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Preoperative Predictors of Survival in Patients With Spinal Metastatic Disease

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ABSTRACT

Background: There remains a number of factors thought to be associated with survival in spinal metastatic disease, but evidence of these associations is lacking. In this study, we examined factors associated with survival among patients undergoing surgery for spinal metastatic disease.

Methods: We retrospectively examined 104 patients who underwent surgery for spinal metastatic disease at an academic medical center. Of those patients, 33 received local preoperative radiation (PR) and 71 had no PR (NPR). Disease-related variables and surrogate markers of preoperative health were identified, including age, pathology, timing of radiation and chemotherapy, mechanical instability by spine instability neoplastic score, American Society of Anesthesiologists (ASA) classification, Karnofsky performance status (KPS), and body mass index (BMI). We performed survival analyses using a combination of univariate and multivariate Cox proportional hazards models to assess significant predictors of time to death.

Results: Local PR (Hazard Ratio [HR] = 1.84, $P = 0.034$), mechanical instability (HR = 1.11, $P = 0.024$), and melanoma (HR = 3.60, $P = 0.010$) were significant predictors of survival on multivariate analysis when controlling for confounders. PR vs NPR cohorts exhibited no statistically significant differences in preoperative age ($P = 0.22$), KPS ($P = 0.29$), BMI ($P = 0.28$), or ASA classification ($P = 0.12$). NPR patients had more reoperations for postoperative wound complications (11.3% vs 0%, $P < 0.001$).

Conclusions: In this small sample, PR and mechanical instability were significant predictors of postoperative survival, independent of age, BMI, ASA classification, and KPS and in spite of fewer wound complications in the PR group. It is possible that PR was a surrogate of more advanced disease or poor response to systemic therapy, independently portending a worse prognosis. Future studies in larger, more diverse populations are crucial for understanding the relationship between PR and postoperative outcomes to determine the optimal timing for surgical intervention.

Clinical Relevance: These findings are clinically relevent as they provide insight into factors associated with survival in metastatic spinal disease.

Level of Evidence: 3.

Tumor

Keywords: spinal metastasis, radiation therapy, preoperative spinal radiation, mortality risk, spinal instability

INTRODUCTION

As many as 30% of cancer patients will develop spinal metastases, with median overall survival of approximately 7 months in this population, depending on primary tumor type.[1] In the United States, upwardmore than 8000 hospital admissions per year are for spinal cord compression due to metastatic disease.[2] Spinal metastases and metastatic spinal cord compression (MSCC) can lead to pain, mechanical instability, and neurological deficits, accounting for significant reduction in life expectancy and quality of life among cancer patients.[3] Early diagnosis and management of spinal metastasis are crucial to limit morbidity and mortality, but as cancer patients live longer, and as more treatment modalities become available for complex spinal tumors, careful attention must be paid to the risks, benefits, and timing of surgery and radiation therapy (RT).

In terms of management for spinal metastases, current data support a combined approach of surgery and RT to treat pain, preserve neurologic function, and maintain spinal stability.[4,5] Surgery has been shown to improve outcomes in the setting of MSCC and has played a crucial role in therapy ever since Patchell et al prospectively demonstrated that surgery and RT offered superior outcomes in ambulation and survival when compared with RT alone.[6–8] However, in

the absence of overt mechanical instability or neurologic compromise, RT remains the initial modality of choice for spinal metastasis.[9] Most patients are treated first with conventional external beam RT (EBRT), which is effective for alleviating cancer-related pain. Although EBRT can offer favorable control for classically radiosensitive pathologies, the development of stereotactic body RT and stereotactic radiosurgery has allowed for durable local control of more radioresistant tumor types while sparing healthy tissues, including the spinal cord.[10,11]

Given the cytoreductive capability of EBRT, stereotactic body RT, and stereotactic radiosurgery modalities, the role of surgery has shifted from maximal safe resection to "separation surgery" that optimizes delivery of postoperative RT.[12,13] A number of conceptual frameworks have been developed to optimize the delivery of both therapies in tandem, including the neurologic, oncologic, mechanical, and systemic decision framework and the LMNOP decision algorithm, which consider anatomic location of disease, mechanical instability, degree of neurologic compromise, oncologic diagnosis and radiosensitivity, and patient fitness and prognosis.[14–17] These hybrid strategies characterize patients not only based on mechanical stability, degree of neurological compromise, and tumor sensitivity but also on their goals of care, systemic disease burden, comorbidities, and performance status. Although variations of these frameworks are in widespread use, their evidence is primarily limited to observational studies, and further investigation is warranted to understand the relationship between surgery and RT in the current treatment paradigm.

For patients with a new diagnosis of spinal metastatic disease, radiation to a spinal lesion is often viewed as preferable to upfront surgery in the absence of frank instability or gross epidural cord compression. Surgical consultation may be offered after a patient has received radiation to the lesion. Nearly 20 years ago, a small retrospective series demonstrated the negative impact of preoperative RT for patients with spinal metastases.[18] As options for RT have improved, it is unclear if this negative impact remains. In this study, we examined factors associated with survival (including preoperative radiation [PR]) among patients undergoing surgery for spinal metastatic disease at an academic medical center. This study is part of an ongoing quality improvement initiative at the authors' institution to improve the coordinated management of patients with spinal metastatic disease in order to maximize outcomes and survival.

MATERIALS AND METHODS

This research study was approved by the institutional review board of the University of Pennsylvania (Protocol Number 826133). A retrospective medical record review was performed for all patients undergoing surgery for spinal metastasis at the University of Pennsylvania Health System between January 2010 and January 2017. Patients were identified using PennSeek, a tool designed to search unstructured and semistructured medical documents residing in the University of Pennsylvania Health System electronic medical records (EMR). EMRs were reviewed for all patients meeting search criteria for "metastatic spine tumor" with at least 1 documented encounter in radiation oncology and at least 1 documented encounter in surgery for open decompression and/or stabilization. Patients who underwent kyphoplasty alone were not included. A total of 109 patients underwent surgery for spinal metastatic disease in the study period, and 5 patients were excluded from the final study due to incomplete medical records. Among the original 109 patients, 34 underwent PR to the surgical site. One patient in the PR group was excluded due to an incomplete medical record. The final study population included 104 patients undergoing spinal surgery, and a subset of 33 patients who received preoperative spinal radiation.

Detailed demographic data, including the distribution of pathologies and the details of the patient's surgical procedures can be found in a previously published analysis.[19] For the current study, lung cancer pathology only included non–small cell lung cancer. We identified 1 patient with small cell lung cancer that we classified in a separate pathological group ("other").

The EMR of each patient was reviewed for the following variables: date of surgery, pathology, preoperative functional impairment including Karnofsky performance status (KPS) and Eastern Cooperative Oncology Group (ECOG) performance status, preoperative body mass index (BMI), preoperative American Society of Anesthesiologists (ASA) physical status classification, date of death, local radiation before or after surgery, chemotherapy before or after surgery, type of radiation, presence of other organ metastasis (lung, liver, brain, solid, etc), operative blood loss, preoperative spine instability neoplastic score (SINS), documentation of surgical complications (return to operating room for hematoma or infection within 30 days and wound dehiscence within 30 days), tumor location, and surgical approach (anterior vs posterior approach, use of posterior instrumentation, corpectomy ± cage/allograft, laminectomy, and number of levels fused).

Of note, the SINS score was calculated based on published criteria, similar to our prior work.[15,19] The pain component of the scale was calculated retrospectively using the patient's EMR. If patients endorsed pain with ambulation or movement, the pain score was marked as a "yes" for mechanical pain. If the patient was on short- or long-acting narcotic medication or endorsed pain at rest and did not endorse pain with ambulation or movement, the pain score was marked as a "no." If the patient did not complain of pain and was not on any short- or long-acting narcotics, the pain score was marked as "pain-free lesion."

Radiation treatment plans and beam contours at the index site were identified from the Aria oncology information system (Varian Medical Systems, Palo Alto, CA). Dates of service were matched to the radiation treatment plan, and computed tomography simulation images were obtained in Aria oncology information system. Computed tomography simulation images were utilized to identify the location, quality of the lesion, alignment, vertebral body collapse, and posterior element involvement for SINS scoring.[15] While a SINS score greater than 6 can indicate potential instability, we utilized a SINS score of 13 or greater to determine instability. The Bilsky score could not be calculated for degree of epidural cord compression, as magnetic resonance imaging is not routinely archived for patients in the radiation oncology system at the authors' institution.[14]

We performed survival analyses using Cox proportional hazards model to assess for significant predictors of time to death. First, we identified significant predictors of survival using univariate models ($P < 0.05$). These included the following: SINS score, local radiation prior to surgery, presence of liver metastasis, melanoma, and genitourinary cancer. We used χ^2 tests to compare categorical distributions and considered $P < 0.05$ to be statistically significant.

RESULTS

One hundred and four patients, 54 (52%) of whom were men, underwent surgery for spinal metastatic disease in the study period. The mean age was 60.9 (range, 32.6–87.4) years, and the mean preoperative BMI was 27.1 (range, 16–42.9). Of those patients, 71 (68.3%) did not undergo RT to the surgical site before surgery, while 33 received preoperative local RT. Eight (7.7%) patients returned to the operating room within 30 days after the index surgery for surgical complications, which included wound infections in 2 (1.9%) patients, hematoma in 3 (2.9%) patients, and wound dehiscence in 2 (1.9%) patients. A total of 55 deaths (53%) were reported with a median postoperative survival of 103 days (interquartile range, 41.5–264.5 days) (Table 1). All patients received postoperative care and subsequent follow-up within our health system and were followed until death or until the end of the study period. The mean follow-up time was 557.38 days (interquartile range, 94.25–885.25 days).

Table 1. Surgical complications and patient mortality ($N = 104$).

Complications	*n* (%)
Surgical complications	
Return to the operating room (within 30 d)	8 (7.7%)
Infection	2 (1.9%)
Hematoma	3 (2.9%)
Wound dehiscence (within 30 d)	2 (1.9%)
Deaths	55 (52.9%)
Postoperative survival, d, median (IQR)	103 (41.5–264.5)
Cases that underwent local preoperative radiation	33 (31.7%)

Abbreviation: IQR, interquartile range.
Note: Data presented as *n* (%) except where otherwise indicated.

The patients underwent surgical procedures either to resect the metastatic spine lesions, stabilize the spine, and/or decompress the neural elements. The procedures included 54 corpectomies, insertion of 39 cages or bone allografts, and 98 laminectomies. Fifteen (14%) patients underwent both anterior and posterior approaches to achieve spine stabilization, 84 (81%) received posterior instrumentation only, and 3 (3%) received anterior spine surgery alone. One patient underwent percutaneous fixation with mini-open decompression.

Preoperative health assessment included KPS scores, ECOG grades, and ASA scores. KPS scores were available for 90 patients, ECOG grades were available in 69 patients, and ASA scores were available in 75 patients. The distribution of patients in each category is represented in Table 2.

We performed survival analysis using Cox proportional hazards model. First, we identified all significant predictors of survival time using univariate models. We found the following variables to show significant univariate effects ($P < 0.05$): SINS score, local radiation before surgery, presence of liver metastasis, primary melanoma, and primary genitourinary cancer. The following variables were not significant in univariate analyses ($P > 0.05$): age, sex, posterior instrumentation, KPS, corpectomy, anterior approach, number of levels fused, location of tumor, local radiation after surgery, chemotherapy before surgery, chemotherapy after surgery, lung metastasis, brain metastasis, other metastasis, or any other primary cancers (eg, gastrointestinal, lung, prostate, and lymphoma).

We performed a multivariate survival analysis only using significant univariate predictors of survival. We found that preoperative RT to the surgical site (HR = 1.84, $P = 0.034$), unstable spinal lesions (SINS >12; HR = 1.11, $P = 0.024$),

Table 2. Preoperative performance status and health markers.

Karnofsky Performance Status Score (%)	*n* (%)	Eastern Cooperative Oncology Group Grade	*n* (%)	American Society of Anesthesiologists Score	*n* (%)
30	3 (3.3%)	0	12 (17.4%)	1	0
40	10 (11.1%)	1	36 (52.2%)	2	13 (17.3%)
50	11 (12.2%)	2	14 (20.3%)	3	59 (78.7%)
60	8 (8.9%)	3	4 (5.8%)	4	3 (4%)
70	23 (25.6%)	4	3 (4.3%)		
80	19 (21.1%)				
90	15 (16.7%)				
100	1 (1.1%)				
Total	90		69		75

and melanoma (HR = 3.60, $P = 0.010$) were significant predictors of reduced survival. Additionally, no PR patients had more frequent reoperations for postoperative wound complications (11.3% vs 0%, $P < 0.001$) (Table 3).

DISCUSSION

In this study, we examined the effect of several preoperative patient factors on survival after surgery for spinal metastatic disease and found that preoperative local RT, mechanical instability, and melanoma were independent predictors of time to death. Historically, RT evolved as the mainstay of therapy for patients with spinal metastasis, especially given the morbidity associated with invasive surgical procedures. In the absence of clear-cut indications for surgery, such as MSCC and mechanical instability, many patients are appropriately irradiated for their metastatic disease before neurological compromise or other symptoms force them to see a surgeon. As new systemic therapies enable cancer patients to live longer, and as RT modalities improve local disease control, it is critical to understand the selection pressures along the care continuum that shape the cohort of patients who ultimately undergo surgery for spinal metastatic disease.

In previous work by our group, patients with evidence of mechanical instability by SINS criteria who underwent RT followed by surgery were found to have higher postoperative mortality rates when compared with SINS-stable patients.[15,19] A majority of radiation-only patients (78%) in that cohort met criteria for potential instability at the time of radiation treatment, but few (5%) had a documented consultation with a spine surgeon prior to radiotherapy. While it is unclear whether patients in this sample would have better

Table 3. Preoperative predictors of time to death in patients with spinal metastatic disease.

Radiation Status	No PR	PR
Number of cases (% of total)	71 (68.3%)	33 (31.7%)
Age, y, mean (range)	59.9 (87.3–35.8)	63 (31.6–85.7)
Body mass index, mean (range)	27.6 (16.8–42.9)	26.2 (16–37.8)
Surgical complications (infection, wound hematoma, and dehiscence), *n* (%)	8 (11.3%)	0
Deaths, *n* (%)	31 (44%)	24 (73%)
Time to death, d, mean (range)	178.5 (2–897)	218.5 (3–889)
Hazard ratio		1.84
P value		0.034
SINS	**Stable (<13)**	**Unstable (≥13)**
Number of cases (% of total)	70 (67%)	34 (33%)
Deaths, *n* (%)	32 (46%)	23 (94%)
Time to death, d, mean (range)	219.7 (14–889)	162.9 (2–897)
Hazard ratio		1.11
P value		0.024
Melanoma	**Total**	
Number of cases (% of total)	5 (4.8%)	
Deaths, *n* (%)	5 (100%)	
Time to death, d, mean (range)	194.5 (24–218)	
Hazard ratio	3.6	
P value	0.010	

Abbreviations: PR, preoperative radiation; SINS, spine instability neoplastic score.
Note: We performed multivariate survival analysis using Cox proportional hazards model while accounting for the following variables, which demonstrated significance on univariate analysis ($P < 0.05$): SINS score, local radiation before surgery, presence of liver metastasis, primary melanoma, and primary genitourinary cancer.

survival if surgery was performed earlier, care pathways should be improved so that neurosurgical evaluation occurs before gross instability is observed.[19] It is possible that without timely multidisciplinary evaluation, these patients may be underscreened for factors that put them at risk for adverse postoperative outcomes.

In this study, we examined our cohort for predictors of time to death and found no association between survival and a number of traditional pre- and postoperative patient factors that have been identified as predictors of survival in other series of spinal metastases, including age, preoperative performance status, number of visceral metastases at the time of surgery, and postoperative adjuvant therapy.[20–26] It is possible that history of PR in our sample was a surrogate of more advanced disease or poor response to systemic therapy, which was not captured in our analysis and could independently portend a worse prognosis. Further study in larger populations is warranted to explore this possibility.

In one of the few multicenter prospective studies assessing predictive factors of survival in MSCC, Nater et al found that in multivariable analysis, only 3 factors were associated with longer survival: breast, prostate, or thyroid tumor type; absence of organ metastasis; and a lower degree of physical disability.[27] Univariate analysis within this prospective cohort, however, did reveal that PR was associated with poorer survival, in agreement with our findings. Further study in larger, more diverse populations is required to better understand these findings, as the Arbeitsgemeinschaft für Osteosynthesefragen (AO) Spine North American metastatic epidural spinal cord compression (MESCC) cohort was limited to specific tumor types and only single MSCC lesions.[27]

It is commonly held that PR puts patients at risk of wound dehiscence and other complications in the postoperative period. Ghogawala et al performed a retrospective of patients at their institution who underwent surgery for symptomatic spinal cord compression over a 25-year period and found that PR was associated with a greater than 3-fold major wound complication rate, as well as poorer functional outcome by Frankel grade.[18] In our sample, interestingly, we found more wound complications requiring reoperation among patients who did not receive PR, which may have been related to individual patient factors that our analysis was not powered to detect. Nevertheless, it should be acknowledged that wound complications following radiation is a well-documented phenomenon, even if there is disagreement in the literature about the extent of this risk.[28–31] It may be that patients who underwent PR presented for surgery with more advanced disease and underwent more limited surgical interventions, perhaps with palliative intent, compared with those who presented earlier in the disease trajectory, when disease control may have been a greater consideration.

The small number of melanoma patients in our sample ($n = 5$) limits interpretation of our result that this diagnosis is a meaningful predictor of survival. The available literature on survival for melanoma patients with spinal metastasis is limited but does suggest poor overall survival postoperatively, estimated between 3 and 6 months as the most prominent series. Goodwin et al found that median overall survival in spinal melanoma metastasis was 4 months, in a systematic review of patients with spinal metastases of skin cancers.[32] Spiegel et al reported median survival of only 86 days in a series of 114 cases over 21 years, while Gokaslan et al reported median survival of 4 months in a series of 133 cases over 11 years and Sellin et al reported a median survival of 5.7 years for 64 total patients.[33–35] Axial and appendicular skeletal metastases typically appear in melanoma patients at more advanced stages of the disease, and in the spine these often exhibit more aggressive, osteolytic behavior that may herald worse prognoses.[36–38] Nevertheless, the small number of melanoma patients in this analysis likely precludes reliable inference from this result, despite its statistical significance.

There are several limitations to this study. Generalizability of these findings is inherently limited by the small overall sample size and our retrospective approach. Patients are drawn from multiple treating physicians at different hospitals within 1 academic medical center, which contributes to heterogeneity within the sample that our collection methods may not have fully captured; although this diversity may be representative of usual practice at a large academic institution, there may be variability in treatment protocols across surgeons or hospitals. As mentioned preivously, the absence of archival magnetic resonance imaging also precluded Bilsky scoring for these patients. Furthermore, other confounders may be present among variables that were unable to be collected for this analysis. In future studies, it may be worthwhile to investigate patient characteristics that have been implicated in other survival series—of melanoma and other cancers—such as pre- and postoperative characteristics, including neurological deficit (eg, Frankel grade), ambulatory status, duration of neurological deficit, tumor histology and molecular markers, systemic therapies, and control of disease burden outside of the spine.[39–46]

CONCLUSIONS

While this study is limited by its small sample size, preoperative local radiation and mechanical instability remained independent predictors of time to death in this single-institution analysis of patients undergoing surgery for spinal metastasis. Preoperative KPS, BMI, and ASA

classification did not explain these differences. Patients who received PR also did not have more wound healing complications. Future studies in larger, more diverse populations are crucial to determine and understand the relationship between PR and postoperative outcomes and to determine the optimal timing for surgical intervention. It is possible that without timely multidisciplinary evaluation, these patients may be underscreened for factors that put them at risk for adverse postoperative outcomes.

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