinal metastases is poor, some patients may benefit long term from surgical intervention.

Disclosures

C. Rory Goodwin, Research grants: NREF, UNCF-Merck Science Initiative, Burroughs Wellcome Fund
Mohamed H. Khattab, none
Eric W. Sankey, none
Benjamin D. Elder, none
Thomas A. Kosztowski, none
Rachel Sarabia-Estrada, none
Ali Bydon, Board membership: MedImmune, LLC; Research grant: DePuy Spine
Timothy F. Witham, Research grant: Eli Lilly and Company
Jean-Paul Wolinsky, none
Ziya L. Gokaslan, Consultancy/speaking/teaching: AO Foundation; Stock/stock options: US Spine, Spinal Kinetics; Research support: DePuy, NREF, AOSpine, AO North America
Daniel M. Sciubba, Consultancy: DePuy, Medtronic, Nuvasive, Globus

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