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ORIGINAL RESEARCH

The role of systemic disease status in treatment outcomes for patients with newly diagnosed brain oligometastases and treated with stereotactic radiosurgery alone

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Abstract
Objective The role of adjuvant whole-brain radiation therapy in the treatment of oligometastatic brain disease with stereotactic radiosurgery (SRS) is not clearly defined. Many clinicians use a systemic disease status factor to determine whether SRS alone is sufficient; however, data is limited to support this approach.
Methods We conducted a retrospective review of patients with newly diagnosed brain metastases treated at our institution between 2005 and 2010 and identified 169 patients who were treated with SRS alone.
Results The overall median survival was 11.8 months (90 % CI [10.1, 14.7]) and the overall median time to brain recurrence was 7.1 months. We have observed that the primary disease status at the time of initial diagnosis is associated with worse overall survival (hazard ratio (HR) 1.7, $p=0.005$), after adjusting for recursive partitioning analysis (RPA) classification, number of lesions, performance status, and prior surgery. Primary disease status is also associated with higher likelihood of CNS disease recurrence (HR 1.8, $p=0.01$), after adjusting for pathology of primary disease, age, RPA classification, and number of lesions.
Conclusion These results might help clinicians with proper selection and counseling of patients regarding treatment modalities for patients with newly diagnosed brain metastases.

Keywords Stereotactic radiosurgery · Brain metastases · Systemic disease status · Treatment outcomes

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Introduction

Brain metastases are frequently a cause of morbidity and mortality in up to 40 % of patients with various solid tumors [1]. Surgery, stereotactic radiosurgery (SRS), and whole-brain radiation therapy (WBRT) are the treatment options, but the optimal combination of these therapeutic modalities is an area of debate. WBRT is estimated to be used in up to 80 % of patients diagnosed with brain metastases [2, 3]. It is a standard treatment modality for patients with multiple brain lesions that cannot be addressed with focal therapies, such as surgery or SRS. However, the adjuvant role of WBRT in the setting of oligometastatic disease treated with surgery or SRS is not as clearly defined. Three randomized controlled trials in patients with one to three metastatic brain lesions have shown improved CNS control with addition of WBRT to SRS, but not improvement in the overall survival [4–6]. The data on the WBRT toxicity is also mixed, although most patients and clinicians worry about the neurocognitive effect of WBRT. A recent survey of clinicians treating patients with brain metastases indicated that Karnofsky performance score (KPS), presence of mass effect, and systemic disease control were the most important factors affecting the decision to treat with SRS alone [7]. Although clinicians tend to use this factor in their decision making, there is not enough data in the literature to support this intuitive approach. We conducted this retrospective review to help determine if there is an association

between the primary disease status at the time of SRS treatment for the newly diagnosed brain metastases and the time to brain recurrence (TTBR).

Methods

Retrospective review

After obtaining approval from our institutional research ethics board, we conducted a retrospective review of patients treated with SRS for newly diagnosed brain oligometastases at our institution between July 2005 and January 2010. All patients provided informed consent at the time of treatment. The medical records were screened to include all patients treated in our department with SRS for newly diagnosed brain metastases. Among this cohort, we excluded patients who received upfront or adjuvant WBRT. Patients who underwent salvage WBRT for in-brain recurrences were included. Data extracted from the retrieved charts and entered into a database included patient age, sex, date of SRS, primary pathology, number of brain lesions, KPS, recursive partitioning analysis (RPA), date of initial oncologic diagnosis, date of diagnosis with brain metastases as defined by the first imaging study identifying the metastatic lesions, date of prior CNS imaging studies, chemotherapy agents and dates of use, location of brain lesions, date of surgery, if used, date of in-brain recurrence, and date of last known status. Local recurrence was defined as the progression of disease in the 50 % isodose coverage line from the SRS treatment. Generally, local recurrence criteria were increased size of an enhanced area on post-Gd T1-weighted MR images and enlarged tumor core on T2-weighted MR images, with confirmation by single photon emission computer tomography to rule out radionecrosis. In-brain recurrence was defined as the identification of new lesions in the brain on MRI imaging after the initial SRS treatment. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Treatment and follow-up

All patients underwent MRI brain evaluations, staging scans with PET or CT, elected not to receive WBRT and were treated by XKnife™ or CyberKnife® radiosurgery. In general, our department used the RTOG published guidelines for maximum tolerated doses of single fraction radiosurgery [8]. The mean dose in our cohort was 20 Gy (range 15–24 Gy), and 3 patients out of 169 had fractionated treatment due to proximity to critical structures. Patients were followed clinically as well as by regular imaging, with a recommended follow-up schedule of 1 month after SRS and every 3 months thereafter. Individuals presenting with interval clinical deterioration suggestive of in-brain disease progression had imaging to confirm the progression. An increase in the lesion size after SRS was carefully evaluated by additional imaging studies to distinguish tumor progression from radionecrosis. If localized progression was associated with worsening neurological symptoms, surgery was offered as a salvage therapy. At the time of confirmed in-brain failure, patients were treated at the discretion of treating physicians, with such treatment modalities as additional SRS, surgery, WBRT, or comfort measures.

Statistical analysis

The date of biopsy or surgical resection providing a definitive histological diagnosis was used as the date of initial diagnosis. The date of imaging study revealing brain lesions consistent radiographically and clinically with the diagnosis of brain metastases was used as the date of diagnosis with brain metastases. Time to brain recurrence was defined as the interval between the initial SRS and the date of imaging study revealing new lesions in the brain or radiographic progression of the treated lesion. Overall survival was defined as the interval between the initial SRS to date of death. Descriptive statistics were used to characterize patients at study entry. The method of Kaplan and Meier was used to describe TTBR and overall survival. Cox proportional hazards regression model and Collett's model selection approach were used to evaluate the effect of primary disease status on TTBR and overall survival (OS) with adjustment for other important covariates.

Results

Patient characteristics

Between July 2005 and January 2010, we identified 169 patients who received SRS for the newly diagnosed brain metastases at our institution. The patient characteristics are summarized in Table 1. Among the 169 patients, the median age at SRS treatment was 61 (range 28–92). Seventy-one patients (42 %) had controlled primary disease. Half of the patients (51 %) had melanoma/renal cancer as primary disease. Sixty-one patients underwent prior surgery. The majority of the patients had KPS greater than 70 and were classified as RPA 1 or 2.

Overall survival

Survival time is defined as the time from SRS treatment until death or date last known alive. As of this analysis, 120 of the 169 patients have died. Median follow-up among patients still alive was 16.2 months. Table 2 shows median survival by different variable categories and the hazard ratio of each

Table 1 Patient characteristics

	Total	
	N	Percentage
Age at SRS treatment		
≤60	83	49
>60	86	51
Median (range)	61 (28–92)	
Primary disease status		
Controlled disease	71	42
Progressive disease	98	58
Primary pathology		
Melanoma	49	29
Renal	38	22
Others	82	49
Number of brain lesions		
1	103	61
>1	66	39
Presence of other sites		
No	46	27
Yes	123	73
Prior surgery		
No	108	64
Yes	61	36
KPS		
>70	112	66
≤70	57	34
RPA classification		
1 and 2	147	87
3	22	13

RPA recursive partitioning analysis

Table 2 OS by patient characteristics

	Number	Median OS (month)	*p* value[a]	Hazard ratio[b]	*p* value[c]
Overall	169	11.8	–	–	–
Age					
≤60	83	13.5	0.53	1.0	0.53
>60	86	10.6	–	1.1	–
Primary disease status					
Controlled disease	71	21.7	0.01	1.0	0.01
Progressive disease	98	10.3	–	1.6	–
Primary pathology					
Melanoma	49	11.3	0.85	0.9	0.85
Renal	38	10.6	–	1.0	–
Others	82	13.9	–	1.0	–
Number of brain lesions					
1	103	14.2	0.02	1.0	0.02
>1	66	10.3	–	1.6	–
Presence of other sites					
No	46	21.7	0.05	1.0	0.04
Yes	123	10.3	–	1.5	–
Prior surgery					
No	108	10.3	0.02	1.0	0.02
Yes	61	16.2	–	0.6	–
KPS					
>70	112	15.1	0.0001	1.0	0.0003
≤70	57	5.5	–	2.0	–
RPA classification					
1 and 2	147	13.9	0.0001	1.0	0.0009
3	22	3.2	–	2.6	–

[a] *p* value based on log-rank test

[b] 1.0 denotes reference category

[c] *p* value based on the likelihood ratio test

category calculated using Cox proportional hazards regression model for all covariates. The category with the longest median survival was used as a reference. The overall median survival was 11.8 months (90 % CI [10.1, 14.7]).

Time to brain recurrence

TTBR is defined as the time from SRS treatment to brain recurrence or the date of last clean MRI. Forty patients who died of systemic disease progression without documented brain recurrence were censored at the date of last clean MRI. Median follow-up duration (from SRS treatment to the date of last clean MRI) and median survival for these patients were 2.8 months (range 0.7–34.5 months) and 5.9 months (range 0.8–36.4 months), respectively. Twelve patients without follow-up information were censored at the date of SRS treatment (TTBR=0) and were excluded from the analysis of TTBR. Table 3 shows median TTBR by different variable categories and the hazard ratio of each category calculated using Cox proportional hazards regression model for all covariates. The category with the longest median TTBR of each covariate was used as a reference. The overall median TTBR was 7.1 months.

Association between primary disease status and time to brain recurrence and death

To evaluate the association between OS and TTBR with primary disease status, Cox proportional hazards regression models were fitted with adjustment for covariates in Tables 2 and 3, respectively. Model selection approach was used in four steps relying first on univariate. Variables with $p<0.2$ were considered for the next steps of model selection.

Table 3 TTBR by patient characteristics

	Number[a]	Median TTBR (month)	*p* value[b]	Hazard ratio[c]	*p* value[d]
Overall	157	7.1	–	–	–
Age					
≤60	79	5.5	0.11	1.4	0.11
>60	78	7.8	–	1.0	–
Primary disease status					
Controlled disease	69	7.8	0.11	1.0	0.11
Progressive disease	88	5.2	–	1.4	–
Primary pathology					
Melanoma	46	4.4	0.13	1.7	0.14
Renal	35	9.9	–	1.0	–
Others	76	7.8	–	1.2	–
Number of brain lesions					
1	98	7.8	0.06	1.0	0.06
>1	59	5.5	–	1.5	–
Presence of other sites					
No	44	7.8	0.45	1.0	0.45
Yes	113	5.5	–	1.2	–
Prior surgery					
No	98	6.6	0.58	1.1	0.58
Yes	59	7.1	–	1.0	–
KPS					
>70	110	6.6	0.42	0.8	0.42
≤70	47	7.1	–	1.0	–
RPA classification					
1 and 2	139	7.1	0.20	1.0	0.23
3	18	3.2	–	1.5	–

[a] Twelve patients without follow-up information were not included

[b] *p* value based on log-rank test

[c] 1.0 denotes reference category

[d] *p* value based on the likelihood ratio test

Backward elimination, forward selection, and stepwise selection (with $p < 0.1$) were then performed. Tables 4 and 5 show the results of the model selection for the association of primary disease status with overall survival and TTBR, respectively.

Discussion

An area of controversy in the treatment of patients with metastatic brain tumors is whether or not the treatment with SRS alone of visible lesions on brain MRI is sufficient in the absence of upfront WBRT. Three prospective randomized trials have established SRS alone as one of the standard treatment options for limited metastatic disease at the initial presentation. Aoyama et al. evaluated 132 patients with one to four brain lesions [4]. Addition of WBRT did not improve the overall survival, which was 8 months in the SRS alone group, but improved a 12-month in-brain control from 24 to 53 %. Chang et al. evaluated 58 patients with one to three brain lesions [5]. Addition of WBRT improved a 12-month in-brain control from 27 to 73 % but resulted in worse overall survival and neurocognitive function at 4 months, resulting in early termination of the trial. The EORTC 22952-26001 trial

Table 4 Summary of Cox proportional hazards regression model for OS ($N = 169$)

Variables	Hazard ratio[a]	*p* value
Primary disease status		
Controlled disease	1.0	0.005
Progressive disease	1.7	
Number of brain lesions		
1	1.0	0.02
>1	1.6	
Prior surgery		
No	1.0	0.03
Yes	0.6	
KPS		
>70	1.0	0.006
≤70	1.9	
RPA classification		
Good/intermediate	1.0	0.03
Poor	2.0	

[a] 1.0 denotes reference category

Table 5 Summary of Cox proportional hazards regression model for brain recurrence ($N = 157$)

Variables	Hazard ratio[a]	*p* value
Primary disease status		
Controlled disease	1.0	0.01
Progressive disease	1.8	
Age		
≤60	1.6	0.04
>60	1.0	
Primary pathology		
Melanoma	2.1	0.06
Renal	1.0	
Others	1.6	
Number of brain lesions		
1	1.0	0.01
>1	1.8	
RPA classification		
Good/intermediate	1.0	0.03
Poor	2.1	

[a] 1.0 denotes reference category

had an impressive 52 % in-brain control at 2 years in the SRS alone arm, which was further improved with addition of WBRT, but the medial survival of 10.9 months was unchanged [6]. Better characterization of patients based on clinical and biological predictors of overall survival and in-brain failure might help clinicians to select patients better suited for SRS alone vs addition of WBRT and as a result improve the overall outcome of the management of brain metastases. The goal of our study was to evaluate some of these clinical characteristics.

Our study evaluated consecutive patients treated with SRS alone at our institution. It had a higher proportion of patients with metastatic renal cell cancer and melanoma, due to the referral pattern. The median survival of 11.8 months was not inferior to the survival rates from the published randomized trials. Retrospective studies with various selection criteria of patients treated with SRS alone reported median survival times between 6.7 and 16 months [9–14]. Our 12-month in-brain control rate of 30 % was similar to the SRS alone arms of the two of the three randomized trials. Literature review indicates a range of 26 to 51 % of in-brain control at 1 year [15, 16], likely due to patient characteristics and follow-up protocols.

We have defined the brain recurrence in this study as the identification of new lesions in the brain on MRI imaging after the initial SRS treatment. Out of 169 patients, only 5 patients had radiological progression of the treated lesion, and 4 of these patients underwent craniotomy and resection of the metastatic lesion. In all four cases, there was only evidence of necrosis on pathological review with no viable tumor. One patient elected comfort care only. These patients were analyzed as having no CNS disease progression in our study. Metastatic brain lesion ablation with initial SRS is very effective, and the goal of this study is to determine which clinical factors are associated with the development of new lesions, to determine whether these factors might be important during the determination of whether adjuvant WBRT would be warranted.

Among various clinical characteristics, having more than one brain lesion was associated with worse OS (hazard ratio (HR) 1.6, $p=0.02$) and CNS disease progression (HR 1.8, $p=0.01$), comparing to a single brain metastasis, after adjusting for other important factors. RPA class 3 patients had a worse OS (HR 2.0, $p=0.03$) and CNS disease progression (HR 2.1, $p=0.03$) after adjusting for other factors. Of interest, primary pathology was associated only with CNS disease progression, but not the OS, suggesting that patients with metastatic melanoma have a higher tendency to recur in the brain in the course of their disease. We are intrigued by the finding of association of younger age (≤60) with increased risk for brain recurrence, but not the overall survival. Perhaps a more aggressive systemic therapy in younger patients leads to improved systemic control, but poor penetration of systemic agents into CNS makes the in-brain progression more clinically evident.

We have observed that the progressive primary disease status at the time of initial diagnosis is associated both with worse overall survival (HR 1.7, $p=0.005$) and higher likelihood of CNS disease recurrence (HR 1.8, $p=0.01$), after adjusting for important clinical factors. This would suggest that patients with no evidence of systemic disease progression clinically and/or radiologically are less likely to progress in the CNS and might derive the most benefit from WBRT omission, given their longevity. This argument may even be stronger for patients with all three clinical characteristics—RPA class I or II, a single brain lesion, and controlled primary disease, all of which are independently associated with better overall survival and better CNS disease control.

Conclusion

Our results suggest that primary disease status is associated with both overall survival and CNS disease progression in patients with newly diagnosed brain metastases. If validated in prospective studies, this finding could help clinicians select the best treatment modality for their patients. Further refinement of clinical factors with incorporation of biological markers and rigorous validation in prospective trials might ultimately lead to a greater extent of personalization of brain metastases management and yield better overall healthcare results.

Conflict of interest Timur Mitin, Yu-Hui Chen, Paul J. Catalano, Scott R Floyd, Ekkehard M. Kasper, and Anand Mahadevan declare that they have no conflict of interest.

Ethical standards This retrospective study was conducted with IRB approval. This article does not contain any studies with human or animal subjects performed by any of the authors.

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