The Cost-Effectiveness of Stereotactic Radiosurgery versus Surgical Resection in the Treatment of Brain Metastasis in Vietnam from the Perspective of Patients and Families

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Key words
- Brain tumors
- Economics
- Stereotactic radiosurgery
- Surgical resection

Abbreviations and Acronyms

BM: Brain metastasis
CEA: Cost-effectiveness analysis
CEAC: Cost-effectiveness acceptability curves
CI: Confidence interval
HR: Hazard ratio
PSM: Propensity score matching
PTS: Primary tumor site
SR: Surgical resection
SRS: Stereotactic radiosurgery

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■ BACKGROUND: **This study aims to evaluate the cost-effectiveness of the treatment of brain metastasis with surgical resection (SR) and stereotactic radiosurgery (SRS) in the lower-middle-income country of Vietnam from the perspective of patients and families.**

■ METHODS: **The treatment of 111 patients with brain metastases who underwent SR (n = 64) and SRS (n = 47) was retrospectively reviewed. Propensity score matching was used to adjust for selection bias (n = 30 each); mean and curves of survival time were defined by the Kaplan-Meier estimator; the cost analysis focused on the time period of relevant treatment.**

■ RESULTS: **The mean survival times of SRS and SR were 11.9 and 10.5 months, and the 18-month survival rates were 32% and 14%, respectively ($P = 0.346$). The mean number of hospital bed days was significantly higher for SR than SRS (16.5 versus 7.6 days, $P < 0.05$), but direct costs of SR were significantly lower (14.5 as opposed to 35.3 million VND per patient, $P < 0.001$). However, indirect costs of SR were 10 times higher (26.0 versus 2.5 million VND per patient, $P < 0.001$). The cost per life year gained was higher for SR than SRS (46.4 and 38.1 million VND, respectively).**

■ CONCLUSIONS: **SRS is similarly effective as SR. However, in the broader context of the cost-effectiveness from the perspective of patients and their families, SRS is more cost-effective. The lower costs directly charged by the hospital for SR may prevent poorer and older patients from choosing SRS. Thus, the overall cost-effectiveness of each treatment option should be taken into consideration in deciding on the treatment.**

INTRODUCTION

Within a given budget, a cost-effectiveness analysis (CEA) is one of the most common measures supporting the decision-making process among various options of treatments or health programs, especially in developed countries. CEA is one form of full economic evaluation, concerned with the assessment of the effect and cost of treatments, resulting in a cost per unit of effect that enables a comparison of different treatments within a given field (10, 28, 35). Brain metastasis (BM), which is the most common central nervous system neoplasm, occurs in 20% to 40% of cancer patients during the course of their disease, possibly even up to 85% based on radiologic, autopsy, surgical, and medical records data (29, 37, 39), and is often considered a terminal stage of the disease (3, 20). Recently, there seems to be a trend toward an increase in the incidence of BM due to the earlier diagnosis and/or more effective treatment regimes of systemic disease. Stereotactic radiosurgery (SRS) and surgical resection (SR) are among those treatment regimens. Of these, SRS has recently become well known in high-income countries as more cost-effective than SR (25, 34, 38). However, less attention has been paid to the cost-effectiveness of the treatment of BM, especially of SRS versus SR, in lower-middle-income countries such as Vietnam, where there is a higher rate of out-of-pocket payment for health services. The aim of this study is to identify the cost-effectiveness of SRS versus SR in the treatment of BM with a main focus on the patient's and family's point of view during the time period of the relevant treatment.

MATERIALS AND METHODS

Patient Profile

We retrospectively reviewed the records of all 141 patients who were consecutively treated with SR (mostly by the conventional operation) at Choray Hospital and Vietnam–Germany Friendship Hospital, and with SRS (by Leksell Gamma Knife) at Choray Hospital and Hue Medical University Hospital, between 2006 and 2008. This group of patients included 87 SR patients within the age range of 17 to 76 years and 54 SRS patients within the age range of 18 to 87 years. Follow-up data were collected by contacting the patient's family or the communal health care station in the area where the patient lived. Twenty-three of the 87 SR patients and 7 of the 54 SRS patients, who were lost to follow-up less than 3 months after the intervention was performed, were excluded from the analysis. A total of 111 patients remained and were included in the analysis. The male-to-female ratio was 2.6:1.

Patients were characterized by sex, age (younger than 60 old versus 60 years and older), number of BM (up to 2 versus 3 or more), primary tumor sites (PTS) (due to the small sample size, PTS were stratified into 2 groups of lung cancer or others), volume of BMs (smaller than 115 versus at least 115 cm³; this was measured by the result given in magnetic resonance imaging compared with the pathology result to make sure that all tumors were removed), and performance status (absence versus presence of hemiparesis). Regarding the performance status, unfortunately medical doctors in Vietnam use only the Glasgow Scale (whereby all samples have the same score of 15). Taking the additional information of neurological impairment related to movement disorders due to paresis, we had to use 2 subgroups, namely patients with and patients without metastasis-related paresis of the arm or leg in our propensity score matching (PSM), instead of using the Karnofsky Performance Score or Recursive Partitioning Analysis.

Treatment Cost Calculations

The treatment cost consists of 2 parts: direct costs (health care costs, food and accommodation costs) and indirect costs (lost working days of patients and their relatives) (8, 34, 38). These costs were limited to the time period that the patient stayed in the hospital to have the treatment and home care according to the relevant treatment. The hospital cost data were based on the hospital charge bill, which involved diagnostic procedures (medical imaging and laboratory services), consumables (medications and disposables), inpatient stay (both at the ward and the intensive care unit), drugs and operation procedures (1.8 to 2.5 million VND for SR and 30 to 35 million VND for SRS). Those direct costs were paid directly (out of pocket) by the patients who have no health insurance. Such a situation applied to 51% of the population (in 2007) (37). Aside from the main cost of the discharge bill, SR patients generally pay the charge of self-purchased drugs that are not available in the hospital inventory and a gift to health care staff, which was roughly estimated to be 10% of the hospital charge (22). The overhead costs of general expenses, administration and operation, maintenance, insurance and other personnel costs of nonpatient services, and the depreciation costs of capital investment on equipment and buildings were not included in the cost calculation, as these costs were mostly paid by the government. Accommodation costs for relatives in or outside of the hospital were assumed to be equal for all 3 cities, at approximately 100,000 VND (US$6.10) per night, and such an amount of money was also estimated for higher expenses for food in the hospital compared with home. Indirect costs were mainly considered the loss of working time of patients (those under 60 years for men, 55 years for women) and their relatives who had to take care of the patient in the hospital and at home while the patient recovered. We estimated that patients treated with SRS needed 1 relative to accompany and attend to the patient, whereas SR patients needed 1 relative before the operative procedure and 2 relatives during the postoperative inpatient time, due to the more intensive care required, so the family had to take turns to look after the patient, to provide additional care in addition to the services of health staff. For the lost workdays, as this information was not recorded, we used the results of Cho et al. as patients treated with SR needed 160 days off work to recover plus 30 days of support from relatives at home (the number of relatives' attendance days was roughly estimated by communicating with relatives by telephone). Patients who received SRS needed 8 days to recover and no further support from their relatives at home (4). The overall average net value added per employee was used to calculate the cost of lost working days (9), as follows: the monthly average income per employee in all kinds of economic activity within the 3 years 2006 to 2008 (14), adjusted to the year 2008 by using the Consumer Price Index of Vietnam for the year 2007 (8.3%), and 2008 (19.89%) (15) (exchange rate 1 USD = 16,506 VND on 30 June 2008) plus the employment benefit at the rate of 50%; resulting in an average cost of 1 working day of around 128,000 VND (7.80 USD) (9, 33). AQ: 2

$$C_i^{tr} = \sum C_i^d + \sum C_i^{id}$$

where: $\Sigma C_i^d = C_i^{hs} + C_i^e + C_i^{af}$

$$\Sigma C_i^{id} = C_i^{w-p} + C_i^{w-r}$$

C_i^{tr}: cost of treatment of patient i; C_i^d : direct cost ; C_i^{hs} : charge from the hospital; C_i^e : cost for the extra drug and gift to the health staff; C_i^{af}: cost of accommodation and food during hospital stay; C_i^{id} : indirect cost; C_i^{w-p} : cost of working time lost; C_i^{w-r} : cost of working time lost of relatives.

Statistical Analysis

For the CEA of health care interventions, survival time is considered the principal outcome of the effect, which was expressed by the mean and median survival time of patients. Of these, the mean survival time provides a better estimate of survival time because its value is equal to all the area under the curve of survival time, whereas the median is a sole point on the survival curve (28). The survival time was measured from the time of the intervention (SRS or SR). Uncensored cases were those that reached the end point of interest (i.e., death) and censored cases were those that were lost to follow-up. Overall survival time was calculated from the date of receiving the intervention (SRS or SR) to the date of last follow-up (24). Survival time mean and survival curves were defined by the Kaplan-Meier estimator (18). The differences between the Kaplan-Meier curves of the 2 treatment groups were determined with the log-rank test (univariate analysis) and univariate Cox proportional hazard models were used to assess the effect of each predictor on the shape of the survival curve, then the prognostic factors were found to be significant with $P < 0.05$, which were included in a multivariate Cox proportional hazards model (6). Death within 30 days was also reported and attributable to complications of the operation (36).

Propensity Score Matching

For the comparison of the cost-effectiveness of the 2 modalities of SRS and SR, potential confounding and selection biases may exist because the treatments were not randomly assigned in this patient population. This problem was minimized by the

PSM approach (7, 32), for those prognostic factors found to be significant in the Cox proportional hazards model (unadjusted sample) and those previously identified from the literature as predictive factors of survival. Finally, matched factors consisted of number of BMs, PTS, volume of brain tumors, as well as demographic factors (age and sex) (11, 19, 21, 30). To estimate the propensity score, a logistic regression model was fitted to assign to each individual a probability (from 0 to 1) based on the prognostic factors. We used a 1:1 optimal matching without replacement, meaning that for each SRS patient, 1 SR patient was identified. The match was conducted by randomly ordering all patients from the treatment groups and choosing the most similar propensity score to the initial patient; these 2 patients formed a matched pair. This matching process was conducted separately for each treatment group. The balance of the baseline characteristics of both unadjusted and adjusted samples is measured by using the standardized difference (7):

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

where X_{srs} and X_{sr} are the sample means in the SRS and SR groups of the i^{th} covariate, respectively, and S^2_{srs} and S^2_{sr} are the corresponding sample variance. Small absolute values of standardized difference (<10%) support the assumption of balance between treatment groups (5).

Then medians of follow-up time were estimated; mean survival times were calculated again for matched pair groups, and adjusted survival curves were plotted for the comparison of the SRS and SR groups by the Kaplan-Meier estimator; a univariate Cox proportional hazard regression was performed to determine whether survival was improved in the SRS group compared with the control group of SR by the effect of treatments. Multivariate proportional hazard regression of prognostic factors (including the propensity score as a covariate in the model for adjusting the selection bias) was used to test the association between those factors and the principal outcomes of the SRS and SR treatments. To evaluate the capacity of the final model of the multivariate analysis to predict the treatment effect on the patient, we calculated the Harrell C statistic, which is the area under the receiver-operator characteristic curve and which provides a measure of predictive power. A value of .50 indicates no discrimination, and a value of 1.0 indicates perfect discrimination (1, 16).

All reported P values are 2-sided and showed a significant difference with a level of 0.05 or less. Statistical analyses were performed with SAS version 9.3.1 (SAS Institute, Cary, North Carolina, USA) and STATA 10 software.

Table 1. Patient Characteristics of the Treatment Groups (Preoperation)

	Before Matching (unadjusted samples)			After Matching (adjusted samples)		
Patient Characteristics	**SRS group**	**SR group**	**SD**	**SRS**	**SR**	**SD**
Number of patients	47	64		30	30	
Gender, female (%)	42.6	32.8	14.88	33.3	40.0	−10.12
Age (<60 vs. ≥60 y),						
<60 y (%)	82.9	62.5	30.11	83.3	86.6	−5.07
Number of BM (<3 vs. ≥3) ≥3 (%)	29.8	6.3	54.05	13.3	13.3	0.00
Volume of BM (<115 vs. ≥115 cm^3), <115 cm^3 (%)	46.8	40.6	9.41	50.0	50.0	0.00
Primary tumor sites (lung vs. others)						
Lung (%)	38.3	34.4	5.97	40.0	36.7	5.06
Others (%)	61.7	65.6				
Breast (n)	6	4				
Unknown (n)	14	23				
Neurological impairment (absence vs. present of hemiparesis) Absence of hemiparesis	76.6	50.0	38.03	73.3	70.0	5.06

BM, brain metastasis; SD, xxx; SR, surgical resection; SRS, stereotactic radiosurgery.

AQ: 14

Sensitivity Activity

Although PSM was well balanced between the 2 groups, a potential selection bias due to imbalances in unmeasured covariates might still be possible. We conducted a formal sensitivity analysis to test the robustness of the results by using the bootstrap method, which used a resample from the original data to build an empirical estimate of the sampling distribution of the incremental cost-effectiveness ratio (17). The un- AQ: 3

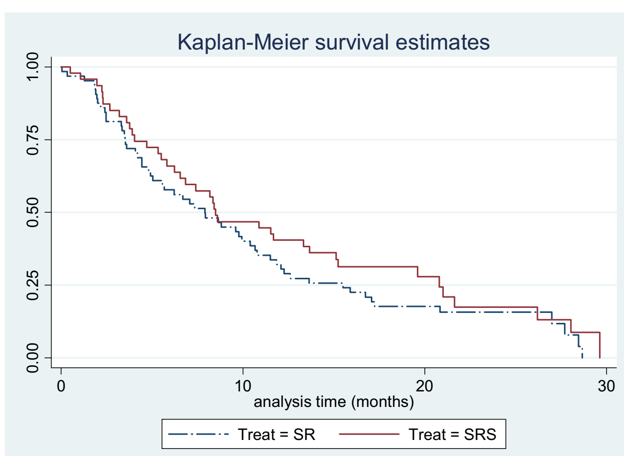

Figure 1. Unadjusted survival curves of 2 treatment groups, months postintervention.

COLOR

Table 3. Univariate Analysis of Treatment Effect (Adjusted Samples)

	Mean Survival Time (months)	Survival Function (%)		Cox PHM		
		12 Months	18 Months	HR	95% CI	*P* Value
Treatment						
SR	10.5	45.5	14.0	0.76	0.43–1.33	0.34
SRS	11.9	46.0	32.0			

CI, confidence interval; HR, hazard ratio; PHM, proportional hazard model; SR, surgical resection; SRS, stereotactic radiosurgery.

would have a lower cost than SR, and 55.5% probability that SRS would have a relatively greater effect than SR. In quadrant IV, 34.2% of the plots of ICER were concentrated, to indicate that SRS has a lower cost and greater effect, in contrast to 16.1% of the plots in quadrant II, where SRS has a higher cost and smaller effect (**Figure 3**); this means that the CEAC never exceeded 95% and the 95% certainty was not estimated. However, **Figure 4** shows that although CEAC associated with SR being more cost-effective was positive, whereupon the curve tended upward, it never rose above .50. Although the curve associated with SRS being more cost-effective tended downward, at any willingness-to-pay threshold it was always more likely to be the more cost-effective treatment compared with SR and above .50.

Table 4. Details of Overall Logistic and Proportional Hazards Model Evaluating the Association of Treatments and Survival (Adjusted Samples)

	Multivariate PHM (95% CI)		
Patient Characteristics	HR	SE	*P* Value
Treatment (SRS vs. SR)	.67	.20	0.19
Propensity score	5.42	49.07	0.85
Gender (female vs. male)	1.05	.57	0.92
Age (<60 vs. ≥60 y)	1.63	2.60	0.75
Number of BM (<3 vs. ≥3)	5.03	17.70	0.64
Volume (<115 vs. ≥115 cm^3)	.92	.85	0.93
Primary tumor sites (lung vs. others)	.48	.39	0.38
Neurological impairment (absence vs. presence of hemiparesis)	.73	1.53	0.88

Receiver-operator characteristic curve (c-statistic) = .63.
BM, brain metastasis; CI, confidence interval; HR, hazard ratio; PHM, proportional hazard model; SE, standard error; SR, surgical resection; SRS, stereotactic radiosurgery.

Table 5. Resource Utilization Per Patient

	Mean	SD	*P* Value
Hospital bed days (d)			0.01
SR group	16.8	21.6	
SRS group	7.6	6.1	
Hospital bed days after operation (d)			0.01
SR group	9.4	14.9	
SRS group	3.0	4.2	
Direct cost (million VND)			<0.001
SR group	14.5	7.7	
SRS group	35.3	1.8	
Indirect cost (million VND)			<0.001
SR group	26.0	9.5	
SRS group	2.5	1.4	
Total of treatment cost (million VND)			0.15
SR group	40.6	14.5	
SRS group	37.8	2.8	
Cost per 1 life year gained (million VND)			
SR group	46.4		
SRS group	38.1		

SR, surgical resection; SRS, stereotactic radiosurgery.

DISCUSSION

The present study compared the cost-effectiveness of SR and SRS in the treatment of BM by evaluating the mean costs of SR and SRS from the perspective of patients and families during the period of the hospital stay for intervention. These mean costs were compared with the outcome in each of the 2 groups. The outcome was considered as the survival time after treatment. According to the current study results, SRS is more cost-effective than SR (cost per life year gained was 38.1 million VND and 46.4 million VND, respectively). Contributing to this difference was the fact that the direct costs of SR were just one-third of the direct costs of SRS (14.5 ± 7.7 million VND and 35.3 ± 1.8 million VND, respectively), but its indirect costs were up to 10 times higher than the indirect costs of SRS (26.0 ± 9.5 million VND for SR versus 2.5 ± 1.4 million VND for SRS).

The lower direct costs of SR versus SRS found in Vietnam are very different from the previous studies in high-income countries conducted by Mehta et al. (in the United States), Rutigliano et al. (a meta-analysis of studies in the United States, United Kingdom, and the Netherlands), and Wellis et al (in Germany), where the net costs of SR were 1.8, 1.3, and 1.9 times higher than those of SRS, respectively (25, 34, 38). However, when the direct and indirect costs are combined, that is, taking the perspective of the patient and the family who must pay for the health services into account, the cost-effectiveness of SRS in the treatment of BMs is also greater than that of SR. This is consistent with earlier studies in high-income countries, such as that of Rutigliano et al., which found that SRS had a better incremental cost-effectiveness than SR ($40,648 versus $52,384 per life year, respectively) (34); and Mehta et al., which concluded that SRS appears to be more cost-effective, with an average cost per week of survival of $524 for SR plus radiation and $270 for SRS plus radiation (25).

In addition to the drugs officially dispensed in the hospital, which comprised the largest proportion of hospital costs (31.4% to 68.2%) (22), the patients also had to pay for additional drugs and consumables that were not available in the hospital and that they self-purchased on the prescriptions of their physicians. These costs were not recorded in the hospital receipt

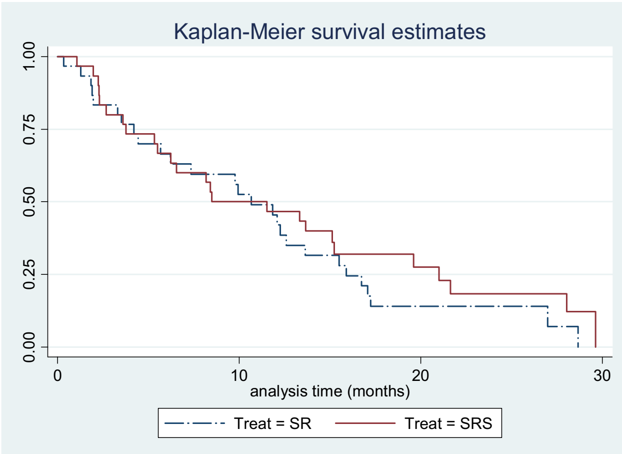

Figure 2. Survival curves of 2 treatment groups after propensity score matching, months postintervention.

that the current study used to calculate the direct costs of the treatments. The study of MOH 2003 reported that the proportion of these costs, as well as a gift to hospital staff, lodging, meals, and transportation, was about 40% of the total cost, and was even higher in higher levels of treatment facilities (26). Based on the costs of lodging, meals, and transportation, we roughly estimated the expenditure on additional drugs, consumables, and gifts to be around 10% of total hospital costs. The gift is actually not given in all cases, but is quite common in Vietnam to express the deep gratitude of the family for the kindness of the health care staff, and also in some cases in the hope of encouraging doctors to give them special attention. The length of stay of the SRS group was found to be rather high, because Gamma Knife is one department inside the general hospitals and almost all SRS patients were first admitted as inpatients. The length of stay was calculated for the whole time in the hospital (not only in the Gamma Knife department) for diagnostic procedure, SRS intervention, and recovery care. In some cases of serious illness, patients were kept longer to relieve symptoms such as pain, seizures, and paresis. For these reasons, the reimbursement through fee-for-service could lead to the longer duration of stays (23, 27).

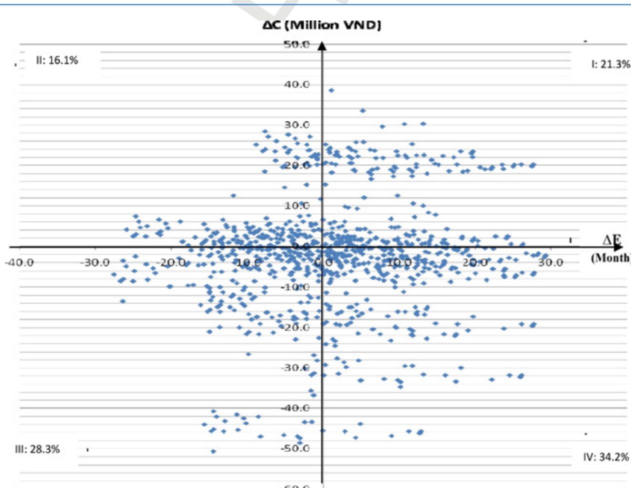

Figure 3. ICER results of bootstrap replication of SRS versus SR in the cost-effectiveness plane (adjusted samples). SR, surgical resection; SRS, stereotactic radiosurgery.

The lower direct costs of SR may be the reason that older and poorer patients use this treatment. In the current study, from the unadjusted samples there were more older patients using SR compared to SRS (37.5% versus 17.1%) which also accorded with the higher number of patients in the SR group who were lost to follow-up (26.4% versus 12.9%) because more of them lived in rural and remote areas where the administration was not thorough enough in regard to the registration of house numbers, and because they also more commonly used temporary prepaid SIM cards to be contactable only during hospital stays. Even for those who were back in the hospital for ongoing treatment (other than SRS or SR), we were also not able to get such information, due to the lack of connections in the patient databases between different hospitals in Vietnam. With this restriction in available information, the additional treatment of whole-brain radiation therapy was not considered in our data analysis, because we could not precisely obtain this information by telephone when contacting the patients or their relatives. However, all these constraints mentioned did not act as a bias because the adjusted samples were matched by PSM and those lost to follow-up (before 3 months from the date of intervention) were excluded in the final model for CEA.

In addition, the current study has some limitations because the sample size is rather small: it consisted of 60 cases, 30 in each group. However, it met the minimum sample size to arrive at reliable estimates of the 3 major functions (survival, probability density, and hazard) and their standard errors at each time interval (13). Patients were not randomly assigned to the treatment. They were assigned by the recommendation of medical doctors plus the patient's ability to pay for the service, regardless of whether the patient was insured or not insured, because the insured still had to pay almost 40% of the cost of SRS, as it exceeded the ceiling cost health insurance would cover. Additionally, the study is limited by the nature of the observational data, which we had to overcome by PSM, but matching was done after exposure, so the treatment subjects and standard subjects in the matched sample do not form 2 independent samples. However, the PSM approach has several theoretical and practical advantages

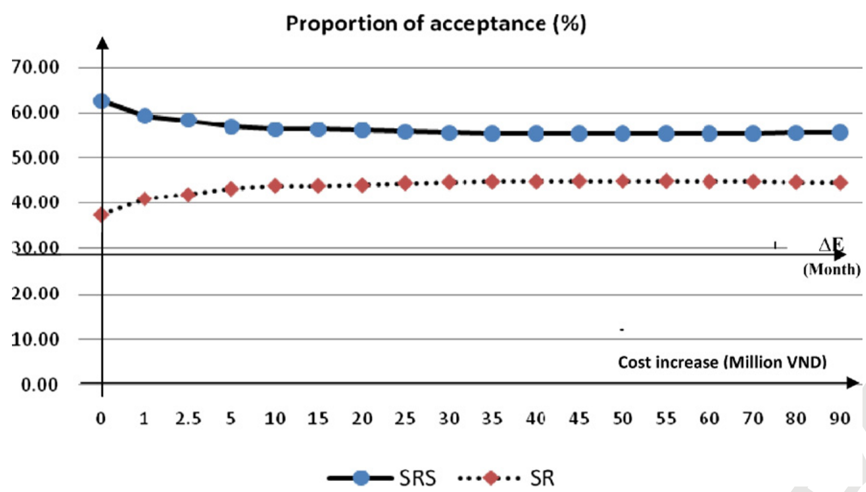

Figure 4. Cost-effectiveness acceptability curve.

compared with other methods such as adjustments based on case mix or severity of illness alone. It has been successfully used in other medical settings in which data from controlled trials were lacking, and is increasingly used to evaluate the effectiveness of medical treatments using data obtained from nonexperimental studies in adjusting for selection bias; the matched nature of the sample was accounted for in the statistical analysis in this study to estimate the precision or significance of the estimated treatment effect (2, 7, 31).

CONCLUSIONS

In the context of the lower-middle-income country of Vietnam, the innovative technology of SRS in the treatment of BM is similarly effective as SR, as it is in high-income countries. However, in the broader context of the cost-effectiveness from the perspective of patients and their families, SRS remained a more cost-effective treatment than SR. The lower costs directly charged by the hospital for SR may prevent poorer and older patients from choosing SRS. Thus, the overall cost-effectiveness of each treatment option should be taken into consideration in deciding on the treatment. **Figure 2**.

UNCITED REFERENCES

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