Original Article

Ambulatory Status After Surgical and Nonsurgical Treatment for Spinal Metastasis

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BACKGROUND: Decisions for operative or nonoperative management remain challenging for patients with spinal metastases, especially when life expectancy and quality of life are not easily predicted. This study evaluated the effects of operative and nonoperative management on maintenance of ambulatory function and survival for patients treated for spinal metastases. **METHODS:** Propensity matching was used to yield an analytic sample in which operatively and nonoperatively treated patients were similar with respect to key baseline covariates. The study included patients treated for spinal metastases between 2005 and 2017 who were 40 to 80 years old, were independent ambulators at presentation, and had fewer than 5 medical comorbidities. It evaluated the influence of operative care and nonoperative care on ambulatory function 6 months after presentation as the primary outcome. Survival at 6 months and survival at 1 year were secondary outcomes. **RESULTS:** Nine hundred twenty-nine individuals eligible for inclusion were identified, with 402 (201 operative patients and 201 nonoperative patients) retained after propensity score matching. Patients treated operatively had a lower likelihood than those treated nonoperatively of being nonambulatory 6 months after presentation (3% vs 16%; relative risk [RR], 0.16; 95% confidence interval [CI], 0.06-0.46) as well as a reduced risk of 6-month mortality (20% vs 29%; RR, 0.69; 95% CI, 0.49-0.98). **CONCLUSIONS:** These results indicate that in a group of patients with similar demographic and clinical characteristics, those treated operatively were less likely to lose ambulatory function 6 months after presentation than those managed nonoperatively. For patients with spinal metastases, our data can be incorporated into discussions about the treatments that align best with patients' preferences regarding surgical risk, mortality, and ambulatory status. ***Cancer* 2019;0:1-7**. © *2019 American Cancer Society*.

KEYWORDS: ambulatory function, propensity score matching, spinal metastases, surgical management, survival.

INTRODUCTION

An estimated 3 million to 5 million patients are living with spinal metastatic disease, with the incidence of this condition increasing over the last 2 decades.[1-5] Neurologic deficits, including paraplegia and quadriplegia, can result from metastatic spread to the epidural space or from pathologic fractures. Up to 50% of patients with spinal metastatic disease die within a year of the diagnosis.[2-4,6,7] Management decisions are challenging for patients with spinal metastases, especially when life expectancy and quality of life are not easily predicted.[2,4-6,8] The benefits of surgery over nonoperative therapy for patients with metastases involving the spinal column have been postulated to include improved ambulatory function and independence, better pain control, enhanced cognition, and prolonged survival.[4,8-10] However, surgery is associated with 90-day mortality rates of 10% to 30%, with major complications documented in 30% to 50% of cases.[4,5,8-10] In the event of a postsurgical complication, patients may suffer accelerated functional deterioration and even early death. Although many of these risks can be avoided with nonoperative treatment, nonsurgical management may not be as efficacious in preserving mobility, quality of life, and overall survival.[9,11-13]

The evidence base at present includes many uncontrolled studies that do not provide the data that physicians need on the comparative effectiveness of operative and nonoperative management.[4-6,10-16] Retrospective studies of surgical

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We acknowledge the contributions of Miguel Hernan, MD, PhD (Department of Biostatistics and Epidemiology, Harvard T. H. Chan School of Public Health), who provided assistance with the propensity-matched analyses. He was not involved in the composition of the manuscript or in the selection of the final models.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.32140, **Received:** December 26, 2018; **Revised:** March 21, 2019; **Accepted:** March 23, 2019, **Published online** Month 00, 2019 in Wiley Online Library (wileyonlinelibrary.com)

cohorts provide details on outcomes for patients who are committed to surgical treatment and may also be limited by selection and indication bias. Moreover, studies restricted to surgical patients provide relatively little guidance for decision making about whether to elect surgery or nonoperative therapy. For example, patients who do best after an operative intervention may similarly benefit the most from nonoperative treatment while also avoiding the risks of postsurgical complications. In another scenario, patients may be willing to accept a more gradual decline and eventual loss of functional independence in the setting of nonoperative care rather than spend 2 months recovering from surgery, which may fail to prolong survival and does not guarantee neurologic preservation. Although a randomized controlled trial (RCT) could address these tradeoffs most incisively, an RCT presents considerable conceptual and logistical challenges in this setting. Thus, we need to rely on analytic approaches that allow simulation of an RCT with observational data.

In this context, we conducted the Spinal Metastasis Treatment in Determining Ambulatory Status (STRIDES) study to evaluate the effects of operative and nonoperative management on maintenance of ambulatory function and survival in patients treated for spinal metastases. We intended to emulate the environment of an RCT[17] by using propensity matching to yield homogeneous clinical cohorts in terms of age, ambulatory status at presentation, and number of medical comorbidities.[17,18] We hypothesized that patients treated surgically would demonstrate higher rates of survival and better preservation of ambulatory function.

MATERIALS AND METHODS

Data Source

The data we used for STRIDES were obtained retrospectively from the Partners Healthcare Research Patient Data Registry (RPDR)[4,8,13,19] and institutional electronic medical records from Massachusetts General Hospital and Brigham and Women's Hospital. The RPDR is a data repository that permitted us to identify patients with a putative diagnosis of spine metastatic disease. We used the electronic medical record to confirm the inclusion and exclusion criteria and abstract the key baseline and outcome variables. We queried the RPDR to identify adult patients, aged 40 to 80 years, who had been treated for spinal metastatic disease at Massachusetts General Hospital or Brigham and Women's Hospital between January 1, 2005, and December 31, 2017.

Emulation of the Target Trial Using Observational Data

Patient eligibility

Patients were considered eligible for this analysis if they received either operative or nonoperative management for spinal metastases during the study period, were independent ambulators at the time of presentation, and had fewer than 5 medical comorbidities as defined by the Deyo-modified Charlson Comorbidity Index.[20] We excluded individuals for whom the ambulatory status could not be defined at the time of presentation or who presented as dependent or nonambulatory.

Sample size calculation

We calculated the sample size for this study on the basis of data reported in the randomized trial of Patchell et al.[9] Patchell et al limited their study to patients with evidence of metastatic spinal cord compression and also included individuals with compromised ambulatory function, including paraplegia.[9] In that study, approximately 55% of the patients treated surgically were nonambulatory at 6 months, whereas 75% of those managed nonoperatively were; this meant a relative risk (RR) of 0.6. Assuming an α value of .05 and a power of 0.80, we determined that data from 300 operative patients were necessary to detect this difference and anticipated the need to abstract information from twice as many nonoperative patients to ensure successful matching in our propensity-matched analysis.

Abstractor training and chart abstraction process

Nonclinician abstractors attended 2 (1-hour-long) training sessions on elements of chart abstraction and identification of patient eligibility with the study's principle investigator (PI). We provided an initial training set of 10 medical records (including records for eligible and noneligible patients) to all abstractors for grading, after which determinations were reviewed with the PI. Subsequently, an additional set of 50 records was independently reviewed by all abstractors to determine the reliability of determinations regarding study inclusion criteria, with ratings rendered by the PI used as the gold standard. Weighted κ coefficients were used to assess interrater reliability, and these were interpreted according to the criteria of Landis and Koch.[21] The results indicated $\kappa = 0.81$. Individual rater agreement with the PI's determinations ranged from 94% to 98%.

We then randomly assigned medical records to abstractors in blocks of 50, stratified by age (40-60 and 61-80 years old), to determine eligibility for inclusion.

Charts were continually abstracted until a total of 300 eligible surgical cases and a total of 600 nonoperative cases were reached. We completed chart abstraction on August 1, 2018.

Treatment strategies and assignment

We classified patients as having received either a primary operative treatment strategy (called *operative* in the remainder of the text) or nonoperative treatment strategy on the basis of interventions administered within the first 8 weeks after presentation. If surgery had been performed within this time period, we classified patients in the operative group, regardless of other treatments (eg, chemotherapy or radiation) received simultaneously or at a later date. Conversely, patients who required surgical intervention at time points beyond the first 8 weeks were maintained in the nonoperative cohort.

Follow-up period and definition of outcomes

All individuals included in this study were independent ambulators at the time of presentation. We categorized the ambulatory status 6 months after presentation as independent, dependent (eg, regularly requiring a cane or walker), or nonambulatory. We considered patients reported in the medical records to have an Eastern Cooperative Oncology Group functional status[22] of 3 or 4 as nonambulatory in this investigation. Our primary outcome was a nonambulatory status 6 months after presentation. We used mortality at 6 months and 1 year as secondary outcome variables.

We recorded complications and readmission events that occurred within the first 90 days after treatment initiation. We defined complications with a previously published algorithm[5] that captured cardiovascular and cerebrovascular events, venous thromboembolic events, infections, skin and wound complications (including decubitus ulcers), sepsis, shock, pulmonary complications (including pneumonia), genitourinary complications (including acute renal failure and urinary tract infections), and delirium. For patients in the nonoperative group, we counted any nonplanned admission to the hospital after the initiation of a treatment protocol as a readmission event.

Development of the propensity-matched cohorts with the causal contrast of interest

We evaluated standardized differences[23] between the operative and nonoperative cohorts and used multivariable logistic regression analysis to identify variables associated with surgical intervention at the time of presentation. We subsequently developed a propensity score based on those variables that demonstrated a standardized difference greater than 0.10.[17,18,23,24] Age, biologic sex, body mass index, number of comorbidities, serum albumin, and vertebral body collapse at presentation were forced into the model on the basis of prior research that identified their importance in a decision for surgery.[2,3,10,12,14] Because serum albumin was not available for all patients, we included this variable in the propensity score model coded as missing, ≤3.5 g/dL, or >3.5 g/dL. We then conducted propensity score matching with 1:1 nearest neighbor matching with a caliper of 0.05 on a logit scale.[23,24] We chose this caliper because of the size of our sample, because we were estimating risk differences, and because it allowed for the best balance across included covariates.[25] We evaluated the postmatch balance in baseline variables between the operative and nonoperative cohorts via a comparison of standardized differences, with a standardized difference greater than 0.10 indicative of a lack of balance.[23,24] In the event that a variable appeared unbalanced after the propensity match, we evaluated the effect of this variable on the primary outcome with logistic regression analysis.

Comparison of outcomes in the matched treatment cohorts

We performed postmatch testing regarding the influence of operative and nonoperative care on the risk of becoming nonambulatory within the 6 months after presentation as well as 6-month and 1-year mortality with the McNemar chi-square test for paired data.[24] We also used contingency tables to determine RRs with 95% confidence intervals (CIs). Statistical significance was set a priori at $\alpha = .05$ with a 95% CI exclusive of 1.0.

Sensitivity analyses

We performed sensitivity tests in which all patients lost to follow-up (eg, without documented ambulatory status at 6 months who were not otherwise known to have died) were assumed to be nonambulatory (worst case scenario) or independently ambulatory (best case scenario) at that time point. We conducted all analyses with Stata (version 15.0; Stata Corporation, College Station, Texas). We received an exempt determination for this study from our institutional review board.

RESULTS

Features of Patients Who Met the Inclusion Criteria

We identified 929 individuals eligible for inclusion. The average age of the population was 57.3 years (SD, 9.4 years), 51% (n = 473) were women, and 84%

(n = 783) were white. Breast and lung cancer were the 2 most prominent primary tumors in the cohort, each with a prevalence of 21% (Supporting Table 1). We identified an operative approach in 306 cases (33%).

Features of the Matched Cohorts

Our propensity model included the following: age, biologic sex, medical comorbidities, serum albumin, primary cancer diagnosis, body mass index, vertebral body collapse, spinal canal compromise, and symptoms at presentation (Supporting Table 2). The propensity matching process retained 201 subjects in each of the operative and nonoperative cohorts (Fig. 1). Clinical and sociodemographic characteristics were balanced across both groups in the postmatch assessment with the exception of serum albumin (standardized difference, 0.15) and symptoms at presentation (standardized difference, 0.18; Table 1 and Supporting Table 3). In the operative group, 26% (53 of 201) received surgery and radiation, whereas 50% (101 of 201) were treated with surgery, chemotherapy, and radiation. Among those treated nonoperatively, 60% (121 of 201) received chemotherapy and radiation, and 19% (38 of 201) received chemotherapy alone. Seventeen percent (35 of 201) of the patients initially treated nonoperatively received a surgical intervention at a later point in their course of care.

In the propensity-matched sample, 18 of the 201 patients in the nonoperative group (9%) and 5 of the 201 patients receiving surgery (2%) were lost to follow-up. We did not identify clinically meaningful differences in baseline variables between those lost to follow-up and patients with complete outcome data.

Primary Outcome in the Matched Cohort

Using the data from the propensity-matched sample, we found that fewer patients treated surgically (3%) were nonambulatory 6 months after presentation in comparison with those treated nonoperatively (16%; RR, 0.16; 95% CI, 0.06-0.46; Table 2). The effect of surgery was statistically significant after McNemar testing ($P < .001$).

Although both serum albumin and neurologic symptoms at presentation demonstrated standardized differences greater than 0.10 after the propensity match, neither strongly influenced the effect of surgery on our primary outcome of ambulatory status at 6 months. In unadjusted testing, surgical treatment was associated with a lower likelihood of nonambulatory function at 6 months (odds ratio [OR], 0.14; 95% CI, 0.05-0.42; $P < .001$). This estimate was preserved in an adjusted analysis accounting for serum albumin and neurologic symptoms at baseline (surgical intervention [OR, 0.14; 95% CI, 0.5-0.42; $P < .001$], albumin ≤3.5 g/dL [OR, 0.49; 95% CI, 0.10-2.29; $P = .36$], and neurologic symptoms at presentation [OR, 0.40; 95% CI, 0.15-1.07; $P = .07$]).

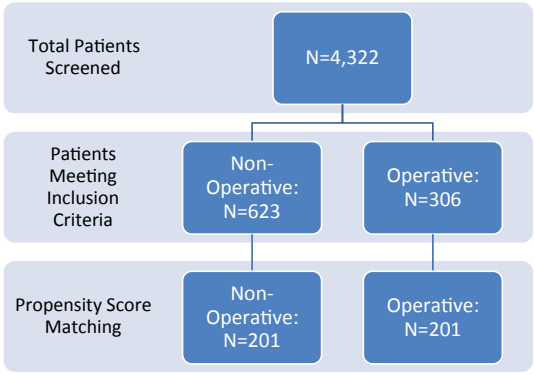

Figure 1. Depiction of the number of patients whose medical records were screened for inclusion, who were deemed eligible for the study, and who were retained in the analysis after propensity score matching.

Secondary Outcomes in the Matched Cohort

We determined that patients receiving an operative approach had lower 6-month mortality (20%) than those treated nonoperatively (29%; RR, 0.69; 95% CI, 0.49-0.98). This was statistically significant in the McNemar test ($P < .001$). Although patients treated surgically also had lower 1-year mortality (37% vs 51%; RR, 0.74; 95% CI, 0.59-0.92), this finding was not significant in the McNemar test ($P = .11$). Although we encountered lower likelihoods of complications (RR, 0.77; 95% CI, 0.57-1.04) and readmissions (RR, 0.79; 95% CI, 0.62-1.00) among patients treated operatively, these findings did not reach our criteria for significance.

We found that the assumption of a worst case scenario, in which all patients lost to follow-up in both cohorts were deemed nonambulatory, resulted in an RR of 0.21 (95% CI, 0.11-0.42), whereas the assumption that all patients lost to follow-up were independently ambulatory at 6 months resulted in an RR of 0.18 (95% CI, 0.06-0.51).

DISCUSSION

In STRIDES, we used strict inclusion criteria and propensity-matched analytical methods to simulate a randomized, prospective trial[17,23,24] evaluating the efficacy of surgery, as opposed to nonoperative care, as an

TABLE 1. Demographic Characteristics of Patients Treated Primarily for Spinal Metastases With a Nonoperative or Operative Approach in the Postmatch Sample (n = 402)

Characteristic	Nonoperative	Operative	Standardized Difference
Cases, No. (%)	201 (100)	201 (100)	—
Age, mean (SD), y	58.8 (9.8)	57.4 (9.4)	0.06
Female sex, No. (%)	92 (46)	103 (51)	0.10
White, No. (%)	169 (84)	168 (84)	0.0
Body mass index, mean (SD), kg/m^2	27.0 (6.1)	27.2 (6.4)	0.03
Number of comorbidities, No. (%)			0.06
1-2	136 (68)	131 (65)	—
3-4	65 (32)	70 (35)	—
Primary cancer, No. (%)			0.02
Breast	23 (11)	30 (15)	—
Lung	46 (23)	48 (24)	—
Other	132 (66)	123 (61)	—
Albumin ≤ 3.5 g/dL, No. (%)[a]	41 (20)	31 (15)	0.15
Vertebral body collapse/pathologic fracture, No. (%)	104 (52)	104 (52)	0.0
Spinal canal compromise, No. (%)	157 (78)	156 (78)	0.0
Symptoms at presentation, No. (%)			0.18
Axial pain/asymptomatic	126 (63)	109 (54)	—
Neurologic symptoms	75 (37)	92 (46)	—

[a]There were 267 patients (66%) in total with albumin levels > 3.5 g/dL, and 63 (16%) were missing this variable.

TABLE 2. Outcomes Among Patients Treated Primarily for Spinal Metastases With a Nonoperative or Operative Approach in the Postmatch Model

Outcome	Nonoperative	Operative	*P*	RR (95% CI)
Ambulatory status 6 mo after presentation, No. (%)[a]				
Independent ambulator or ambulatory with assistance	105 (84)	150 (97)	Referent	Referent
Nonambulatory	20 (16)	4 (3)	<.001	0.16 (0.06-0.46)
6-mo mortality, No. (%)				
Alive at 6 mo	142 (71)	160 (80)	Referent	Referent
Deceased at 6 mo	59 (29)	41 (20)	.04	0.69 (0.49-0.98)
1-y mortality, No. (%)				
Alive at 1 y	99 (49)	126 (63)	Referent	Referent
Deceased at 1 y	102 (51)	75 (37)	.007	0.74 (0.59-0.92)
Posttreatment complications, No. (%)				
No complications	131 (65)	147 (73)	Referent	Referent
1 or more complications	70 (35)	54 (27)	.08	0.77 (0.57-1.04)
Readmission, No. (%)				
No readmission	112 (56)	131 (65)	Referent	Referent
Readmission	89 (44)	70 (35)	.05	0.79 (0.62-1.00)

Abbreviations: CI, confidence interval; RR, risk ratio.
[a]Calculated from the total number of patients whose ambulatory status 6 months after presentation was known.

initial treatment strategy in patients with spinal metastases. Propensity score methods provide estimates of the average treatment effect among individuals receiving an intervention.[17,23] Our results indicated that, compared with a group of patients with similar demographic and clinical characteristics, individuals who underwent surgery had a lower likelihood of becoming nonambulatory 6 months after presentation. Furthermore, compared with a nonoperative cohort with similar demographic and clinical characteristics, those who underwent surgery also had a lower likelihood of mortality at 6 months.

Our results offer important insights for physicians engaged in the treatment of patients with spinal metastases. For individuals who present with clinical characteristics similar to those used for inclusion in this study, the incorporation of surgery as part of the primary treatment strategy may confer advantages in terms of preserving ambulatory function 6 months after presentation. We also found evidence that the primary use of surgery may result in improved survival, which could be expected because of the known association between functional capacity and mortality reported elsewhere.[2,3,9,10,14-16] Preservation of ambulatory capacity is a key component of maintaining functional independence and has been linked to patient-centered assessments of quality of life in the setting of metastatic disease.[14-16]

We acknowledge several limitations. Foremost, because of the retrospective design, we were restricted to

information imparted in the electronic medical record. Although our propensity model accounted for a number of factors known to influence the decision for surgery, the potential for residual confounding from unmeasured variables persists. We also recognize that our propensity match did not achieve a standardized difference less than 0.10 across all covariates. With a larger sample, we may have been better able to adjust for these factors, including serum albumin and symptoms at presentation. However, adjustments for these covariates did not alter the association of the treatment variable with our primary outcome.[26] Because our analyses were limited to patients aged 40 to 80 years with relatively few comorbidities and with functional independence at baseline, the results cannot be generalized to the entire spectrum of patients presenting with spinal metastases. Lastly, this work was conducted with patient data derived from 2 academic medical centers in a single city that treated a disproportionately large proportion of white patients. Brigham and Women's Hospital and Massachusetts General Hospital share a medical school as well as many training programs. Because the clinicians in these hospitals work in the same heath care system and participate in the same teaching programs, there may be less variability in physician behavior than would otherwise be anticipated.

In conclusion, our use of strict inclusion criteria and causal inference techniques enabled this work to simulate a randomized trial. We found that individuals treated surgically maintained independent ambulatory function to a greater degree 6 months after presentation. Maintenance of ambulatory capacity is an important component of both functional independence and quality of life and may also contribute to improved survival in patients with spinal metastases. In light of these findings, our data can be incorporated into discussions between clinicians and patients about the treatments that align best with the patients' preferences regarding surgical risk, mortality, and ambulatory status.

FUNDING SUPPORT

This research was funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health (grant K23-AR071464 to Andrew J. Schoenfeld, grant K24-AR057827 to Elena Losina, and grant P30-AR072577 to Jeffrey N. Katz). The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the National Institutes of Health or the Federal Government.

CONFLICT OF INTEREST DISCLOSURES

Andrew J. Schoenfeld reports grants to his institution from the Orthopaedic Research and Education Foundation and the US Department of Defense, nonfinancial support of his institution from the Centers for Medicare and Medicaid Services and its Office of Minority Health, and royalties from Wolters-Kluwer and Springer Publishing outside the submitted work, and he is deputy editor of the *Journal of Bone and Joint Surgery*. Elena Losina reports personal fees from the *Journal of Bone and Joint Surgery* and Regeneron and grants from Pfizer, Samumed, and Flexion outside the submitted work. Marco L. Ferrone reports grants to his institution from the Orthopaedic Research and Education Foundation. Joseph H. Schwab reports personal fees from Stryker outside the submitted work. John H. Chi reports personal fees from K2M outside the submitted work. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Andrew J. Schoenfeld: Conception and design of the study, data acquisition, data analysis, drafting of the manuscript, critical revision of the manuscript for intellectual content, and full access to all data. **Elena Losina:** Conception and design of the study, data analysis, critical revision of the manuscript for intellectual content, and full access to all data. **Marco L. Ferrone:** Conception and design of the study, data acquisition, drafting of the manuscript, and full access to all data. **Joseph H. Schwab:** Conception and design of the study, data acquisition, drafting of the manuscript, and full access to all data. **John H. Chi:** Data acquisition, drafting of the manuscript, and full access to all data. **Justin A. Blucher:** Data acquisition, data analysis, drafting of the manuscript, and full access to all data. **Genevieve S. Silva:** Data acquisition, drafting of the manuscript, and full access to all data. **Angela T. Chen:** Data acquisition, drafting of the manuscript, and full access to all data. **Mitchel B. Harris:** Data acquisition, drafting of the manuscript, and full access to all data. **James D. Kang:** Conception and design of the study, drafting of the manuscript, and full access to all data. **Jeffrey N. Katz:** Conception and design of the study, data analysis, critical revision of the manuscript for intellectual content, and full access to all data.

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