Technical Appendix

Analytic Overview

We developed a state-transition Markov model for patients with spinal metastatic disease that could be treated using either operative or non-operative management. We constructed the Markov model using TreeAge Pro (TreeAge software, Williamstown, MA) to depict the post-treatment course of patients using a series of transitions between health states over their remaining life expectancy. We derived the transition probabilities from secondary data analysis and published literature. We assigned a utility to each health state. Utilities represent the impact of disease burden on a patient's quality of life and are presented on a scale from 0 to 1, with 1 representing perfect health and 0 equivalent to death. Utility values are used as a scalar reflecting diminished quality of life to convert a year of life into a quality-adjusted life year (QALY). Costs consisted of expenditures associated with the resources utilized within each health state. We expressed costs in 2019 US dollars with 3% annual discounting applied for quality of life and costs. We applied annual cancer specific mortality, adjusted to 30-day time periods.

Outcomes from the model included QALYs and lifetime direct medical costs. We used the difference in costs over the difference in QALYs between the simulated operative and non-operative strategies to calculate an incremental cost-effectiveness ratio (ICER), which quantifies the value of resources spent against willingness-to-pay thresholds, or the maximal cost that society is willing to spend for each additional QALY gained. In this study, we used willingness-to-pay thresholds of $100,000 and $150,000. Treatments that have ICERs below the willingness-to-pay threshold are considered cost-effective. We performed analyses from a healthcare system perspective, excluding patient and time costs.

Model Structure

The model's health states are characterized by ambulatory function and defined as independent, dependent (requiring use of assistive device such as cane or walker for all ambulatory activities) and non-ambulatory (bed or wheelchair bound), or death. We defined the efficacy of operative and non-operative treatment as the likelihood of maintaining, or returning to, independent ambulation. Patients could transition to dependent and non-ambulatory states due to pain or neurologic deterioration. Patients could transition to death from any other health state. Transitions occur at 30-day intervals, based on current ambulatory state, treatments received and any post-treatment events (e.g. complications, revision surgery). Patients initially treated non-operatively could receive a surgical intervention if they developed a deterioration in ambulatory function. Similarly, patients treated surgically could also undergo a revision procedure if they developed subsequent deterioration in ambulatory function. The time-frame of the model was 5 years, or until all simulated patients died, whichever occurred first.

The methods used for determining transition probabilities, deriving costs for operative and non-operative treatment, as well as quality of life estimates are described below. We also provide a complete delineation of the input parameters for complications, revision surgery, transition probabilities, costs and utilities for patients receiving operative and non-operative treatment in the cost-effectiveness analysis (Appendix Table 1) as well as the input parameters for mortality, complications, transition probabilities and utilities for patients receiving operative and non-operative treatment in the probabilistic sensitivity analyses (Appendix Table 2).

Determination of transition states for ambulatory function

We estimated the probability of entering a dependent, or non-ambulatory state, as well as maintaining independent ambulatory status following initial treatment based on underlying cancer progression, treatment failure and post-treatment complications. We derived these probabilities from retrospective encounter data of 713 adult patients who were independent ambulators and received operative (n=370) or non-operative (n=343) treatment for spinal metastases at three tertiary referral cancer centers in Boston, MA between 2005-2017.

Of those receiving operative treatment, ambulatory function at 30-days following surgery was available for 174 patients. Of these, 50 (28.7%) were independently ambulatory, 74 (42.5%) were dependent ambulatory and 50 (28.7%) were non-ambulatory. Of those receiving non-operative treatment, ambulatory function at 30-days was available for 182 patients. Of these, 76 (41.8%) were independent ambulators, 55 (30.2%) were dependent ambulators and 51 (28.0%) were non-ambulatory. Of those patients who were non-ambulatory after operative treatment, 5/50 (10.0%) experienced improvement, while 34/50 (68.0%) died. None of the patients who were non-ambulatory after non-operative treatment regained ambulatory function, with 41/51 (80.3%) deceased at 6-months following presentation.

Determination of complication rates

The complication rate was estimated at 51.0% for operative patients and 6.9% for non-operative patients. The complication rate for surgical patients was derived from American College of Surgeons-National Surgical Quality Improvement Program data from cases of 776 patients. This population captured a great deal of the variety in clinical presentation for spinal metastases, including different primary tumors, extent of metastatic disease, functional status, surgical approaches and co-morbidity profiles. Surveillance for complications in this study was exhaustive and included surgical as well as medical complications (wound infections, urinary tract infections, postoperative cardiopulmonary events, postoperative neurologic events, venous thromboembolic events, renal failure, unplanned reintubation, sepsis and shock.[1]) Similar events were surveilled in the investigation used for the probability of complications after radiation therapy.[6] Because there is limited data available for differences in complication events between primary and revision surgical procedures, we used the same point estimate for both.

Quality of Life Estimates

Each ambulatory state was associated with a quality of life utility and costs, including those related to complications, readmissions, the need for surgery in individuals initially managed non-operatively and revision procedures for patients treated surgically. We derived quality of life values from prospective EuroQol 5-dimension (EQ5D) surveys completed by participants in the Prospective Observational study of Spinal metastasis Treatment (POST; 2017-19). Surveys were completed at baseline enrollment, 1-month, 3-months, 6-months and 12-months following presentation, or until death for those who died over the course of the study. These data consisted of 675 completed surveys of patients in different stages of treatment for spinal metastatic disease, including 430 independent ambulatory patients, 205 dependent patients and 40 non-ambulatory patients. Raw data were transformed to utilities using normative US values for the EQ5D. Standardized estimations for each of the health states, including 95% confidence intervals (CI), were then calculated using generalized linear modeling that accounted for age, biologic sex, surgical or non-operative treatment, length of follow-up and repeated measures in the same individual. These estimations for utility were performed using STATA v15.1 (STATA Corp., College Station, TX).

The utility for independent ambulatory status was estimated at 0.756 and the utilities for dependent ambulatory status and non-ambulatory status were 0.599 and 0.175, respectively.

Calculation of Costs

We used the Medicare fee schedule to calculate unit costs of operative and non-operative treatment including hospital admission, outpatient physician visits, emergency room encounters, imaging, anesthesia and surgeon fees, post-treatment care and evaluations, prescription medications, cost for treatment of complications including readmission and revision surgical procedures, post-treatment rehabilitation, durable medical equipment, home nursing care and hospice care. Frequency of resource use for each category was determined from expert consultation.

Pre-operative costs

Pre-operative costs included the initial physician consultation and imaging were derived from the Centers for Medicare and Medicaid Services (CMS) 2019 physician fee schedule and Hospital Outpatient Prospective Payment System rules.

Procedure costs

Anesthesia professional fees were determined from the CMS Anesthesia Fee Schedule for 2019. Surgeon fees were determined from the 2019 physician fee schedule. Surgery-related technical costs and acute inpatient recovery expenditures were determined using appropriate diagnosis-related group (DRG) codes.

Post-acute recovery costs

Expenditures associated with post-treatment rehabilitation, utilization of outpatient physical therapy, home health care, durable medical equipment and hospice were determined from the CMS Medicare fee schedule, Red Book from Truven Health analytics and published estimates for hospice costs, respectively. Post-treatment medication expenses were determined by applying average medication process to a typical post-treatment medication regimen.

Cost of Complications and Revision Surgery

Complication costs included the initial physician consultation, emergency department evaluation and imaging were derived from the Centers for Medicare and Medicaid Services (CMS) 2019 physician fee schedule and Hospital Outpatient Prospective Payment System rules. Post-complication medication expenses were determined by applying average medication process to a typical post-treatment medication regimen. If the complication necessitated a hospital admission, acute inpatient expenditures were determined using appropriate diagnosis-related group (DRG) codes.

In the event of a revision procedure, anesthesia professional fees were determined from the CMS Anesthesia Fee Schedule for 2019. Surgeon fees were determined from the 2019 physician fee schedule. Surgery-related technical costs and acute inpatient costs were determined using appropriate diagnosis-related group (DRG) codes.

Sensitivity Analyses

We conducted one-way deterministic sensitivity analyses to evaluate how the cost-effectiveness of operative treatment changes as a function of different surgical procedures as well as the efficacy of operative management. We considered the following types of surgery: posterior decompression, posterior decompression and fusion; and different levels of hospital reimbursement based on varying the diagnosis related group (DRG). We varied the efficacy of operative management incrementally at 1-percentage point intervals, starting at the initial probability (28.7%) of remaining independently ambulatory immediately following operative treatment. We also incrementally reduced the complication rate following surgery, starting at the probability (51.0%) used in the base model.

We also performed probabilistic sensitivity analysis to assess the uncertainty in cost effectiveness of surgical strategy as a function of mortality, complications, utilities and transition to dependent and non-ambulatory states simultaneously by repeating the cost-effectiveness testing in 10,000 simulations. In each simulation, the model varied selected parameters within pre-specified beta distributions, accounting for variations in the size of the sample used to generate the primary point estimate employed in the model. We constructed a cost-effectiveness acceptability curve to depict the proportion of runs where a surgical or non-surgical strategy was cost-effective given pre-specified willingness-to-pay thresholds. We performed probabilistic sensitivity analysis for each of the populations under consideration.

Appendix Table 1. Input parameters for complications, revision surgery, transition probabilities, costs and utilities for patients receiving operative and non-operative treatment in our cost-effectiveness analysis.

Present Ambulatory Independent Operative Treatment

Complication		Mort	Revision Surgery		
51%[1]		3%[1]			
SSI	Other		^No Comp	SSI	Other
5.1%[2]	94.9%		8%[1]	11%[3]	11%[3]

Transition Probabilities

First Month[4]		Each Additional Month[4]			
		Ind	Dep	NA	Mort
Ind	28.7%	97.1%	2.9%	--	2.8%
Dep	42.5%	4.8%*	94.1%	1.1%	6.5%
NA	28.7%	--	8.6%*	91.4%	21.9%

Present Non-Ambulatory Operative Treatment

Complication		Mort	Revision Surgery		
51%[1]		3%[1]			
SSI	Other		^No Comp	SSI	Other
5.1%[2]	94.9%		8%[1]	11%[3]	11%[3]

Transition Probabilities

First Month[5]		Each Additional Month[4]			
		Ind	Dep	NA	Mort
Ind	10.1%	97.1%	2.9%	--	2.8%
Dep	87.3%	4.8%*	94.1%	1.1%	6.5%
NA	2.5%	--	8.6%*	91.4%	21.9%

Present Ambulatory Independent Non-Operative Treatment

Complication		Mort	Primary Surgery		
6.9%[6]		2.5%**			
VF	Other		No Comp	VF	Other
3.6%[7]	96.4%		0.8%[8]	4.8%[9]	11%[3]

Transition Probabilities

First Month[4]		Each Additional Month[4]			
		Ind	Dep	NA	Mort
Ind	41.8%	97.6%	1.8%	0.6%	2.8%
Dep	30.2%	1.2%*	96.9%	1.9%	6.5%
NA	28.0%	--	--	100%	21.9%

Present Non-Ambulatory Non-Operative Treatment

Complication		Mort	Primary Surgery		
6.9%[6]		2.5%**			
VF	Other		No Comp	VF	Other
3.6%[7]	96.4%		0.8%[8]	4.8%[9]	11%[3]

Transition Probabilities

First Month[+]		Each Additional Month[4]			
		Ind	Dep	NA	Mort
Ind	0%	97.6%	1.8%	0.6%	2.8%
Dep	0%	1.2%*	96.9%	1.9%	6.5%
NA	100%	--	--	100%	21.9%

Costs [10,11,12,13,14,15,16,17,18,19,20,21] / **Utilities [22]**

Treatment		Health State		Event				Entering Status	
				SSI	VF	Become Dep	Become NA		
Surgery	$33,529	Ind	$2,407					Independent	0.756
Rev. Surg	$7,405	Dep	$2,542					Dependent	0.599
Radiation	$12,932	NA	$5,582	$7,780	$2,040	$53	$94	Non-Amb	0.175

* Designates a value that is only applied for the first 6 months; it then reverts to 0. The complement probability to stay in the respective health state is thus increased to ensure the sum remains at 1.
** Designates an assumption made based on operative overall mortality.
+ Designates an assumption made that radiation cannot cause someone to improve from non-ambulatory status.
^ If non-ambulatory and the number of months is <8, this revision surgery/primary surgery probability is used.

Mort = Mortality
Ind = Independent

Dep = Dependent
NA = Non-Ambulatory
Rev. Surg = Revision Surgery
SSI = Surgical Site Infection
VF = Vertebral Fracture
Become Dep = Event that causes subject to become ambulatory dependent from some other health state
Become NA = Event that causes subject to become non-ambulatory from some other health state
No Comp = No complication

Appendix Table 2. Input parameters for mortality, complications, transition probabilities and utilities for patients receiving operative and non-operative treatment in our probabilistic sensitivity analyses.

Operative			
		Independent Ambulatory Status at Presentation	*Non-Ambulatory Status at Presentation*
Health State	Parameter	Distribution (r, N)	Distribution (r, N)
Surgery	Mortality	Beta (4, 130) [1]	Beta (4, 130) [1]*
	Complication	Beta (395, 776) [1]	Beta (395, 776) [1]
	Independent	--	Beta (37, 135) [1]
	Dependent	Beta (74, 174) [4]	--
	Non-Amb	Beta (50, 174) [4]	Beta (10, 135) [1]
Independent	Mortality	Beta (20, 126) [4]	Beta (20, 126) [4]
	Dependent	Beta (6, 37) [4]	Beta (6, 37) [4]
Dependent	Mortality	Beta (43, 129) [4]	Beta (43, 129) [4]
	Independent	Beta (12, 47) [4]	Beta (12, 47) [4]
	Non-Amb	Beta (3, 47) [4]	Beta (3, 47) [4]
Non-Amb	Mortality	Beta (78, 101) [4]	Beta (78, 101) [4]
	Dependent	Beta (5, 12) [4]	Beta (5, 12) [4]
Non-Operative			
Radiation	Mortality	Beta (3, 130) *	Beta (3, 130) *
	Complication	Beta (70, 201) [6]	Beta (70, 201) [6]
	Dependent	Beta (55, 182) [24]	-- **
	Non-Amb	Beta (51, 182) [24]	-- **
Independent	Mortality	Beta (20, 126) [4]	Beta (20, 126) [4]
	Dependent	Beta (6, 57) [4]	Beta (6, 57) [4]
	Non-Amb	Beta (2, 57) [4]	Beta (2, 57) [4]
Dependent	Mortality	Beta (43, 129) [4]	Beta (43, 129) [4]
	Independent	Beta (2, 28) [4]	Beta (2, 28) [4]
	Non-Amb	Beta (3, 28) [4]	Beta (3, 28) [4]
Non-Amb	Mortality	Beta (78, 101) [4]	Beta (78, 101) [4]
Utilities			
Ambulatory Status	95% CI Range	Distribution (Mean, SD)	
Independent	0.741 – 0.772 [22]	Beta (0.756, 0.165) [22]	

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Dependent	0.576 – 0.622 [22]	Beta (0.599, 0.166) [22]
Non-Ambulatory	0.124 – 0.227 [22]	Beta (0.175, 0.166) [22]

* Designates an assumption made based on overall mortality.
** Designates a distribution that could not be made based on the assumption that anyone who presents as non-ambulatory is unable to become ambulatory from radiation alone.

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