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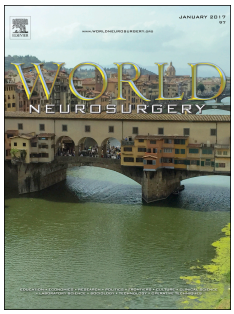

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Cost-utility analysis of surgery and radiotherapy for symptomatic spinal metastases in a Belgian specialist center.

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Running title

Spinal metastasis surgery in Belgium, a cost-utility analysis

Cost-utility analysis of surgery and radiotherapy for symptomatic spinal metastases in a Belgian specialist center.

Introduction

Spinal metastases represent the most frequent bone metastases in systemic cancer,[1] and may result in spinal pain, muscle weakness, gait difficulties or sphincter disturbance. Surgery has improved significantly over the past 20 years, and the added value of surgery combined with radiotherapy compared to radiotherapy alone has been demonstrated for solid metastases causing spinal cord compression and/or spinal instability.[2-4] In a prospective cohort study of 922 consecutive surgical patients presenting with spinal metastases, Choi et al. found improvements in pain, functional performance and quality of life that were sustained[5]. As improvements in cancer therapies lead to longer survival, surgical strategies aimed at maintaining quality of life have become more relevant. New possibilities in spinal stereotactic radiosurgery following minimally invasive 'separation surgery' have led to new treatment paradigms.[6] An increase in the use of surgery for treating spinal metastases is recognized,[7] and it is expected that surgery will continue to play an important role in the multidisciplinary management of spinal metastases in the future.

Several studies have reported costs of surgery for spinal metastases, and figures vary widely: €15,267 for both inpatient care and outpatient follow up in a Belgian study using Diagnosis Related Groups (DRG) codes and national tariffs[8], an average inpatient cost of £16,885 in a United Kingdom study with patient-level actual costs,[9] but an average of $50,098 for direct costs to the hospital for inpatient stays in a San Francisco study,[10] and an average total of €87,814 over a lifetime horizon in a Danish study.[11] Detailed cost-utility analyses comparing surgical versus non-surgical approaches were performed by three authors. Turner et al. found that over a lifetime horizon the mean incremental cost was £12,839 cheaper for the surgical group, but with a large standard deviation of £37,896 and a median incremental cost difference that was slightly more expensive for the surgical group.[12] Furlan et al. calculated an incremental cost-effectiveness ratio (ICER) of US$250,307 using a Markov model approach based on the Patchell study data and Ontario-based physician fee and

hospital cost data.[13] Finally, Miyazaki et al. found an ICER of US$42,003 per QALY in a prospective patient-level study in Kobe, Japan.[14] The huge variation in reporting costs is explained not only by differences in healthcare funding systems, but also by different methods of calculating costs. The societal perspective is best reflected in reimbursement from central funders to the hospitals, but to the hospital the direct costs are more relevant.[9] In addition, it is clear that patient-level costs yield more robust data than national averages.

Since 2011, data of patients undergoing surgery for spinal metastases at the University Hospitals Leuven, Belgium, have been included in the Global Spine Tumour Study Group database forming a prospective cohort of over 2,000 surgical patients including outcome data.[15] In addition, the management data and reporting unit in our hospital has invested in a thorough cost allocation model. The goal of our present paper is to perform a cost-utility analysis of surgery for spinal metastases based on patient-level data in a specialist spine center in Belgium. Belgium is a European mainland country with a Bismarck healthcare system, i.e. an insurance system jointly financed by employers and employees through payroll deduction and regulated by the government.

Material and methods

Subjects

Subjects were recruited consecutively in a specialist spinal center in Leuven, Belgium. The patients' details were anonymized and entered prospectively into the GSTSG secure online database. Subjects were considered eligible if they presented with symptomatic spinal metastases requiring surgical intervention and gave informed consent, but were excluded if they were unable to give consent or were under 18. Subjects were recruited between 2011 to 2015. Local institutional ethical approval was granted in Leuven for participation in the GSTSG database.

Hospital costs

Hospital costs were extracted from the financial database, identified using unique hospital number identifiers, and limited to those encounters relating to neurosurgical

management of a symptomatic spinal metastasis. Post-operative radiotherapy was included in this capture. To capture all spending activity related to this treatment, inpatient, outpatient and day cases were included. Concomitant oncological treatments for the primary tumor and rehabilitation were excluded. The hospital's financial database is further able to separate costs from each of these encounters into cost subtypes: depreciation; medical staffing; non-medical staffing; daily operational costs; drugs and implants. All financial details were inflated to the 2015/2016 financial year.

The alternative treatment strategy for symptomatic spinal metastases is radiotherapy only. Due to the superiority of surgical management in the study by Patchell et al,[2] it was not appropriate to carry out a randomized controlled trial. Instead, treatment costs from a radiotherapy-only cohort were identified. Patients with symptomatic spinal metastases that underwent radiotherapy but without surgical intervention were retrospectively retrieved from the hospital database between 2011 to 2015. Karnofsky performance indices of the non-surgical patients were matched with the surgical patients. Costs relating to radiotherapy treatment for the spinal metastasis, both inpatient and outpatient, were extracted.

Outcome measures

Subject demographics, clinical and surgical information were collected preoperatively for those undergoing surgery, including number and type of admissions, primary tumour type, pain (visual analogue scale), Frankel score, Karnofsky performance index, health status (EQ5D index calculated using UK value sets, a score of 0 was applied on death),[16] American Society of Anaesthesiologists' physical status classification (ASA), Tokuhashi and Tomita score, number of levels operated on, and presence of post-operative complications. EQ5D health status was also collected at 3, 6, 12, 24 months.

Patient demographics, primary tumour location and Karnofsky performance index were also extracted for those having radiotherapy only.

Statistical analysis

All statistical analysis was carried out in Stata/SE version 13.1 (Statacorp LP, College Station, Texas, USA). Costs, subject demographics and clinical details were

initially analysed using descriptive statistics. Costs were reported as medians due to skewness, as well as means. Univariate regression analysis assessed how total cost related to demographic and clinical variables, grouped by better or worse health. Multivariate analysis reviewed how total costs, non-medical or operational costs were related to groups of covariates, chosen following stepwise selection due to the exploratory nature of this analysis, and corrected for length of stay. A generalized linear model with gamma family and log link were used to account for the skewness of the cost data.[17] Average marginal effects of included covariates were calculated, showing the adjusted impact of each on cost. Statistical significance was set at P=.05.

Quality adjusted life years (QALYs) for surgical patients were generated by calculating the area under the curve when directly connecting health utility scores over time, including discounting at 3.5% a year, as described previously.[12,18] QALY calculation for the non-surgical group was modelled on the surgical group. Survival was reduced to 79% based on the study by Patchell et al.[2] Health utility was modelled as staying at the pre-operative level, as it is assumed immediate improvement in status is related to surgery, then declining linearly until point of death once the matched surgical patient's health status started to decline. Two sensitivity analyses representing an initial over- and underestimation of QALYs were completed to make the analysis more robust, as described previously.[12]

Results

Surgical patients

Thirty-eight patients were identified who had information available for cost-utility analysis. Twenty-three were males (60.5%) and the mean age was 60.1 (SD 15.2) years. Subjects presented with diverse secondary tumours: the largest groups were breast cancer (15.8%), followed by gastric and lung cancer (10.5% each). Median Karnofsky performance index at presentation was 70 (IQR 50-80). Health status was

available for 95% of subjects at baseline (36 of 38), 88% of subjects surviving at 3 months (29 of 33) and 100% at 6, 12 and 24 months (n=28, 22 and 16 respectively). The median initial health status was 0.33 (IQR 0.15-0.55, mean 0.36 SD 0.29). The median length of stay of the surgical admission was 11 days (IQR 6-17). Two patients (5.3%) had a pre-operative admission and three patients (7.9%) had a second, post-operative admission. 31.6% of subjects had pre-surgical outpatient appointments (n=12, mean 1.3 each) and 63.2% of subjects had post-operative outpatient visits (n=24, mean 2.2 each).

The median total cost of treatment for surgery and subsequent radiotherapy was €15,462 (IQR 10,911-23,116, mean €16,989 SD €8,148). Of the total cost, 89.6% related to the initial surgical admission, 3.1% to associated non-rehabilitation hospitalisations and 7.1% to outpatient visits (table 1). Radiotherapy costs were, depending on the in- or outpatient setting, included in the admissions and/or visits. The majority of spend was a result of non-medical staffing cost (mean €7,721, 45.9%), followed by day-to-day operational costs (€2,963, 17.6%) and medical staffing cost (€2,621, 15.6%) (table 2).

Univariate regression analysis of factors affecting total cost of treatment indicated higher costs if subjects had a slower growing tumour (P=0.02), greater neurological impairment (P=0.04), lower health status on EQ-5D (P=0.02) and presence of post-operative complications (P=0.004). Being in a different category of Tomita score also had an effect on total cost, but this did not follow a uniform trend (table 3).

Multivariate regression analysis for total cost followed the pattern of the univariate analysis (table 4). The primary tumour being a slower growing primary, as well as presence of post-operative complications had a significant impact on all cost categories; total costs were on average €20,633 for subjects with slower growth tumours, and €15,072 for those with faster growing primary tumours; and €22,433 in the presence of complications compared to €14,056 without. Total costs were additionally increased by having a lower health status (€20,439 vs. €14,154), as were non-medical staffing costs when combined with being male, and higher levels of pre-operative pain. A lower functional status, as measured by the Karnofsky score also impacted on day-to-day operational costs.

Non-surgical patients

In the non-surgical group, eight subjects were identified who matched the surgical group. These were patients that either had refused surgery or that had not been offered the option of surgery because the oncologist or attending neurosurgeon did not believe in the added value of it. Two were males (25%) and mean age was 60.1 years. Tumour origin was breast in 50% of cases. The Karnofsky performance index at presentation was ≥70 in 50% of cases, as in the surgical group. 50% of subjects had their radiotherapy as an inpatient, with a median length of stay of 14 days. 75% of subjects had associated outpatient clinic visits (n=6, mean 1.2 each). The mean total cost associated with radiotherapy in the non-surgical group was €9,354.

Calculation of ICER

The ICER of surgery for spinal metastases is calculated by dividing the difference in total cost between the surgery group (surgery + radiotherapy) and the non-surgery group (radiotherapy alone) by the difference in QALYs between the two groups. Subjects treated with surgery in addition to radiotherapy generated costs on average €7,636 higher than the radiotherapy only patients. The median post-operative QALYs in the surgical patients were 0.70 (IQR 0.18-1.70, mean 0.95 SD 0.96)(Figure 1). In the non-surgical group, the sensitivity analyses returned median QALYs of 0.17 (IQR 0.01-0.56, mean 0.42 SD 0.64) in the QALY over-estimation scenario and 0.10 (IQR 0.01-0.35, mean 0.26 SD 0.36) in the QALY under-estimation scenario (Figure 1).

, Applying the ICER formula results in an ICER of €13,635 per QALY, and with a range of €12,726-€14,407 per QALY in the sensitivity analyses.

Discussion

In this study of 38 patients who underwent surgery with or without radiotherapy for treatment of symptomatic spinal metastases in a specialist hospital in Belgium between 2011 and 2015, the median total cost of treatment was €15,462. The median total cost for radiotherapy only in a cohort of 8 patients with matched disease severity and functional status dating from the same period was €7,636. Quality of life using EQ-5D scores was assessed in the surgery cohort and modelled in the

radiotherapy-only cohort; the ICER for spinal metastasis surgery was €13,635 per QALY. The ICER varied up to 6.7% in the sensitivity analysis. In order to assess whether a procedure is cost-effective, the ICER is compared with a threshold that is calculated based on the Gross Domestic Product per capita of the country in question. For Belgium, this threshold is €37,300 per QALY.[18] This means that the management of a symptomatic spinal metastasis by surgery and radiotherapy is cost-effective. Also according to the much cited U.K. threshold of £30,000 per QALY, the combination of surgery and radiotherapy is cost-effective.[19] To the best of our knowledge, this is the first cost-utility analysis for this type of surgery in a Bismarck health system in Europe.

Reimbursement tariffs may be more appropriate in assessing societal costs paid by the tax payer, whereas hospital costs reflect the actual costs of a certain treatment. Therefore, the present analysis has focused on actual hospital costs. Ideally, both match as far as possible, but in practice these costs may diverge.[12] Furthermore, in assessing costs, patient-level data are more reliable and robust than calculations based on national averages, given the varied presentation, disease load, response to systemic treatment and outcome in this patient group. This explains the variability in costs for surgery and/or radiotherapy, with a standard deviation equalling 48% of the average cost and an IQR stretching over almost 50% of the median cost. Cost-utility analyses are interesting not just to policy makers, but also to physicians, as justification in terms of cost-effectiveness should marry with clinical decision making and the indication for surgical intervention. When considering surgery for a spinal metastasis, neurological, mechanical, oncological as well as patient-related variables need to be considered; expected survival being one of the most difficult to assess, and while prognostic scores have been developed, [20-23] they offer limited guidance in individual patients. In the current analysis, lower preoperative health status is associated with higher costs. This is not surprising, since these patients will require a higher intensity of care and it has been shown that worse preoperative health status is associated with worse post-operative status and greater number of complications.[24,25] A worse preoperative condition and greater number of complications are particularly associated with higher non-medical staffing and operational costs. A similar observation was made in the cost analysis by Lau et al.,[10] while Turner et al. found higher costs for patients admitted in a better conditions

and explained this by the more extensive surgeries performed in these patients.[9] The latter is reflected in our finding of higher costs associated with slower growing tumors, which is likely to be explained by more aggressive surgeries performed in these patients. It is possible that the development of stereotactic radiosurgery, may lead to less variable, more effective and more cost-effective 'separation surgery' strategies in the future.[6] However, evidence for the long-term effectiveness of such strategies is awaited.

The mean QALY for surgical patients in the current analysis equaled 0.95 (SD 0.96), which is higher than reported QALYs in similar cost-utility studies: 0.64 in the UK study,[12] 0.57 in the Canadian study,[13] and 0.43 in the Japanese study.[14] Patient-level surgical costs were higher in the UK (median cost per surgical patient was £20,752), as well as in Japan (mean cost per surgical patient was US$25,770), compared with the current median and mean cost of €15,462 and €16,989 respectively. While the UK and Canadian study included long term follow up or lifetime horizon costs in the cost-utility analysis, the only direct comparison can be made with the Japanese cost-utility analysis, which also has a Bismarck healthcare system. Given the higher QALYs and lower costs in the present study, the ICER of €13,635 per QALY is significantly lower than the reported ICER of $42,003 per QALY in the Kobe study.[14]

One of the limitations of the present study is the absence of prospectively collected health status data in the radiotherapy-only group. Therefore, their health status was modelled on that of the surgical group, based on the Patchell outcome data.[2] The latter method was also applied by Turner et al. in the UK cost-utility study.[12] However, in addition to the UK study, the non-surgical patients in the present analysis were not a modelled cohort, but real patients with real patient-level costs. Mean QALYs in the non-surgical cohort (0.31 ± 0.42) were much higher than in the Japanese study by Miyazaki et al (0.024 ± 0.028).[14] However, non-surgical as well as surgical patients in the Japanese analysis were in a much worse neurological status and quality of life at presentation than in our study. Secondly, the sample size in the current analysis was rather low. Sample sizes in the UK and Japanese studies were in the same order of magnitude.[12,14] One may wonder whether higher sample sizes would lead to less variation in both costs and QALYs, given the heterogeneity in clinical presentations, primary tumour types and individual outcomes. Thirdly, recent advances in the treatment of spinal metastases, such as stereotactic

radiosurgery, were not included in the present analysis, since they were not available in our center.

In conclusion, our results demonstrate that surgery for symptomatic spinal metastases in a specialist in Belgium is cost-effective. This is the first cost-utility analysis on this patient population in a Bismarck healthcare system in mainland Europe.

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Figure captions

Figure 1. Quality-adjusted life year calculations. QALYs were calculated as the area under the curve. The solid line represents patients treated with surgery, and the dashed lines represents the non-surgical series with sensitivity analyses (dotted lines).

Table 1. Mean costs per patient in Euros in the surgical cohort broken down by inpatient or outpatient stay (n=38).

	Mean cost	Percent
Surgical stay	15,227.43	89.63
Outpatient before	737.47	4.34
Outpatient after	462.00	2.72
Hospital before	76.24	0.45
Hospital after	457.41	2.69
Day visit after	28.80	0.17

Table 2. Costs per patient in Euros in the surgical cohort over all stays and visits, broken down by cost subtype (n=38).

	Mean cost	Percent	Median	IQR
Depreciation	394.08	2.34	390.65	254.81-447.97
Medical staffing	2,621.33	15.57	2,547.94	1,959.06-3,164.57
Non-medical staffing	7,720.88	45.85	5,660.47	4.126.14-11,275.53
Operational costs	2,962.57	17.59	3,049.22	2,259.01-3,676.51
Drugs	1,258.54	7.47	574.24	350.56-1,101.05
Implant cost	1,882.25	11.18	1,927.54	249.56-2,918.50

Table 3. Univariate regression analysis of factors affecting total cost (in Euros) in the surgical cohort (n=38).

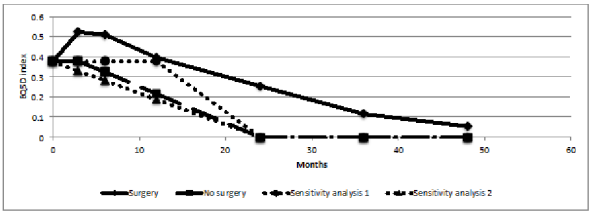
Variable	n (%)	Mean	SE	P-value
Gender				0.79
Female	15 (39.5%)	17,434	2,181	
Male	23 (60.5%)	16,700	1,686	
Age				0.06
<median (64)	19 (50)	14,490	1,582	
>median	19 (50)	19,239	1,993	
Secondary tumour				*0.016
Slow growth	14 (36.8%)	21,146	2,611	
Fast growth	24 (63.2%)	14,564	1,373	
Pain pre-op				0.61
VAS 1-6	19 (50%)	17,949	1,957	
VAS 7-10	18 (47.4%)	16,569	1,856	
missing	1 (2.6%)			
Frankel pre-op				*0.037
E	19 (50)	14,422	1,492	
A-D	19 (50)	19,557	2,023	
Karnofsky pre-op				*0.005
>=70	23 (60.5%)	14,062	1,334	
0-60	15 (39.5%)	21,477	2,523	
EQ5D index pre-op				*0.015

>median (0.33)	19 (50)	14,020	1,465	
<median	19 (50)	20,288	2,235	
ASA				0.56
2	19 (50)	16,212	1,802	
3	19 (50)	17,766	1,975	
Tokuhashi score pre-op				0.347
Good (12-15)	5 (13.2%)	13,722	2,946	
Medium (9-11)	12 (31.6%)	19,502	2,703	
Poor (0-8)	21 (55.3%)	16,332	1,711	
Tomita score pre-op				*0.001
Best (2-3)	9 (23.7%)	18,563	2,582	
Second best (4-5)	3 (7.9%)	15,781	3,802	
Second worst (6-7)	10 (26.3%)	23,396	3,087	
Worst (8-10)	16 (42.1%)	12,327	1,286	
Number of levels with mets				0.44
1-2				
>=3	20 (52.6%)	16,025	1,709	
	18 (47.4%)	18,060	2,030	
Complications during admission				*0.004
No				
Yes	23 (60.5%)	14,135	1,333	
missing	14 (36.8%)	22,113	2,672	
	1 (2.6%)			

Table 4. Multivariate regression analysis for total cost, non-medical staffing and operating cost in Euros in the surgical cohort, controlling for length of stay.

	Mean	SE	p-value
Multivariate analysis for total cost, n=37			
EQ5D index			0.005
> median (0.33)	14,154	1,317	
< median	20,439	1,974	
Secondary tumour			0.02
Slow growth	20,633	2,218	
Fast growth	15,072	1,299	
Complications during admission			0.001
No	14,056	1,183	
Yes	22,433	2,438	
Multivariate analysis for nonmedical staffing, n=36			
Gender			0.043
Female	6,522	881	
Male	9,367	1,146	
EQ5D index pre-op			<0.001
>median (0.33)	5,788	690	
<median	10,317	1,232	
Pain pre-op			0.029
VAS 1-6	9,804	1,296	
VAS 7-10	6,621	833	

Secondary tumour			0.001
Slow growth	11,726	1,814	
Fast growth	6,117	695	
Complications during admission			0.001
No	6,246	695	
Yes	10,786	1,452	
Multivariate analysis for operational costs, n=36			
Gender			0.062
Female	2,653	207	
Male	3,229	215	
Karnofsky pre-op			0.009
>=70	2,660	168	
0-60	3,436	258	
Secondary tumour			0.001
Slow growth	3,674	300	
Fast growth	2,568	160	
Complications during admission			0.017
No	2,709	165	
Yes	3,417	265	



Abbreviations

EQ-5D-3L	EuroQol 5 Dimension 3L measure of health-related quality of life
DRG	Diagnosis Related Groups
GSTSG	Global Spine Tumour Study Group
ICER	Incremental cost-effectiveness ratio
NICE	National Institute for Health and Care Excellence
QALY	Quality Adjusted Life Year