Clinical Neurology and Neurosurgery xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Comparing the cost-effectiveness of two brain metastasis treatment modalities from a payer's perspective: Stereotactic radiosurgery versus surgical resection

Duong Anh Vuong[a,b,*], Dirk Rades[c], Albertus T.C. van Eck[d], Gerhard A. Horstmann[d], Reinhard Busse[a]

[a] Department of Health Care Management, Berlin University of Technology, Berlin, Germany
[b] Medical Service Administration, Ministry of Health of Vietnam, Viet Nam
[c] Department of Radiation Oncology, University Hospital Schleswig-Holstein, Campus Luebeck, Germany
[d] Gamma Knife Centre Krefeld, Germany

ARTICLE INFO

Article history:
Received 10 March 2011
Received in revised form 28 April 2012
Accepted 12 May 2012
Available online xxx

Keywords:
Brain tumors
Economics
Stereotactic radiosurgery
Surgical resection

ABSTRACT

Objectives: This study aims to identify the cost-effectiveness of two brain metastatic treatment modalities, stereotactic radiosurgery (SRS) versus surgical resection (SR), from the perspective of Germany's Statutory Health Insurance (SHI) System.

Methods: Retrospectively reviewing 373 patients with brain metastases (BMs) who underwent SR ($n = 113$) and SRS ($n = 260$). Propensity score matching was used to adjust for selection bias ($n = 98$ each); means of survival time and survival curves were defined by the Kaplan–Meier estimator; and medical costs of follow-up treatment were calculated by the Direct (Lin) method. The bootstrap resampling technique was used to assess the impact of uncertainty.

Results: Survival time means of SR and SRS were 13.0, 18.4 months, respectively ($P = 0.000$). Medians of free brain tumor time were 10.4 months for SR and 13.8 months for SRS ($P = 0.003$). Number of repeated SRS treatments significantly influenced the survival time of SRS ($R^2 = 0.249$; $P = 0.006$). SRS had a lower average cost per patient (€9964 – SD: 1047; Skewness: 7273) than SR (€11647 – SD: 1594; Skewness: 0.465), leading to an incremental cost effectiveness ratio of €–3740 per life year saved (LYS), meaning that using SRS costs €1683 less than SR per targeted patient, but increases LYS by 0.45 years.

Conclusion: SRS is more cost-effective than SR in the treatment of brain metastasis (BM) from the SHI perspective. When the clinical conditions allow it, early intervention with SRS in new BM cases and frequent SRS repetition in new BM recurrent cases should be advised.

1. Introduction

There are approximately 427,000 new cancer cases occurring annually in Germany. Men are affected 1.16 times more frequently than women. Compared to 1980, this number has increased by 35% for women and 80% for men. Age-standardized incidence rates have gone up by 15% and 23% respectively. The relative five year cancer survival rates have improved considerably from approximately 50% to 60% for women and from 40% to 55% for men [1]. With early diagnosis and more effective treatment prolonging survival, an increase in the occurrence of brain metastasis (BM) has been observed. 10–15% of patients suffer from BMs at first diagnosis of cancer [2] and during the course of the disease BMs appear in 20–40% of the patients [3–6]. In Germany, this means 43,000–64,000 new patients developing BMs per year and a total of 300,000–550,000 patients with BMs. Besides the impact on the individual cases these figures show that BM is a serious and growing clinical and socioeconomic problem.

The health care system of Germany is characterized by a predominance of Statutory Health Insurance (SHI). Around 85% of the population is covered by SHI that pays for the vast majority of cancer therapeutic costs [7,8]. As in most European countries, in Germany cost efficiency and reimbursement are more and more formalized in health technology assessments (HTA) and are of great importance in the decision making process about which costly therapies are worth paying for [8]. Recent studies on cost-effectiveness assessment (CEA) and the treatment of BM show higher cost-effectiveness for SRS than for SR [9–12]. Despite of this outcome most HTA recommend more overall studies on CEA concerning therapies and combinations of therapies especially for the German health care system [13]. The scope of this study is the CEA of two treatment modalities which are SR and SRS from the perspective of Germany's SHI system.

* Corresponding author at: Department of Health Care Management, Berlin University of Technology, Berlin, Germany. Tel.: +49 15140323892.
E-mail addresses: vuong@mailbox.tu-berlin.de, vuonganhduong_byt@yahoo.com.vn (D.A. Vuong).

0303-8467/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.clineuro.2012.05.005

2. Materials and methods

2.1. Patient profile

All patients with single or multiple BM who received an initial SR or patients who had an initial SRS with the diameter of the largest tumor smaller than 3 cm, the number of tumors less than 10 on a magnetic resonance imaging (MRI) scan, but the total volume of the brain which was exposed to more than 10 Gy less than 100 cm^3, were considered for this study. In the SR group, we excluded previous SRS, and leptomeningeal metastasis (LMM); prior SR and LMM were excluded in SRS group. Follow-up had to be limited to 5.5 years for both groups due to limitations in the SR database. Patients in both of the two arms with less than 6 months of follow-up were also excluded unless a specific event like death occurred.

All patient data were retrieved from retrospective and prospective patient databases created between 1999 and 2009. For SRS we used data from the Gamma Knife Centre Krefeld metastatic database. This centre is located in Nordrhein-Westfalen state and is specialized in gamma knife radiosurgery. It provides services for local and regional patients as well as patients from the rest of Germany. Data for the SR group were from the Radiation Oncology Department of a Hospital located in Schleswig-Holstein state. Eventually 373 patients met all of the above-mentioned criteria and remained for propensity score matching (PSM), 260 patients in the SRS arm and 113 in the SR group. All patients were followed at regular intervals which involved contrast enhanced MRI and neurological examination data on additional treatment associated with local or distant recurrence within the brain was available and is shown in Fig. 1 [14].

SR was performed in general anaesthesia. Patients were treated with 24 mg dexamethasone at least 10 days postoperatively. The use of anticonvulsive medication depended on clinical circumstances. A state-of-the-art tumor resection was performed with microsurgical techniques, and neuro-navigation was only used if indicated. Postoperative whole-brain radiotherapy (WBRT) was applied in all SR patients as soon as possible after healing of the skin incision. There were three possible fractionation schemes applied: 5×4 Gy, 10×3 Gy or 20×2 Gy. Radiation was applied using a two field technique or 3D computer plan.

SRS was performed as an outpatient procedure. The Leksell stereotactic frame was applied with local anaesthesia. MRI scans were performed in a dedicated MRI scanner which was submitted to a rigid quality assurance regime to guarantee a spatial accuracy within a margin of 0.4 and 0.6 mm for the entire diagnostic, planning and treatment chain. Dose plans were calculated on the Leksell gamma plan. The radiosurgical procedure was performed with a C type Gamma knife with APS which was later upgraded to a 4C type. Conformal dose plans were created using 4, 8, 14 and 18 mm collimators. The mean marginal dose was 21.4 Gy (Standev. 2.38). The mean isodose was 50.3% (Standev. 4.62). Dexamethasone and anticonvulsive medication was applied in an identical fashion as for the SR group.

2.2. Statistical analysis

2.2.1. Treatment cost calculations

From the SHI perspective, the costs were calculated for the utilization of direct health sector costs only [15], which were measured in the current study for medical costs of initial intervention (SRS or SR) and retreatment cost of more potentially life-saving procedures such as SRS, SR, LINAC, WBRT until death or during 5.5 years of follow-up. We excluded the cost of follow-up visits and the adjunct treatment of the chemotherapy, rehabilitation and other pain relief therapies as we considered those to be equal between the two treatment arms [3]. There was no co-payment by the patients. The treatment costs of SR were calculated based on the year 2009 rates of the Diagnosis Related Group (DRG) system for inpatient services, the weighting of each single case in SR arm was based on our available information of International Classification of Diseases (ICD), Standard of Operation and Procedure (OPS – Operationen und Prozedurenschlüssel), sex, age, and length of stay (LOS) [16]. It was previously determined for an average of 15.4 days [12]. The DRG rate in Germany does not include equipment and infrastructure investments, which are generally paid for by local authorities. However, it is considered a standard price or fee, as it represents the actual cost of care for a large proportion of the population [17]. The price of other procedures such as LINAC, local radiation therapy (LRT), WBRT, SRS was based on the outpatient tariff in the year 2009 provided by the actual figures of the two centers where our patient samples treated. Finally, the price of each procedure included in our current study is 4700 EUR for SRS; 9419 EUR for SR; LRT and WBRT: 718 EUR for 5×4 Gy; 927 EUR for 10×3 Gy; 1344 EUR for 20×2 Gy; and 552 EUR for any single fraction LINAC.

No discounted rate was implemented due to the fact that the life expectancy of BM is usually short, around 12 months, and due to the cost of resource utilization based on the same year tariff (2009) [18]. Censored cases were those in which the retreatment cost was not fully observed before event (i.e. death) occurred. Because the censored cost is a common issue in estimating the average lifetime cost, in our sample population, patient was obviously by chance lost follow-up, it is reasonable to assume that censored cases are independent of all other random variables [19,20].

We applied the Direct (Lin) method with the non-history cost using approach, rather only using the observed total cost at the last follow-up date to estimate the medical cost of our incomplete follow-up sample population [21]. Following this method, the mean total cost (E_T or E_S) of the whole sample size in each arm (T stands for SRS and S stands for SR) was estimated by the sum of the deduction of the Kaplan–Meier estimator for the probability of being alive at the start of each interval S_k and S_{k+1}, which was partitioned by the entire time period of interest into small intervals (k), multiplied by the average total cost A_k of those who died at the start of such relevant interval, which is described below in greater detail:

$$\hat{E}_T = \sum_{k=1}^{k+1} \hat{A}_k(\hat{S}_k - \hat{S}_{k+1})$$

$$\hat{A}_k = \frac{\sum_{i=1}^{n} Y_{ki} \cdot C_i}{\sum_{i=1}^{n} Y_{ki}}$$

where, $Y_{ki} = 1$ for patient i being observed to die and $Y_{ki} = 0$ for patient i being censored in the k interval, C_i is the total cost of each patient, since our main concern is to compare the effect of two treatments on the patient-related variables of total medical cost. For simplicity we did not include the coefficients of monthly dummy variables, so it was calculated by the sum of the price of each resource used multiplied with the quantity of resource used for patient i [22]. S_k is S step function that decreases at those times of death occurred that was estimated using the product-limit method of the Kaplan–Meier estimator:

$$\hat{S}_k = \prod_{j:tj<a_k} \frac{n_j - d_j}{n_j}$$

where d_j is the number of deaths occurring at those times; n_j is the number of patients at risk of death at those times.

The estimator of the difference between the two arms in the mean cost is given by

$$\Delta_c = E_T - E_S$$

Please cite this article in press as: Vuong DA, et al. Comparing the cost-effectiveness of two brain metastasis treatment modalities from a payer's perspective: Stereotactic radiosurgery versus surgical resection. Clin Neurol Neurosurg (2012), http://dx.doi.org/10.1016/j.clineuro.2012.05.005

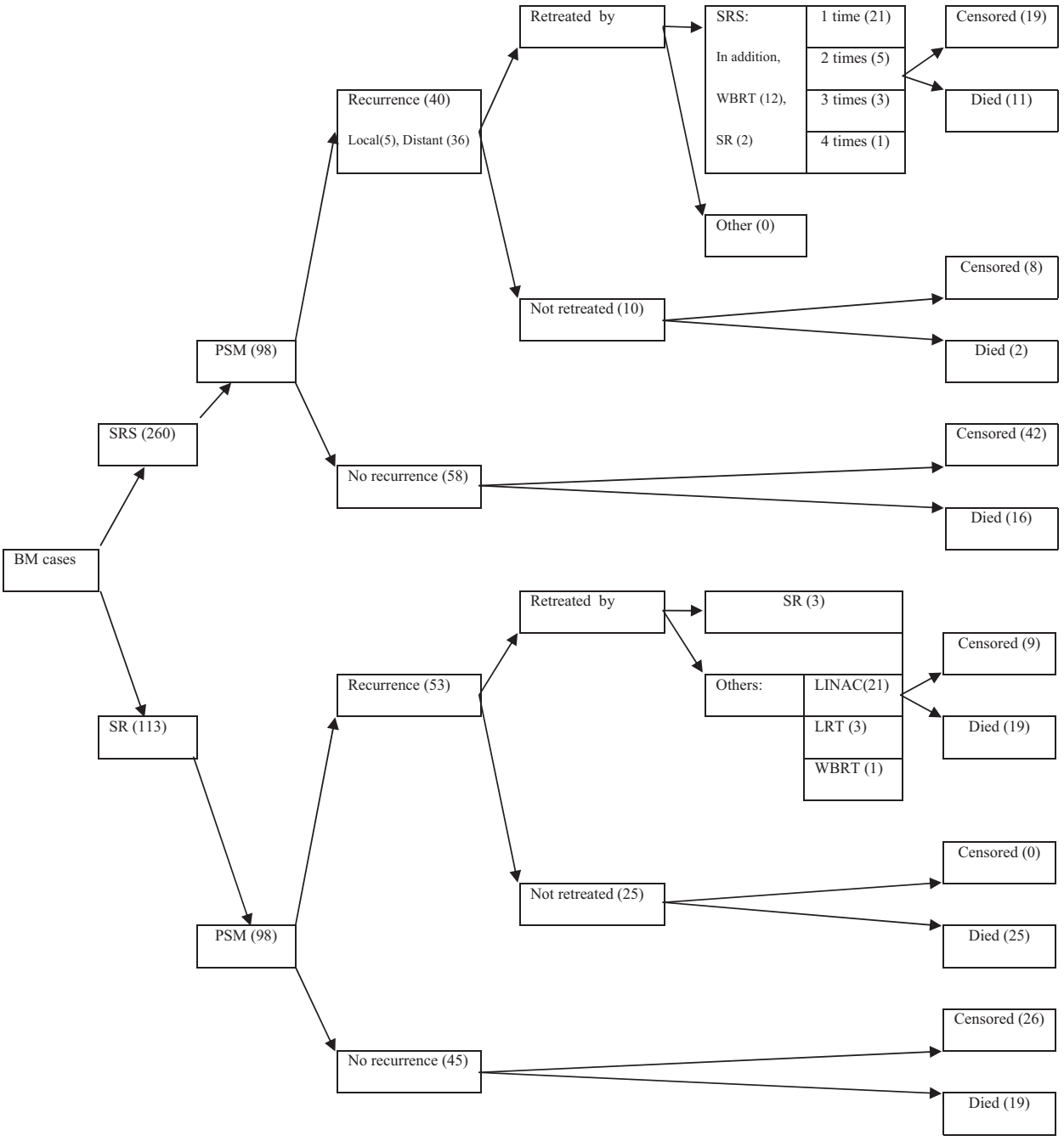

Fig. 1. Algorithm indicating the flows of patient under SRS, SR and other retreatment regimens (number in parentheses represent number of patients).

An algorithm indicating the flows of patients treated with SRS or SR and other repeated interventions for brain tumor recurrence that were constructed for the estimation of the total medical cost (Fig. 1).

2.2.2. *Propensity score matching*

In this current retrospective observational study of two heterogenic populations, maybe there was no random assignment of patients to the treatment arms, and hence the validity of the results compromised by selection bias and confounding factors. To minimize this problem we applied the statistical method of PSM, to balance the prognostic factors between two treatment arms [23–25].

In order to find the prognostic factors used for PSM, survival time of the entire cohort was measured from the time of the initial intervention, either with SRS or SR. Uncensored cases were those who reached the endpoint of interest (i.e. death). Those who had no additional follow-up data available were censored on the last seen date. Survival curves were constructed by the Kaplan–Meier estimator, the mean survival time was estimated as the area under the survival curve [26]. The difference between the Kaplan–Meier curves of the two arms were determined with the Log-rank test (univariate analysis) and Cox proportional hazard model (multivariate analysis), the prognostic factors were found to be significant with $P < 0.05$ [27]. Then, the propensity score was calculated by a multivariable logistic regression model with those covariates of treatment methodologies, number of brain tumors, extra-cranial metastases which have been found significant in the

Please cite this article in press as: Vuong DA, et al. Comparing the cost-effectiveness of two brain metastasis treatment modalities from a payer's perspective: Stereotactic radiosurgery versus surgical resection. Clin Neurol Neurosurg (2012), http://dx.doi.org/10.1016/j.clineuro.2012.05.005

Table 1
Median survival time, univariate and multivariate analysis (unadjusted samples).

Patient characteristics	Survival function at 12 months (%)	Median survival time (month)	Univariate analysis	Multivariate analysis	
			Log-rank test ($P > \text{Chi}^2$)	Cox prop. hazard model	
				HR/P	CI 95%
Treat			<0.001*	0.25/<0.001*	0.17–0.37
SRS	81.7	14.0			
SR	55.1	10.2			
Gender			0.05	1.19/0.38	0.79–1.79
Female	77.6	13.7			
Male	68.2	11.3			
Age groups			0.12	1.41/0.07	0.96–2.07
≤60 years	79.0	13.9			
>60 years	66.6	11.4			
Primary tumor sites			0.53	1.13/0.36	0.86–1.49
Breast	73.0	14.0			
Lung	76.5	12.9			
Others	70.1	11.3			
Number of BMs			0.21	1.78/<0.001*	1.20–2.63
1 BM	73.9	12.9			
≥2 BMs	74.1	12.7			
Extra-cranial metastasis (prior)			0.38	1.68/0.04*	1.01–2.80
No active	75.8	13.6			
Active	70.3	12.1			
KPS			0.87	0.76/0.60	0.28–2.08
<70	60.3	12.4			
≥70	74.2	12.6			
RPA			0.97	0.88/0.67	0.50–1.55
Class 1	76.7	14.3			
Class 2	73.1	12.0			
Class 3	63.7	13.1			

* Statistically significant.

multivariate Cox proportional hazard model of unadjusted sample to be the prognostic factors for the survival time of brain metastatic patients (Table 1); and covariates of gender, age groups, primary tumor sites, Karnofsky performance status (KPS), recursive partitioning analysis (RPA) were previously defined from the literature and available in our database [3,27–30]. The regression model calculates for each patient a propensity score (0–1). A ratio of 1:1 optimal matching without replacement was applied to randomly match each SR patient to SRS patients with the most similar propensity score. The balances of the prognostic factors in the two arms of both unadjusted and adjusted samples are measured by using the standardized difference (SD) [31].

$$\text{Standardized difference} = \frac{100(X_{\text{srs}} - X_{\text{sr}})}{2(S^2_{\text{srs}} + S^2_{\text{sr}})^{1/2}}$$

where X_{srs} and X_{sr} are the means of ith covariate of SRS and SR group, respectively; S^2_{srs} and S^2_{sr} are the corresponding sample variances. Small (<10%) absolute values of SD support the assumption of balance between treatment groups [32].

For the matched sample (adjusted sample), the mean survival time was used as the best estimate of the principal outcome (survival time) for CEA [33]. The survival time means and curves were constructed by the Kaplan–Meier estimator, for which it was determined whether survival improvement was attributable to the effect of treatment modalities of SRS versus SR by the univariate Cox

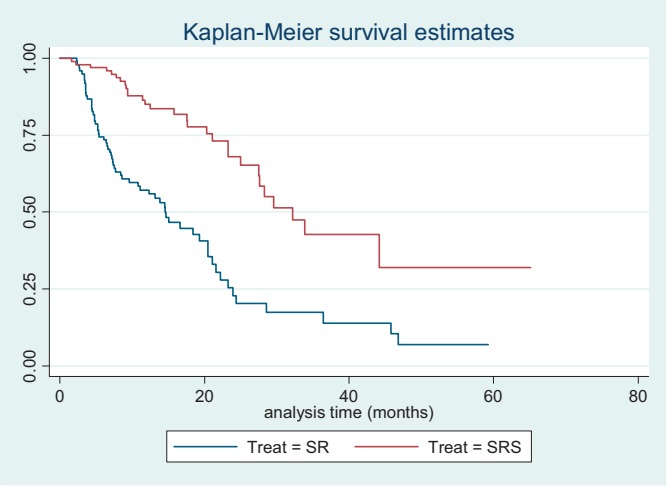

Fig. 2. Survival curves of two treatment groups (adjusted samples) – months post interventions.

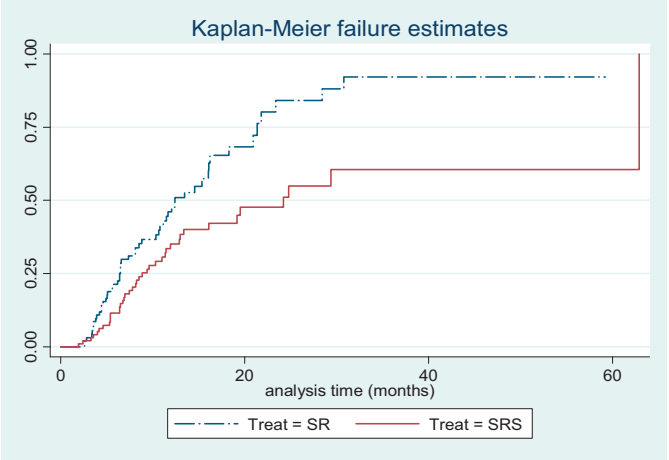

Fig. 3. Free BM interval curves of two treatment groups (adjusted samples).

Table 2
Patient characteristics of the two arms before and after PSM and the overall logistic and proportional hazards model evaluating the association of treatments and survival in adjusted samples.

Patient characteristics	Before PSM (unadjusted sample)			After PSM (adjusted sample)			Multi-analysis proportional hazards model survival (95% CI – adjusted sample)		
	SRS	SR	SD	SRS	SR	SD	HR	SE	*P*-value
Treat (*n*)	260 (100)	113 (100)		98 (100)	98 (100)		0.27	0.06	<0.001
Gender (*n*)							1.18	0.29	0.49
Female (%)	153 (58.9)	59 (66.7)	9.54	54 (55.1)	48 (49.0)	8.7			
Age groups (*n*)							0.67	1.45	0.85
<60 years (%)	156 (60.0)	52 (58.8)	20.24	54 (55.1)	58 (59.2)	−5.9			
Primary tumor sites (*n*)							1.26	0.33	0.38
Breast (%)	68 (26.2)	28 (31.6)	2.56	23 (23.5)	19 (19.4)	8.57			
Lung (%)	108 (41.5)	52 (58.8)	−6.45	47 (48.0)	54 (55.1)	−10.16			
Others (%)	84 (32.3)	33 (37.3)	5.16	28 (28.6)	25 (25.5)	5.49			
Number of brain tumors (*n*)							4.61	12.65	0.57
<2 tumors	136 (52.3)	92 (104.0)	−49.89	79 (80.6)	80 (81.6)	−2.36			
Extra-cranial metastasis (prior) (*n*)							2.03	0.84	0.08
No active (%)	77 (29.6)	69 (78.0)	−49.72	56 (57.1)	57 (58.2)	−1.48			
KPS (*n*)							2.48	10.03	0.82
<70	16 (6.2)	6 (6.8)	5.49	6 (6.1)	6 (6.1)	0.00			
RPA (*n*)							2.05	5.84	0.79
Class 1	44 (16.9)	48 (54.2)	−45.32	35 (35.7)	31 (31.6)	6.47			
Class 2	162 (62.3)	59 (66.7)	14.73	57 (58.2)	61 (62.2)	−6.03			
Class 3	15 (5.8)	6 (6.8)	3.10	6 (6.1)	6 (6.1)	0.00			
Propensity score							70.71	823.58	0.71

Note: ROC curve c-statistic = 0.731; SE, stands for standard error; HR, stands for hazard ratio.

proportional hazard regression model. Multivariate Cox proportional hazard regression of prognostic factors and propensity score was used to test the association between prognostic factors and the survival time of the treatments on patients. The capacity of the final multivariate analysis model to predict the treatment effect on the patient was evaluated by Harrell's C statistic, which is the area under the receiver operating characteristic (ROC) curve, claiming to be a measure of predictive power [34]. This model yielded a C-statistic of 0.73 that indicated a rather good ability to predict higher probabilities for patients who lived for a shorter survival period than a longer survival one. The highest predictable capability was given by the factor of the number of brain tumors (1 versus >1 tumors) (Table 2). The linear regression was used to test the survival time of SRS patients (of those who died) on the number of repeated SRS treatments.

All reported *P* values were 2-sided and detected a significant difference with a level of 0.05 or less.

Statistical analyses were performed with SAS version 9.3.1 and STATA 10 software.

2.2.3. Sensitivity activity

Although prognostic factors between two treatment arms was well balanced by PSM, as both costs and effects were determined from data that sampled from the same patients in the study, a potential selection bias due to imbalances in unmeasured covariates might be possible. In addition, cost-effectiveness of the treatments would be highly sensitive to the number of deaths and the cost of these. It would be important to analyze the sensitivity of results. We applied in the current study a formal sensitivity analysis, by using the bootstrap resampling technique to assess the impact of uncertainty on the estimated incremental cost-effectiveness ratio (ICER). A resample from the observed data of both arms was used to build an empirical estimate of the sampling distribution of ICER [35].

3. Results

For the entire cohort, the median survival time was 10.2 months in the SR group compared to 14.0 months in the SRS group. The Log-rank test determined statistically significant differences between the two survival distribution curves (Table 1, $P = 0.000$). Improved survival probability of the entire cohort was identified by multivariate analysis of the Cox proportional regression with respect to potential predictors of survival, which found the statistically significant associations with the covariates of the treatment methodologies (SRS versus SR), number of BMs (1 versus >1), extra-cranial metastasis (non active versus active) (Table 1).

PSM identified a total of 196 patients (98 patients on each arm). The baseline characteristics of the adjusted samples are summarized in Table 2. The SD of each prognostic factor confirmed no difference between the two arms, except for the primary tumor site of lung cancer (SD-10.16) (Table 2). The medians of follow-up were 13.8 months in the SRS arm and 13.6 months in the SR arm. The follow-up treatment was SRS in 31 patients, WBRT in 12 patients, SR in 2 patients of the SRS arm; and WBRT, LINAC, SR, LRT, and WBRT in 98, 21, 3, 3, and 1 patients in the SR arm, respectively (Fig. 1).

At last follow-up, 30% of SRS patients and 64% of SR patients in the adjusted sample had died. The Kaplan–Meier curves demonstrated differences between the two curves (Fig. 2). The differences between survival time means of the two treatment arms (18.4 months in the SRS arm compared to 13.0 months in the SR arm) determined by the Cox proportional hazard regression model that were statistically significant ($P = 0.000$; Table 3), which indicated the treatment modalities of SRS versus SR significantly influenced the survival times of BM patients.

The brain metastatic recurrence (combination of local and distant recurrence) in the adjusted samples at last follow-up occurred in 40.8% (5 out of 40 patients with tumor recurrence had local

Please cite this article in press as: Vuong DA, et al. Comparing the cost-effectiveness of two brain metastasis treatment modalities from a payer's perspective: Stereotactic radiosurgery versus surgical resection. Clin Neurol Neurosurg (2012), http://dx.doi.org/10.1016/j.clineuro.2012.05.005

Table 3
Univariate analysis of treatment effect on the survival function (adjusted samples).

		Survival time (month)					
		Mean	12 months	18 months	HR	95% CI	*P*-value
Treatment	SR	13.0	57.1	44.7	0.30	0.19–0.48	<0.001
	SRS	18.4	85.0	77.6			

Table 4
Univariate analysis of treatment effect on the failure function of free tumor control (adjusted samples).

		Free tumor interval time (month)		Cox proportional hazard model		
		Mean	Median	HR	95% CI	*P*-value
Treatment	SR	10.4	8.1 (2.3–59.2)	0.53	0.34–0.80	0.003
	SRS	13.8	10.8 (1.5–62.9)			

Table 5
Mean interval of SRS patients' retreatment regarding to the brain tumor recurrence (months).

Time of SRS patient's retreatment (months)	*N*	Mean	Range
1st SRS to 2nd SRS	30	13.3	1.9–62.9
2nd SRS to 3rd SRS	8	13.5	4.0–28.4
3rd SRS to 4th SRS	3	11.2	4.1–22.5
4th SRS to 5th SRS	1	3.6	

recurrence) of the SRS patients and 54.1% of the SR patients (53 patients). Using Kaplan–Meier failure function analysis for tumor control of BMs (Fig. 3), the difference of the mean tumor control interval time between the two treatment arms (10.4 months in the SR arm versus 13.8 months in the SRS arm) tested by the Cox proportional hazard regression model, to determine that the treatment of SRS versus SR had a significant influence on the failure function of tumor control for BMs ($P = 0.003$; Table 4). It was relevant to the interval time of retreatment. Thirty three out of 40 patients with tumor recurrence in the SRS arm underwent repeated SRS. The mean interval between the initial and the subsequent treatments of SRS were 13.3, 13.5, and 11.2 between the first and second; second and third; third and fourth treatments (Table 5). The number of repeated SRS treatments significantly influenced the survival time of SRS patient ($R^2 = 0.249$; $P = 0.006$). In the SR arm, 28 out of 53 patients with tumor recurrence underwent repeated treatment by different interventions such as SR, LINAC, LRT, and WBRT (Fig. 1).

The distribution of patient cost was positively skewed, with some patients having much higher costs than the majority (Figs. 4 and 5). SRS had a lower average cost per patient (€9964 – SD: 1047; Skewness: 7273) than those of SR (€11647 – SD: 1594; Skewness: 0.465); and was also significantly more effective in terms of LYS than SR (1.53 LYS versus 1.08 LYS). Adjusting to the ICER expressed in Euro per LYS that is minus €−3740/LYS. Which is derived from the negative of different cost (Δc) and positive of different effect (Δe), the treatment arm of SRS is dominant to the standard arm of SR (Table 6). In practice, this means that using SRS costs the equivalent of €1683 less than the cost of SR per targeted patient, and could lead to a mean increase in targeted patient life expectancy of 0.45 year.

Result of sensitivity analysis Fig. 6 shows 9000 bootstrap replicates of ICER and the scattering of points on the cost-effectiveness plane is based on the results of a nonparametric bootstrap analysis.

Table 6
Incremental cost-effectiveness ratio (in Euros/LYS) of SRS in relation to SR.

Treatment	Mean costs per case (in Euros)	Effect (LYS)	ICER
Treatment arm (SRS)	9.964	1.53	
Standard arm (SR)	11.647	1.08	
Difference	−1.683	+0.45	−3740

Within a 95% CI of the bootstrap replications, the cost difference of SRS compared to SR ranged from $−10356 to $−8848; the prolonged life years were between −31.8 months and 41.7 months for SRS compared to SR. In terms of the proportions of the ICER estimates falling in each of the four quadrants, 66% of the points in concentrated in SW + NW quadrants of the plane to indicate that SRS is more effective; the 92% of the points distributed in SE + SW to show the SRS is lower cost. The 59% of the points are in SW quadrant to indicate that SRS has a lower cost and higher effect, compared to 2% of the points distributed in NE which expresses SRS having a higher cost and lower effect. The hypothesis of higher cost-effectiveness of SRS versus SR is definitely confirmed, meaning that the T arm (SRS) dominates the *S* arm (SR) or that SRS is more effective and less costly than SR.

4. Discussion

This study uses costs and clinical trial data from Germany to compare the cost-effectiveness of SRS and SR for the treatment of BMs, from the perspective of Germany's SHI System. The mean of medical costs from initial intervention to event occurrence (i.e. death or censored) was taken into account for the outcome effect determined for each of the two treatment arms. The outcome effect was measured as the LYS after the initial treatment (SRS in the SRS arm and SR in the SR arm) until event occurred (i.e. death). The two treatment arms were well-balanced in terms of prognostic factors, with the majority of matched samples cases of single BM (81%) and KPS of ≥70 (94%) (Table 2). The results have definitely confirmed that the SRS treatment was more cost-effective, associated with less costs and higher effect (LYS) compared to the SR treatment option. These results favorably compared to those previously reported. Rutigliano et al. conducted a meta-analysis from some studies in US, UK, Netherlands and found that SRS had better ICER than SR ($40,648 versus $52,384 per life year) [11]; Mehta et al. also confirmed in another meta-analysis that SRS appeared to be the more cost-effective procedure (an average cost per one life week saved of $524 for SR + RT versus $270 for SRS + RT) [9]; Sperduto and Hall found the marginal cost of SR plus WBRT versus SRS plus WBRT ranged from $10,609 to $15,236 and SRS was more cost-effective than SR [36].

What could contribute to this higher cost-effectiveness of SRS versus SR? The effect of SR was found here to be relatively similar to the previous studies. Although SR plus WBRT typically resulted in 6–10 months survival gained [37–40], there were some reports with longer survival after SR and WBRT. In a retrospective analysis of 231 patients Wronski et al. found the overall median survival time for the entire cohort was 11 months from the time of initial craniotomy (a mean of 21 months). However, 47 out of 231 patients had more than one resection (maximum 5 times) [41].

Please cite this article in press as: Vuong DA, et al. Comparing the cost-effectiveness of two brain metastasis treatment modalities from a payer's perspective: Stereotactic radiosurgery versus surgical resection. Clin Neurol Neurosurg (2012), http://dx.doi.org/10.1016/j.clineuro.2012.05.005

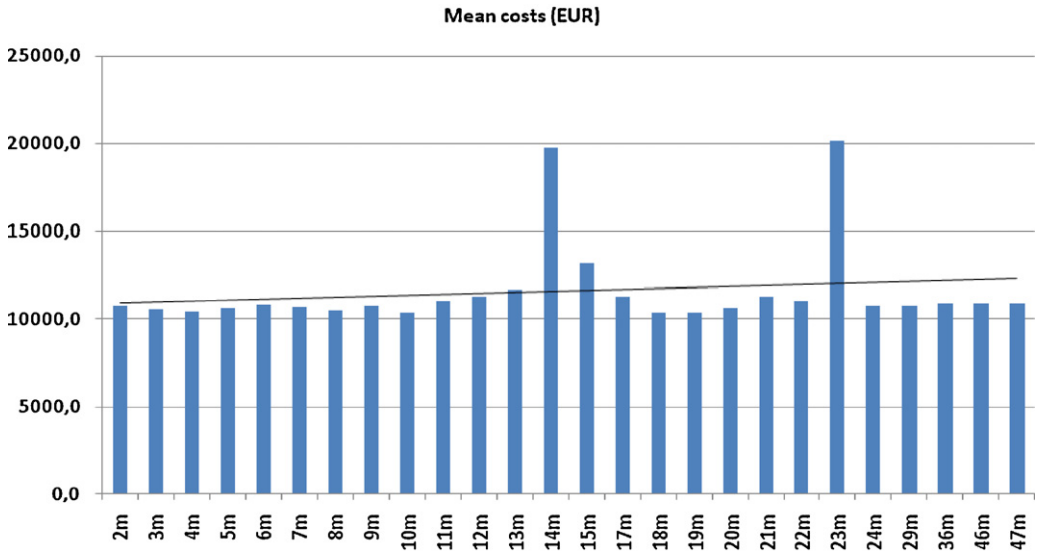

Fig. 4. Medical cost associated to relevant interval of survival functions in SR arm according to Kaplan–Meier estimator (in *x*-axis, m stands for month).

Schackert [42], Penar and Wilson [43] even found the median survival time average was up to 16 months, or 26 months depending on the different subgroups of the primary tumor site. In the SRS arm, LYS was also not discordant to previous findings, which frequently reported 8–12 months for the median survival time after the first SRS [31,44–48]. However, some cohort studies had resulted in longer survival times than our current study. Pan et al. studied a cohort of 191 patients who underwent treatment for 424 BMs and found that the median survival was 15 months after GKS alone and 14 months after a combination of SRS plus WBRT [49]; and in a subgroup of patients with no extracranial metastases, no neurologic deficits and a small tumor without necrosis Kim et al. found a median survival time of up to 26 months [50], and some patients were even found to survive up to 90.8 months after initial SRS [45]. To our knowledge, the statistical significant difference in the effect of treatments found in this study was not confirmed in previously published studies concerning the comparison between SRS and SR with WBRT [51,52].

This significant difference is plausibly attributable to the lower tumor recurrence rate in the SRS arm versus the SR arm [5,53], as our study found that the interval free from intracranial metastatic relapse after SRS as opposed to SR was significantly different ($P = 0.003$). Recurrence rates of BMs are associated with survival period, taking advantage of the less potentially radio toxicity of SRS, this regiment can be repeated to treat the intracranial tumor recurrence months to years after the initial treatment [54,55]. In a randomized controlled trial study of Kim et al., 48% of the patients had repeated SRS, and one patient had undergone 7 procedures over a survival period of 10 years [50]. Our study supports the claim that frequent repetition of the SRS treatment when new BMs appeared resulted in longer patient survival times compared to SR treatment. That was proved by the positive linear regression between survival time and number of SRS retreatment.

The strength of our study is that the result is derived from a large database which allows us to restrict appropriate criteria such as the minimum follow-up period; and that the SRS or SR procedure was the initial intervention in the SRS or the SR arm, respectively. The database had sufficient information associated to vital prognostic factors for the final outcome of survival time such as KPS, RPA, primary tumor site, extracranial metastases, number of BMs, gender, ages, which resulted in a good predictive model (C-statistic 0.73). The application of PSM was well-balanced in the sufficient covariates between the two samples.

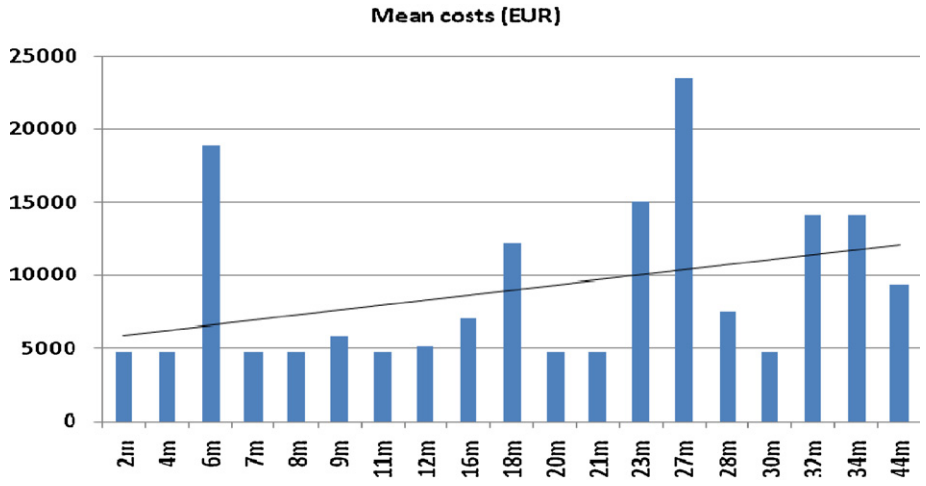

Fig. 5. Medical cost associated to relevant interval of survival functions in SRS arm according to Kaplan–Meier estimator (in *x*-axis, m stands for month).

Please cite this article in press as: Vuong DA, et al. Comparing the cost-effectiveness of two brain metastasis treatment modalities from a payer's perspective: Stereotactic radiosurgery versus surgical resection. Clin Neurol Neurosurg (2012), http://dx.doi.org/10.1016/j.clineuro.2012.05.005

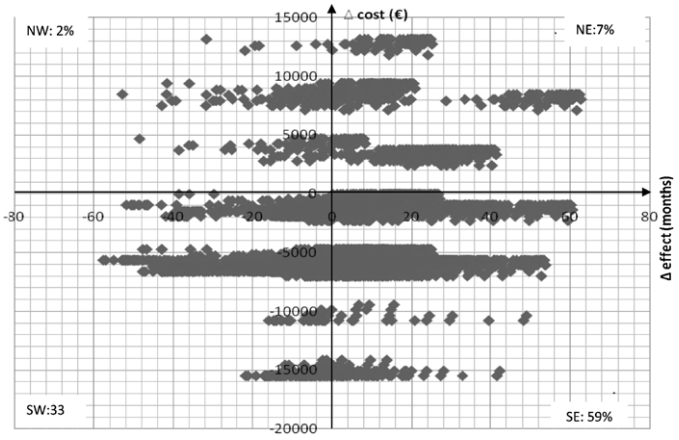

Fig. 6. ICER results of CI 95% bootstrap replications of SRS versus SR in the cost-effectiveness plane (adjusted samples) (NW, NE, SE, SW stand for North West, North East, South East, and South West quadrant, respectively).

The higher censored rate in the SRS arm of 70%, compared to 35% in the SR arm, may influence the prediction capacity of the model [56]. This can be explained by the patients' location. The SRS patients were not only those living in Nordrhein-Westfalen, they were more scattered throughout all states of Germany and some were even from surrounding countries. SR patients were more concentrated in the area of Schleswig-Holstein. However, the higher censored rate in the current study could not influence the result due to the facts that, first, the follow-up time in the two arms were well-balanced (13.8 months for SRS versus 13.6 months for SR), the total time at risk was even higher for SRS than for SR (1811 months and 1211 months, respectively), and 17 patients were still alive at last contact near the end of the period of study. Second, Kaplan–Meier assumed that all censored survival times occur immediately after their censored times, which perhaps means that the survival times predicted are underestimated compared to the actual times, but only at the component level, not necessarily at the system level [57,58]. The incremental effectiveness rate between SRS and SR is actually confirmed to be even higher, so it cannot influence the significant difference between the effects on the two treatment groups. One possibility in the direct (Lin) method biases the assumption that was the withdrawn of the patient from the study, which was due to health or cost reasons [21]. However, this would not be really a problem in Germany with SHI-insured patients who are covered for the payment of health interventions, and patients could receive radiosurgery it was indicated.

In addition, PSM also had certain limitations, as matching was done following exposure, so the two treatment arms the adjusted samples did not form two independent samples, it still suffered from certain limitations of such a retrospective study; some prognostic factors' absences in the PSM such as causes of deaths; exact positions of brain tumor recurrence. However, it had been recognized as having more advantages in both theory and practice compared to other methods such as adjustments based on case mix or severity of illness alone. It made sure the matched nature of the samples was accounted for in the statistical analysis to estimate the precision or significance of the estimated treatment effect [24,25].

5. Conclusion

SRS is a more cost-effective treatment modality than SR in the treatment of BM from the point of view of health insurance. When the clinical condition allows it, early intervention with SRS treatment in new cases of BM and frequently repeated SRS treatment in new cases of recurrent BM should be advised in order to prolong survival time.

Conflict of interest

None.

Acknowledgements

The authors would like to acknowledge the scholarship provided by the MOET of Vietnam and DAAD; grateful to Michael Bäumler (Berlin University of Technology), and three anonymous reviewers for valuable comments on an earlier draft of this paper. Any remaining errors are the responsibility of the authors.

References

[1] Cancer in Germany 2003–2004. Incidence and Trends. 6th ed. Berlin: Robert Koch Institute/Association of Population-Based Cancer Registries in Germany; 2008.
[2] Petrovich Z, Yu C, Giannotta SL, O'Day S, Apuzzo MLJ. Survival and pattern of failure in brain metastasis treated with stereotactic gamma knife radiosurgery. Journal of Neurosurgery 2002;12(Suppl. 5):499–506.
[3] Eichler AF, Loeffler JS. Multidisciplinary management of brain metastases. The Oncologist 2007;12(7):884–98.
[4] Kondziolka D, Martin JJ, Flickinger JC, Friedland DM, Brufsky AM, Baar J, et al. Long-term survivors after gamma knife radiosurgery for brain metastases. Cancer 2005;104(12):2784–91.
[5] O'Neill BP, Iturria NJ, Link MJ, Pollock BE, Ballman KV, O'Fallon JR. A comparison of surgical resection and stereotactic radiosurgery in the treatment of solitary brain metastases. International Journal of Radiation Oncology, Biology, Physics 2003;55(5):1169–76.
[6] Arnold SM, Patchell RA. Diagnosis and management of brain metastases. Hematology/Oncology Clinics of North America 2001;15(6):1085–107, vii.
[7] Busse R, Riesberg A. Health care systems in transition: Germany. Copenhagen: WHO Regional Office for Europe on Behalf of the European Observatory on Health System and Policies; 2004.
[8] Drummond MF, Mason AR. European perspective on the costs and cost-effectiveness of cancer therapies. Journal of Clinical Oncology 2007;25(2):191–5.
[9] Mehta M, Noyes W, Craig B, Lamond J, Auchter R, French M, et al. A cost-effectiveness and cost-utility analysis of radiosurgery vs. resection for single-brain metastases. International Journal of Radiation Oncology, Biology, Physics 1997;39(2):445–54.
[10] Cho DY, Tsao M, Lee WY, Chang CS. Socioeconomic costs of open surgery and gamma knife radiosurgery for benign cranial base tumors. Neurosurgery 2006;58(5):866–73.
[11] Rutigliano MJ, Lunsford LD, Kondziolka D, Strauss MJ, Khanna V, Green M. The cost effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of solitary metastatic brain tumors. Neurosurgery 1995;37(3):445–53.
[12] Wellis G, Nagel R, Vollmar C, Steiger HJ. Direct costs of microsurgical management of radiosurgically amenable intracranial pathology in Germany: an analysis of meningiomas, acoustic neuromas, metastases and arteriovenous malformations of less than 3 cm in diameter. Acta Neurochirurgica 2003;145(4):249–55.
[13] Riemenschneuder FM, Schwarzbach C, Bockelbrink A, Ernst I, Vauth C, et al. Medizinische und gesundheitsoekonomische Bewerting der radiochirurgie zur behandlung von hirnmetastasen. In: DIMDI 2009. 2009. HTA-Bericht 84.
[14] Mindermann T. Tumor recurrence and survival following gamma knife surgery for brain metastases. Journal of Neurosurgery 2005;102(Suppl.):287–8.
[15] Chernyak N, Petrak F, Plack K, Hautzinger M, Müller MJ, Giani G, et al. Cost-effectiveness analysis of cognitive behaviour therapy for treatment of minor or mild-major depression in elderly patients with type 2 diabetes: study protocol for the economic evaluation alongside the MIND-DIA randomized controlled trial (MIND-DIA CEA). BMC Geriatrics 2009;9(25).
[16] UKM: DRG Research Group – Webgrouper. In: DRG Research Group Medizinisches Management. Available from: http://drg.uni-muenster.de/index.php?option=com_webgrouper&view=webgrouper&Itemid=26.
[17] Kreinsen DS, Geissler A, Busse R. The ABC of DRGs. Euro Observer 2009;11(4).
[18] Johannesen TB, Norum J, Lote K, Scheie D, Hirschberg H. A cost-minimising analysis of standard radiotherapy and two experimental therapies in glioblastoma. Radiotherapy and Oncology 2002;62(2):227–31.
[19] Willan AR, Briggs A. Statistical analysis of cost-effectiveness data. England (West Sussex): John Willey & Sons Ltd.; 2006.
[20] Heitjan DF, Kim CY, Li H. Bayesian estimation of cost-effectiveness from censored data. Statistics in Medicine 2004;23(8):1297–309.
[21] Lin DY, Feuer EJ, Etzioni R, Wax Y. Estimating medical costs from incomplete follow-up data. Biometrics 1997;53(2):419–34.
[22] Hlatky MA. Economic endpoints in clinical trials. Epidemiologic Reviews 2002;24(1):80–4.

[23] Rubin D. The use of matched sampling and regression adjustment to remove bias in observational studies. Biometrics 1973;29:185–203.
[24] Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. Statistics in Medicine 2008;27(12):2037–49.
[25] D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Statistics in Medicine 1998;17(19):2265–81.
[26] Kaplan EL, Meier P. Nonparametric estimate from incomplete observations. Journal of the American Statistical Association 1958;53:457–81.
[27] Cox DR. Regression models and life tables. Journal of the Royal Statistical Society 1972;34:187–220.
[28] Kim DG, Chung HT, Gwak HS, Paek SH, Jung HW, Han DH. Gamma knife radiosurgery for brain metastases: prognostic factors for survival and local control. Journal of Neurosurgery 2000;93(Suppl. 3):23–9.
[29] Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. International Journal of Radiation Oncology, Biology, Physics 1999;43(4):795–803.
[30] Rades D, Bohlen G, Pluemer A, Veninga T, Hanssens P, Dunst J, et al. Stereotactic radiosurgery alone versus resection plus whole-brain radiotherapy for 1 or 2 brain metastases in recursive partitioning analysis class 1 and 2 patients. Cancer 2007;109(12):2515–21.
[31] Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. Journal of the American Medical Association 2006;295(21): 2483–91.
[32] Cohen J. Statistical power analysis for the behavioral sciences. rev. ed. New York: Academic Press; 1997.
[33] Neymark N, Adriaenssen I, Gorlia T, Caleo S, Bolla M. Estimating survival gain for economic evaluations with survival time as principal endpoint: a cost-effectiveness analysis of adding early hormonal therapy to radiotherapy in patients with locally advanced prostate cancer. Health Economics 2002;11(3):233–48.
[34] Ash A, Shwartz M. R2: a useful measure of model performance when predicting a dichotomous outcome. Statistics in Medicine 1999;18(4):375–84.
[35] Hlatky MA, Boothroyd DB, Johnstone IM. Economic evaluation in long-term clinical trials. Statistics in Medicine 2002;21(19):2879–88.
[36] Sperduto PW, Hall WA. The cost-effectiveness for alternate treatments for single brain metastases. In: Kondziolka D, editor. Radiosurgery 1995. Basel: Karger; 1996. p. 180–7.
[37] Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. The New England Journal of Medicine 1990;322(8):494–500.
[38] Auchter RM, Lamond JP, Alexander E, Buatti JM, Chappell R, Friedman WA, et al. A multiinstitutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis. International Journal of Radiation Oncology, Biology, Physics 1996;35(1):27–35.
[39] Wroński M, Arbit E. Resection of brain metastases from colorectal carcinoma in 73 patients. Cancer 1999;85(8):1677–85.
[40] Bindal RK, Sawaya R, Leavens ME, Lee JJ. Surgical treatment of multiple brain metastases. Journal of Neurosurgery 1993;79(2):210–6.
[41] Wroński M, Arbit E, Burt M, Galicich JH. Survival after surgical treatment of brain metastases from lung cancer: a follow-up study of 231 patients treated between 1976 and 1991. Journal of Neurosurgery 1995;83(4):605–16.
[42] Schackert G. Resection of brain metastases. Acta Chirurgica 1996:18–23. Heft 1.
[43] Penar PL, Wilson JT. Cost and survival analysis of metastatic cerebral tumors treated by resection and radiation. Neurosurgery 1994;34(5):888–93.
[44] Huang CF, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for brainstem metastases. Journal of Neurosurgery 1999;91(4):563–8.
[45] Williams BJ, Suki D, Fox BD, Pelloski CE, Maldaun MVC, Sawaya RE, et al. Stereotactic radiosurgery for metastatic brain tumors: a comprehensive review of complications. Journal of Neurosurgery 2009;111(3):439–48.
[46] Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. International Journal of Radiation Oncology, Biology, Physics 1999;45(2):427–34.
[47] Chen JC, Petrovich Z, O'Day S, Morton D, Essner R, Giannotta SL, et al. Stereotactic radiosurgery in the treatment of metastatic disease to the brain. Neurosurgery 2000;47(2):268–79.
[48] Flickinger JC, Lunsford LD, Somaza S, Kondziolka D. Radiosurgery: its role in brain metastasis management. Neurosurgery Clinics of North America 1996;7(3):497–504.
[49] Pan HC, Sheehan J, Stroila M, Steiner M, Steiner L. Gamma knife surgery for brain metastases from lung cancer. Journal of Neurosurgery 2005;102(Suppl.):128–33.
[50] Kim YS, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for patients with nonsmall cell lung carcinoma metastatic to the brain. Cancer 1997;80(11):2075–83.
[51] Muacevic A, Wowra B, Siefert A, Tonn JC, Steiger HJ, Kreth FW. Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial. Journal of Neurooncology 2008;87(3):299–307.
[52] Muacevic A, Kreth FW, Horstmann GA, Schmid-Elsaesser R, Wowra B, Steiger HJ, et al. Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter. Journal of Neurosurgery 1999;91(1):35–43.
[53] Matsunaga S, Shuto T, Kawahara N, Suenaga J, Inomori S, Fujino H. Gamma Knife surgery for metastatic brain tumors from primary breast cancer: treatment indication based on number of tumors and breast cancer phenotype. Journal of Neurosurgery 2010;113(Suppl.):65–72.
[54] Kondziolka D, Lunsford LD, Flickinger JC. The radiobiology of radiosurgery. Neurosurgery Clinics of North America 1999;10(2):157–66.
[55] Chang SD, Adler JR. Current treatment of patients with multiple brain metastases. Neurosurgical Focus 2000;9(2):e5.
[56] Kretowska M. The influence of censoring for the performance of survival tree ensemble. In: ICAISC 2010, part II, LNAI 6114. 2010. p. 524–31.
[57] QCP: Does your data violate Kaplan–Meier assumptions? Available from: http://www.quality-control-plan.com/StatGuide/kaplan_ass_viol.htm. [accessed December 2010].
[58] Reineke DM, Pohl EA, Murdock WP. Survival analysis and maintenance policies for a series system, with highly censored data. In: Reliability and Maintainability Symposium 1998. 1998. p. 182–8.

Please cite this article in press as: Vuong DA, et al. Comparing the cost-effectiveness of two brain metastasis treatment modalities from a payer's perspective: Stereotactic radiosurgery versus surgical resection. Clin Neurol Neurosurg (2012), http://dx.doi.org/10.1016/j.clineuro.2012.05.005