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Analysis of the drivers of cost of management when patients with brain metastases are treated with upfront radiosurgery

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ABSTRACT

Objectives: We aimed to assess the driving factors for increased cost of brain metastasis management when using upfront stereotactic radiosurgery (SRS).

Patient and Methods: 737 patients treated with upfront SRS without whole brain radiotherapy (WBRT). Patients were evaluated for use of craniotomy, length of hospital stay, need for rehabilitation or facility placement, and use of salvage SRS or salvage WBRT. Costs of care of these interventions were estimated based on 2013 Medicare reimbursements. Multiple linear regression was performed to determine factors that predicted for higher cost of treatment per month of life, as well as highest cumulative cost of care for brain metastasis.

Results: Mean cost of brain metastasis management per patient was $42,658, and $4673 per month of life. Upfront SRS represented the greatest contributor of total cost of brain metastasis management over a lifetime (49%), followed by use of any salvage SRS (21%), use of initial surgery (14%), use of salvage surgery (10%), hospitalization (3%) and cost of salvage WBRT (3%). Multiple linear regression identified brain metastasis velocity (BMV) ($p < 0.001$), use of cavity-directed SRS (< 0.001), and CNS symptoms at time of presentation ($p = 0.005$) as factors that increased costs of care per month of survival. Use of salvage WBRT decreased per month cost of care in patients requiring salvage ($p < 0.001$).

Conclusion: The cost of upfront SRS is the greatest contributor to cost of brain metastasis management when using upfront SRS. Higher BMV, progressive systemic disease and presence of symptoms are associated with increased cost of care.

1. Introduction

There are approximately 170,000 patients in the US each year who develop brain metastases [1]. If brain metastases represented a primary cancer type, it would represent the third most common solid malignancy behind only breast and lung cancer [2]. Common treatment options for brain metastases include surgery, whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS). While the indications for surgery tend to be fairly well defined, the usage of WBRT vs SRS can be quite controversial because of issues of cost and quality of life [3]. Recent randomized trials have demonstrated that in patients with 4 or fewer brain metastases, there is improvement in cognition [4,5] and health-related quality of life [6] when SRS is used without upfront WBRT.

Beyond four brain metastases, there are far fewer guidelines to dictate when to use WBRT vs SRS. A recent phase II study showed that treating up to 10 metastases with SRS alone was feasible and can yield similar survival outcomes to patients with 2–4 brain metastases [7]. However, when upfront WBRT is withheld, there is a higher need for salvage treatments [8], and a greater number of metastases at time of first SRS is an important factor determining the need for future salvage therapies [9].

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SRS is two- to six-fold more expensive than WBRT [10], and multiple applications of SRS can increase the cost of treatment greatly. As the usage of SRS rises with increasing access of stereotactic techniques and linear accelerators to community practices, it has become paramount to determine the proper utilization of both WBRT and SRS. While data continues to be generated regarding this issue, it has been unclear what factors drive the total costs of brain metastasis management in the era of modern SRS utilization. To this end, we conducted a single institution retrospective analysis of patients treated with SRS without upfront WBRT and used multivariate analyses to determine the cost effectiveness of such treatment.

2. Patient and methods

2.1. Data acquisition

This study was approved by the institutional review board at the Wake Forest School of Medicine. Patients from this study were identified from a departmental database of patients receiving stereotactic radiosurgery for the diagnosis of brain metastases. Patients who received upfront WBRT were excluded from this study. Electronic medical records (EMR) were used to determine patient clinical characteristics, socioeconomic factors and clinical outcomes. Patient characteristics included age, gender, ethnicity, primary malignancy, presence of symptoms, and burden of extracranial disease. Patients were considered to have oligometastatic disease if their extracranial disease burden included 5 or fewer sites of extracranial disease without diffuse involvement of a single organ as has previously been defined by Harris et al [11]. Patient characteristics are summarized in Table 1.

Table 1
Patient Characteristics.

n	737
Age (median [range])	62.00 [5.00, 91.00]
Male gender (%)	396 (53.7)
Ethnicity (%)	
African American	72 (9.8)
Hispanic	8 (1.1)
Other	4 (0.5)
White	653 (88.6)
Primary malignancy (%)	
Breast	102 (13.8)
Lung	366 (49.7)
Melanoma	117 (15.9)
Other	83 (11.3)
Renal Cell Carcinoma	69 (9.4)
Symptomatic at diagnosis (%)	539 (73.1)
Systemic disease burden (%)	
None	129 (18.8)
Oligo	305 (44.5)
Widespread	252 (36.7)
Unknown	51 (6.9)
Stable systemic disease (%)	399 (54.1)
Received post-SRS WBRT [a] (%)	165 (22.4)
Neurologic death (%)	223 (35.6)
DS-GPA [b] ≥ 2 (%)	262 (36.7)
Number of brain metastases (median [range])	1 [1, 25]
Lowest SRS margin dose (median [range])	19 [10,24]
Brain metastasis velocity (median [range])	2.62 [0.00, 156.52]
KPS [c] (median [range])	80 [50, 100]
Number of single-fraction SRS treatments (median [range])	1 [1,6]
Length of hospitalization (median [range])	0 [0, 44]
Number of craniotomies (median [range])	0 [0,[4]

[a] post-stereotactic radiosurgery whole brain radiotherapy.
[b] disease specific-grade prognostic assessment.
[c] Karnofsky performance status.

2.2. Radiosurgical technique

Patients were treated with the Leksell Model B (years 2000–2004), Model C (years 2004–2009) or Perfexion (years 2009–2013) Gamma Knife Units (Elekta AB, Stockholm, Sweden). Prior to radiosurgery, patients underwent a high-resolution contrast-enhanced stereotactic magnetic resonance imaging (MRI) study of the brain. Median dose delivered to the tumor margin was 19 Gy (IQR 17–22 Gy). Dose was generally prescribed to the 50% isodose line and were generally based on the guidelines published by Shaw et al for single fraction radiosurgical treatment of brain metastases [12].

2.3. Response assessment, follow-up, and salvage therapy

Patients underwent surveillance MRI of the brain and clinical follow-up 4–8 weeks after initial SRS. Surveillance MRI was then performed every 3 months for the first 2 years, and then every 4–6 months thereafter. Local failure was determined either by pathologic evidence of tumor recurrence, or a 25% increase in the greatest dimension of an axial slice on conventional MRI sequences with corresponding increase in perfusion on perfusion MRI. Brain metastasis velocity (BMV) was calculated as previously reported by Farris et al [13]. In brief, brain metastasis velocity is calculated as number of developed metastases from initial SRS divided by the time in years from initial SRS until distant brain failure noted by MRI. For patients with at least a single distant brain failure (DBF) event, BMV was defined as the number of new metastases over the time from initial GKRS until the DBF event.

New metastases were generally treated with SRS alone with WBRT reserved for patients with greater than 4 new lesions. Local failures were treated based on clinical judgment of the multi-disciplinary team. Salvage options for local failures included but were not limited to craniotomy and resection, laser thermotherapy, repeat radiosurgery and WBRT. Neurologic death was determined as previously reported by McTyre et al [14].

2.4. Estimation of costs of care

Costs of care were estimated based on the Medicare reimbursement rate in North Carolina as of 2013 for craniotomy, hospitalization related to brain metastasis, WBRT and SRS. Estimates were $24,000 for craniotomy, $21,000 for SRS, $4600 for WBRT, and $300 per hospitalization day that was not covered under craniotomy admission. Per day cost of inpatient stay at a rehabilitation or subacute nursing facility was estimated to be $150. For consistency, the same cost was used for each patient, regardless of his/her insurance coverage and year of service. We computed total costs of care for each patient based on actual services rendered multiplied by the Medicare reimbursement rate. We added the costs of care across all patients and computed the share of each treatment component relative to the total.

2.5. Statistics

Linear regression was performed for predictor variables of interest for total cost of care and cost of care per month of survival. Stepwise regression was used to identify the multiple regression model with the lowest AIC [15]. All clinical patient characteristics including age, gender, ethnicity, primary cancer, symptom status, extent of extracranial disease, status of extracranial disease, disease specific-GPA (DS-GPA), number of brain metastases, use of WBRT, number of metastases, KPS, cavity-directed SRS, and lowest margin dose used at radiosurgery, were included in the full multiple regression models before performing stepwise regression to arrive at the final models. For patients with multiple DBF events, BMV was estimated by performing a separate linear regression for each patient to obtain the slope representative of the best fit line.

Estimates of the effects of upfront WBRT on the need for further salvage treatments (both SRS and WBRT) to treat new brain metastases were derived from data from multiple available published randomized trials [5,6,8]. These estimates were then used to approximate the effect of using upfront WBRT instead of upfront SRS on a hypothetical population.

Statistical analysis was performed using R version 3.2.1 software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

There were 737 patients with a median follow-up of 53.9 months (95% confidence interval [CI], 41.0–75.5 months) by Kaplan-Meier method. Median overall survival was 8.6 months (95% CI 7.7–9.6 months). Median BMV was 5.7 metastases/year. Cumulative incidence to distant brain failure at 1 year was 40.9% months (95% CI 37.2–44.4%).

3.1. Costs of care

Mean cost of brain metastasis management per patient was $42,658 until death, and $4673 per month of remaining life. Median cost of brain metastasis management was $42,000. Across all patients, the total cost of care was $31,434,950. Upfront SRS represented the greatest contributor of total cost of brain metastasis management over a lifetime (49%), followed by use of any salvage SRS (21%), use of initial surgery (14%), use of salvage surgery (10%), hospitalization (3%) and cost of salvage WBRT (3%). Fig. 1 depicts the fractional contribution of surgery, SRS, WBRT, hospitalization and imaging to the cumulative costs of care for all patients in the series.

3.2. Predictors of total cost of care

Multivariate analysis using multiple linear regression was performed to assess for variables that affected cumulative lifetime cost of care for brain metastasis patients. A decreased cost of treatment was identified with primary lung cancer ($p = < 0.001$). WBRT ($p = < 0.001$), KPS ($p = < 0.001$), and cavity directed SRS therapy ($p = < 0.001$) were the factors associated with a higher cumulative cost of care.

As the use of multiple salvage procedures can increase the cost of treatment, but since BMV can only be calculated after new metastases develop (and multiple patients are removed from analysis if they have no new metastases), a second analysis was performed using BMV as a covariate to assess its effect on cost of care. Multiple linear regression identified higher BMV ($p = < 0.001$) and cavity directed SRS therapy ($p = < 0.001$) as the only factors associated with an increased cost of management per unit time. Table 2 depicts a summary of the multivariate analysis of factors that affect cost of care.

Table 2
Multivariate Analysis of Predictors of Total cost of care.

	Beta ($)[a]	CI	p-value
All patients with brain metastases			
Lung Cancer Primary	−0.17	−0.27 – -0.08	< 0.001
Melanoma	−0.03	−0.14 – 0.08	0.6
Other Primary Cancer	−0.05	−0.19 – 0.08	0.4
Renal Cell Carcinoma Primary	−0.09	−0.22 – 0.04	0.2
Received salvage WBRT [b]	0.29	0.22 – 0.37	< 0.001
CNS symptoms at presentation	0.06	−0.01 – 0.14	0.1
KPS [c]	0.01	0.00 – 0.01	< 0.001
Cavity Directed SRS [d]	0.63	0.55 – 0.70	< 0.001
Patients requiring salvage therapy			
Lung Cancer Primary	−0.07	−0.19 – 0.05	0.2
Melanoma	0.03	−0.11 – 0.18	0.6
Other Primary Cancer	0.17	−0.03 – 0.36	0.09
Renal Cell Carcinoma Primary	0.03	−0.15 – 0.20	0.8
Progressive systemic disease	−0.02	−0.12 – 0.08	0.7
Unknown systemic disease	−0.08	−0.24 – 0.07	0.3
CNS symptoms at presentation	0.08	−0.03 – 0.19	0.1
BMV [e]	−0.07	−0.11 – -0.04	< 0.001
KPS	0.003	−0.00 – 0.01	0.4
Cavity Directed SRS	0.42	0.32 – 0.53	< 0.001

[a] Beta in units of log (dollars) divided by unit of the independent variable (for histology, reference breast cancer = 0; for salvage WBRT, reference not receiving WBRT = 0; for CNS symptoms at presentation, reference for no symptoms = 0; for cavity directed SRS, reference not receiving cavity-directed SRS = 0; for systemic disease status, reference not progressive = 0). A positive value indicates an increase of cost, while a negative value indicates a decrease of cost.
[b] Whole Brain Radiotherapy.
[c] Karnofsky Performance Status.
[d] Stereotactic radiosurgery.
[e] Brain metastasis velocity in new metastasis per year.

3.3. Predictors of cost of care per month of survival

Multivariate analysis using multiple linear regression was also

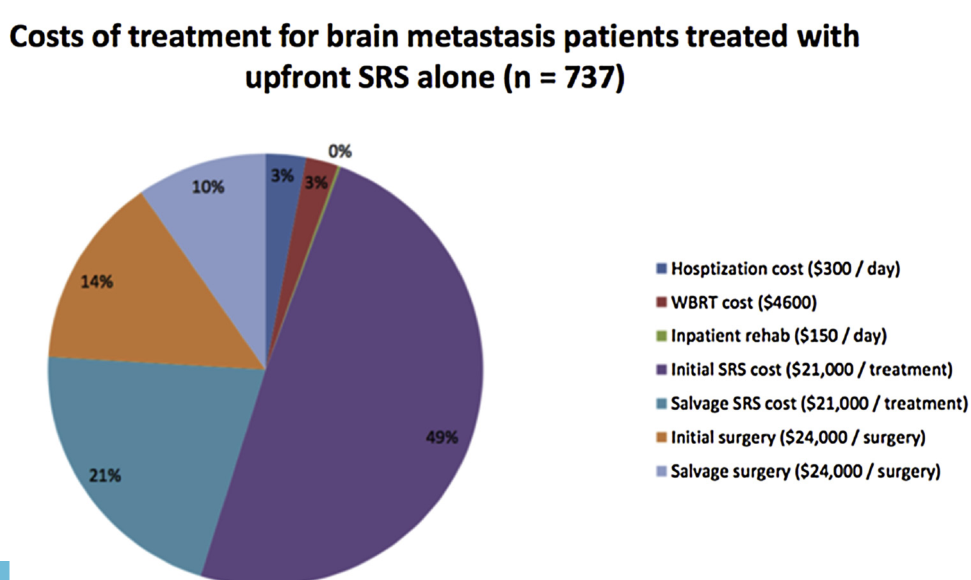

Fig. 1. Proportional costs of treatment for brain metastasis patients treated with upfront SRS alone (n = 737).

Table 3
Multivariate Analysis of Predictors of Cost of Care per month.

	Beta ($) [a]	CI	p-value
All patients with brain metastases			
Lung Cancer Primary	0.41	0.18 – 0.63	< 0.001
Melanoma	0.41	0.15 – 0.68	0.002
Other Primary Cancer	0.54	0.23 – 0.86	< 0.001
Renal Cell Carcinoma Primary	0.21	−0.08 – 0.51	0.2
Oligometastatic Disease Burden [b]	0.27	0.05 – 0.48	0.01
Unknown Disease Burden	0.27	0.05 – 0.48	0.01
Widespread Disease Burden	0.42	0.19 – 0.65	< 0.001
Salvage WBRT	−0.14	−0.31 – 0.03	0.1
CNS [c] symptoms at presentation	0.30	0.12 – 0.48	< 0.001
Number of metastases	0.07	0.03 – 0.10	< 0.001
Minimum Dose to any brain metastasis	−0.02	−0.05 – 0.00	0.09
KPS [d]	−0.02	−0.03 – -0.02	< 0.001
Cavity Directed SRS	0.21	0.02 – 0.41	0.03
Progressive Systemic Disease	0.23	0.07 – 0.40	0.007
Unknown Systemic Disease	−0.02	−0.30 – 0.25	0.9
Patients requiring salvage therapy			
Lung Cancer Primary	0.11	−0.08 – 0.29	0.3
Primary Melanoma	0.27	0.04 – 0.51	0.02
Other Primary Cancer	0.42	0.12 – 0.72	0.006
Renal Cell Carcinoma Primary	−0.09	−0.37 – 0.19	0.5
Progressive systemic disease	0.14	−0.01 – 0.30	0.07
Unknown systemic disease	0.19	−0.04 – 0.43	0.1
Salvage WBRT [e]	−0.26	−0.41 – -0.11	< 0.001
CNS symptoms at presentation	0.24	0.07 – 0.41	0.005
Age at 1 st Gamma Knife	0.005	−0.00 – 0.01	0.1
Number of metastases	−0.03	−0.07 – 0.01	0.1
BMV [f]	0.36	0.29 – 0.43	< 0.001
KPS	−0.01	−0.02 – -0.00	0.04
Cavity Directed SRS	0.47	0.30 – 0.63	< 0.001

[a] Beta in units of log (dollars) divided by unit of the independent variable (for histology, reference breast cancer = 0; for disease burden, reference no other metastatic disease = 0; for salvage WBRT, reference not receiving WBRT = 0; for CNS symptoms, reference no symptoms = 0; for cavity directed SRS, reference not receiving cavity-directed SRS = 0; for systemic disease status, reference not progressive = 0). A positive value indicates an increase of cost, while a negative value indicates a decrease of cost.
[b] Oligometastatic defined as 5 or fewer sites of extracranial disease.
[c] Central nervous system.
[d] Karnofsky performance status.
[e] Whole brain radiotherapy.
[f] Brain metastasis velocity in new metastasis per year.

performed to assess for variables that yield higher cost of care per month of survival in brain metastasis patients. Primary lung cancer (p = < 0.001), melanoma (p = 0.002), oligometastatic disease burden (p = 0.014), widespread disease burden (p = < 0.001), CNS symptoms at presentation (p = < 0.001), an increased number of metastases (p = < 0.001), and progressive systemic disease (p = 0.007) are all factors associated with increased cost of care per month of survival. Increased KPS was the only factor associated with decreased cost of care per month of survival (p = < 0.001).

Of the patients requiring salvage therapy, primary melanoma (p = 0.022), CNS symptoms at presentation (p = 0.005), a higher BMV (p = < 0.001), and cavity directed SRS (p = < 0.001) were associated with an increased cost of management per unit time. Use of WBRT as salvage treatment (p = < 0.001) and increased KPS (p = 0.038) were associated with decreased cost of management per unit time. The results of this analysis are summarized in Table 3.

3.4. Estimated effects of WBRT vs. SRS on the cost of management

To estimate the effects of upfront WBRT instead of SRS on the use of salvage treatments for new brain metastases, data from multiple available randomized trials were used. In these randomized trials, WBRT decreased the use of salvage SRS by approximately 25% and the use of salvage WBRT by 95%. This estimated decrease in salvage rates

Table 4
Comparative Costs of Salvage Therapies for Brain Metastases: Upfront SRS vs Upfront WBRT.

Calculated Costs Based on Patients with Follow-up to Time of Death	< 5 BM[a]	≥ 5 BM	BMV[b] 4-13	BMV > 13
Total n (present series)	580	52	91	62
% patients receiving salvage WBRT [c]	24%	27%	56%	77%
Mean SRS [d] salvage cost/ patient	$8291	$6865	$21,923	$13887
Mean surgery salvage cost/ patient	$3600	$2769	$5538	$3870
Mean WBRT salvage cost/ patient	$1110	$1239	$2578	$3562
Mean salvage cost/patient	*$13,001*	*$10,873*	*$30,039*	*$21319*
Estimated Costs assuming Upfront WBRT instead of SRS				
SRS salvage cost/patient	$6230	$5159	$16,473	$10435
Surgery salvage cost/patient	$2705	$2081	$4162	$2908
% patients receiving salvage WBRT	1%	1%	2%	4%
Total salvage cost/patient	*$8986*	*$7296*	*$20,753*	*$13,506*

[a] Brain Metastases.
[b] Brain metastasis velocity in new metastasis per year.
[c] Whole Brain Radiotherapy.
[d] Stereotactic radiosurgery.

by using WBRT instead of SRS was then used to estimate the costs of treatment for subpopulations of patients who receive SRS vs WBRT in the upfront setting. The estimated difference in salvage costs for treating < 5 brain metastases and ≥ 5 brain metastases with upfront SRS vs upfront WBRT is $4015 and $3577 per person, respectively. The estimated per person difference in salvage costs for patients with BMV of 4–13 metastases/year and > 13 metastases/year with upfront SRS vs upfront WBRT is $9286 and $7813 per person, respectively. Results are summarized in Table 4.

4. Discussion

The present study looks at the dominant factors driving cost for patients receiving upfront SRS without WBRT. As the upfront use of SRS represented 49% of the cost of care of brain metastasis management in this population, the decision for SRS vs WBRT represents a significant clinical decision. Using WBRT instead of SRS in these patients is estimated to decrease the total costs of brain metastasis management by 32%, though with increased toxicity. An analysis by Savitz et al suggested that the cost effectiveness of using upfront SRS could be improved by concentrating the population with patients who are more likely to benefit from upfront SRS, such as those who with longer life expectancy and those with longer latency to needing salvage treatment [16]. Several statistical models have been devised to help triage patients for upfront SRS vs WBRT based on the likelihood of DBF, though the efficacy and cost-effectiveness of their use remain to be validated in a prospective setting [17–19].

Higher brain metastasis velocity (BMV) was associated with a higher cost of management per unit time in the present study, but lower cumulative cost compared to the rest of the population. This is likely due to the combination of the cost of salvage procedures, but lower life expectancy of these patients. Cost of salvage SRS represented 21% of the estimated cost of treatment, and also the second largest contributor to cost for patients receiving upfront SRS. 30% of patients in the series received a second course of SRS. Brain metastasis velocity was proposed as a model to aid in the guidance of triaging salvage modality as a higher brain metastasis velocity is associated with both worsened survival and decreased time to requiring whole brain radiotherapy [13]. In a validation of the brain metastasis velocity model, patients whose disease kinetics had reached a brain metastasis velocity of greater than

13 metastases/year were generally considered better candidates for WBRT as salvage therapy [20]. Use of WBRT in the salvage setting was confirmed to be a factor associated with decreased cost of management in the present study. Moreover, the cost savings from using upfront WBRT was estimated to be higher in patients with higher BMV, than it would be by assigning patients with greater than 5 brain metastases to receive upfront WBRT. This suggests that future studies to identify patients at risk of having high BMV would be useful. It also suggests that salvaging patients with high BMV with WBRT is likely cost effective.

As medical care for oncology patients continues to evolve, it will be increasingly important to assess the cost of various interventions given the often limited life expectancy of cancer patients, the rising costs of cancer therapy, and the increasing prevalence of cancer in an aging population. Several steps must be taken in order to assess the value of therapies including the evaluations of efficacy and cost. The CCTG CE.7 study is looking at SRS vs WBRT for 5–15 brain metastases with survival, quality of life and patient reported outcome endpoints. The CE.7 trial also intends to look at economic endpoints, but as a study that spans both Canada and the US, it may be difficult to evaluate the value of SRS over two very different health care systems. Ultimately, with cognitive toxicities being the major toxicity with WBRT, it will be important to assess quality adjusted life years (QALY) with regards to cognition that is gained by using SRS instead of WBRT [16].

There are several limitations to the current study. As a retrospective review, it is subject to patient selection biases and therefore conclusions should be limited to hypothesis generation. Patients who find their way to a center that specializes in SRS already represent a self-selected population [21]. In addition, the costs estimated in this study are based on Medicare rates, which are generally lower than what are paid by private insurers. Although using individual hospital charges may provide a more precise value, there is a limitation as individual payer reimbursement typically varies by state and regionally. Thus, the decision to use a standardized national reimbursement rate was made in order to make this study the most applicable to the general population. As such, the current series may underestimate true costs of treatments. Moreover, the current study represents a simplification of the costs based on the most costly procedures associated with management of brain metastases, but does not take into account costs of chemotherapy, doctors' visits, or medication costs. Future trials, including the active Canadian Cancer Trials Group CE.7 Trial will attempt to prospectively evaluate the costs of brain metastasis management [22].

5. Conclusion

The cost of upfront SRS is the greatest contributor to cost of brain metastasis management when using upfront SRS. Higher BMV, progressive systemic disease and presence of symptoms are associated with increased cost of care.

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None.

Conflicts of interest

Authors report no financial disclosures or conflicts of interest.

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