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ORIGINAL RESEARCH

Stereotactic Radiosurgery of Brain Metastasis in Patients with a Poor Prognosis: Effective or Overtreatment?

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Purpose: Stereotactic radiosurgery (SRS) of brain metastasis in patients with a poor prognosis remains controversial. Here, we compared results of SRS alone to whole brain radiotherapy (WBRT) in poor-prognosis patients and defined the most important unfavorable prognostic factors related to early death after SRS alone.

Patients and Methods: In this retrospective analysis of prospective SRS data, 180 patients with brain metastases not previously treated with WBRT were analyzed. Results of SRS were compared to WBRT by propensity score matching in patients with a poor prognosis defined by graded prognostic assessment (GPA) <2. Further, SRS patients were divided into training (n=82) and validation (n=48) cohorts. Overall survival (OS) and the risk of early death were defined by univariable and multivariable analyses.

Results: Median survival of the WBRT and SRS cohorts was 86 days (IQR: 38–172 days) and 201 days (IQR: 86-not reached), respectively (p<0.0001). OS in patients with GPA<2 was significantly longer in the SRS vs WBRT group (123 vs 58 days; p=0.008). Survival was longer in the SRS group in a propensity score matched analysis. In multivariable analysis, GPA (OR: 0.44, 95%CI: 0.21–0.95; p=0.001), extensive extracranial disease (OR: 0.13, 95% CI: 0.02–0.66; p=0.013), and serious neurological deficits (OR: 0.13, 95%CI: 0.04–0.45; p=0.001) were associated with early death. If one factor was favorable, 73% (training) and 92% (validation) of patients survived three months. Patients with GPA <2 presenting with serious neurological deficits and extensive extracranial disease had a low expected benefit due to the highest risk of death within three months (AUC: 0.822 training; 0.932 validation).

Conclusion: SRS is a viable treatment option for patients with a poor prognosis defined as GPA <2. Good neurological status, extracranial oligometastatic disease, or GPA ≥2 should be present to justify SRS in patients with brain metastases.

Keywords: brain, neoplasm, metastasis, radiosurgery, radiotherapy, risk factors

Plain Language Summary

The value of stereotactic radiosurgery (SRS) alone in poor-prognosis patients with brain metastases is not well defined. Here we report a survival benefit of treating patients with SRS alone compared to whole brain radiotherapy in patients with low graded prognostic assessment (GPA) scores. The value of SRS treatment was limited when GPA, neurological status, and extensive extracranial disease were consistently unfavorable, with the risk of death increasing to >90%. The risk was significantly reduced when at least one of these factors was favorable. Therefore, extracranial oligometastatic disease, good neurological status, or GPA ≥2 should be present to justify SRS in patients with brain metastases.

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Introduction

Recent studies have now shown that whole brain radiotherapy (WBRT) compromise quality of life without survival benefits in patients with brain metastases (BM) and a poor prognosis.[1–5] The most commonly used diagnosis- or molecular-specific graded prognostic assessment (GPA) is a practical and simple tool for assessing prognosis in patients with BM according to risk group.[6–8] The QUARTZ trial reported that WBRT did not improve survival in patients aged 60 or older with GPA scores lower then 2.5, poor neurological status, or uncontrolled primary tumors.[4] Other unfavorable prognostic factors for patients with BM are a lack of effective systemic therapies, unfavorable histopathological or molecular types, and the presence of a tumor mass effect.[9,10] While SRS is standard of care for patients with favorable prognostic factors,[10] the benefit of SRS in patients with unfavorable prognostic factors has not been well studied.

Therefore, how to properly select patients that might benefit from SRS with unfavorable prognostic factors and whether SRS may improve the survival of patients with a poor prognosis are unknown. The aim of this study was to define the most important unfavorable factors associated with a risk of early death when treated with SRS and to verify if SRS alone in patients with unfavorable prognostic factors can extend survival in comparison to WBRT.

Patients and Methods

Patients, Inclusion and Exclusion Criteria, and Risk Factors

One hundred and eighty patients with BM and adverse prognostic factors not previously treated with WBRT were studied. All patients were treated with radiation therapy at the Prof. Franciszek Lukaszczyk Memorial Oncology Center, Bydgoszcz, Poland. Inclusion criteria were BM treatable with SRS alone; with or without previous surgical resections; presence of at least one adverse clinical factor; neurological status that allowed informed consent; and histopathological confirmation of the primary cancer. Exclusion criteria were prior WBRT; classical leptomeningeal disease; small-cell lung carcinoma (SCLC) diagnosis; large BM without extracranial disease; lost to follow-up; or incomplete medical records. After BM were controlled, patients received further systemic therapy or best supportive care according to decisions made by the medical oncologists.

Patients were divided into three cohorts: (i) a training cohort (n=82) treated with SRS alone between March 2018 and March 2019; (ii) a validation cohort (n=48) treated with SRS alone between April 2019 and August 2019; and (iii) a comparison cohort (n=50) treated with WBRT alone before March 2018, when SRS for patients with adverse risk features was implemented in our department.

The study was performed in accordance with the principles of the Declaration of Helsinki. All SRS data were retrieved from a prospective registry of patients treated with SRS. The local ethics committee approved the collection and analysis of registry data (KB 720/2018). Data from patients treated with WBRT were retrospectively assessed. Overall survival (OS) was defined as date from SRS or WBRT to death or last follow-up. Follow-up with MRI was routinely scheduled every three months after treatment. At the time of intracranial recurrence, SRS was considered depending on the number of new lesions, systemic disease options, and overall performance status. Patients who were alive at the time of data collection were censored.

The training cohort was analyzed focusing on symptomatic relief during two to three visits after SRS (median eight months) based on their medical history. Major neurological symptoms in each patient at the time of treatment were listed and defined as improvement, stabilization, or deterioration at time of follow-up visits.

Unfavorable prognostic factors were defined according to extracranial disease status, molecular results, age, line of systemic therapy, mass effect, and neurological symptoms (Table 1). Factors were summed, ie, 1 when one factor was favorable and 5 when five factors were favorable. Additionally, the number of brain metastases, intracranial disease volume, surgical resection, dose, fractions, histopathology, GPA score, and type of systemic treatment were analyzed.

Comparison of Effectiveness of SRS vs WBRT

To verify whether SRS in patients with 1–12 BM and unfavorable prognostic factors was clinically effective, we compared SRS-treated groups with 50 consecutive patients treated with WBRT alone. WBRT was standard of care for the treatment of multiple BM with unfavorable prognostic factors in our institution prior to March 2018. Inclusion criteria for WBRT patients were available data to calculate GPA scores and histopathological and survival data. Comparative analyses

Table 1 Definition of Unfavorable Prognostic Factors for SRS

Prognostic Factor	1 Point (Favorable)	0 Points (Unfavorable)
Extracranial disease defined on CT±USG or PET	Patients with primary disease limited to primary site no matter of size or up to three oligometastatic tumors (including lymph node metastases) and sum of maximum diameters of 3 cm	>3 extracranial metastases and/or sum of diameters >3 cm
Chemotherapy	First line of systemic therapy after SRS	2nd or more lines of chemotherapy after SRS
Biological profile	$ER^+PR^+HER2^-$ breast cancer, $EGFR^+$, ALK^- lung cancer, $BRAF^+$ melanoma	Others or unknown
Neurological status	Asymptomatic Oligosymptomatic or glucocorticoids below 4 mg, in special cases when glucocorticoids >4 mg but prophylactic	Severe neurological symptoms or therapeutic daily doses of glucocorticoids 4 mg and above
Mass effect	No mass effect on the MRI for SRS planning	Mass effect on MRI
Age	Below 65	Equal and above 65

Abbreviations: *ALK*, anaplastic lymphoma kinase; CT, computed tomography; *EGFR*, epidermal growth factor receptor; ER, estrogen receptor; *HER2*, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; PET, positron-emission tomography; PR, progesterone receptor; SRS, stereotactic radiosurgery; USG, ultrasound guided.

(SRS vs WBRT) included all primary sites and restricted to NSCLC but equivalent age, number of BM, Karnofsky Performance Status (KPS), molecular results, and extracranial disease presented as GPA scores, as shown in Table 2.

Treatment

SRS treatment planning was based on fusion of CT simulations with axial postgadolinium T1-MPRAGE MRI with 1 mm slice thickness performed no more than 7 to 10 days before treatment. The planning target volume (PTV) was defined as 1 mm margin to gross tumor volume based on the enhancing lesion on the T1 postgadolinium treatment images.

All patients were treated with the frameless image guidance system (ExacTrac, Brainlab, Germany, Munich) for SRS using a TrueBeam linear accelerator (Varian, Palo Alto, CA, USA) equipped with a 2.5 mm multileaf collimator and a six degrees of freedom robotic couch top. Patients were immobilized with a thermoplastic mask. Either volumetric modulated arc therapy (for single lesions) or single isocenter dynamic conformal arc therapy (for multiple metastases) was performed. The threshold for patient repositioning based on the ExacTrac was 0.5 mm and 1°. Large lesions >2–3 cm were treated with three to five fractions on consecutive days. Forty-three patients in the training cohort and 20 patients in the validation cohort had 2–10 lesions.

WBRT consisted of 5–10 fractions to a dose of 20–30 Gy using opposed lateral fields with a median dose of 20 Gy administered in five fractions.

Statistical Analysis

Statistical analyses were performed using Statistica 13 (TIBCO Software Inc.) and PQStat (PQStat Software). Categorical variables are expressed as percentages. Continuous data were checked for normality with Shapiro–Wilk's test and are presented as means and SDs. Variables measured on an ordinal scale are presented as the medians with IQRs.

Multiple factors were analyzed to find the relationship with early death risk. For univariable analyses, non-normally distributed continuous data and ordinal variables

Table 2 GPA Score According to Treatment Modality in Whole Study Group and Restricted to BM from NSCLC

	n	GPA Median	GPA Minimum	GPA Maximum	*p*-value
All tumor types SRS	82	2	1	4	0.082
All tumor types WBRT	50	1.5	0	3.5	
NSCLC SRS	46	2	1	4	0.068
NSCLC WBRT	26	2	0.5	3.5	

Abbreviations: GPA, Graded Prognostic Assessment; NSCLC, non-small-cell lung cancer; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

Table 3 Clinicopathological Characteristics of the Cohorts

	SRS (n=82)	WBRT (n=50)	Validation Group (n=48)
Patient-specific variables			
Age	62 (29–82)	59.5 (34–77)	64 (34–82)
Zubrod scale	1 (0–3)	2 (1–4)	1 (1–3)
Number of tumors	2 (1–12)	2 (1–12)	2 (1–8)
Primary site Lung			
Adenocarcinoma	31	11	24
Squamous	15	9	7
Breast	11	6	4
Gastrointestinal	9	7	2
Genitourinary	8	8	4
Melanoma	5	3	1
Other	3	6	6
Course-specific variables			
Dose	18 (10–24)	20	18 (16–24)
Follow-up variables			
3-month survival	64 (78%)	23 (46%)	36 (75%)
Median survival (days)	201	86	128
Shortest follow-up	5 months (censored)	Observation completed	4 months (censored)
Follow-up (median)	9.5 months (censored)	Observation completed	5 months (censored)

Abbreviations: SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

were compared with the Mann–Whitney *U*-test. Categorical variables were analyzed with the chi-squared test, Fisher's exact test, or the Fisher–Freeman–Halton test, as applicable. ORs with 95%CI were calculated for significant associations.

Stepwise forward logistic regression was performed using variables associated with three-month survival, with ORs and 95%CIs estimated for statistically significant variables. The Wald test was used to test the overall contribution of variables to the model. Receiver operating characteristics (ROC) analysis was used to determine the optimal cutoff for the most important factors determining risk of early death. Sensitivity, specificity, and the area under the ROC curve (AUC) were calculated.

Kaplan–Meier curves were plotted for survival analysis. The survival function percentiles and the probability of three-month survival were calculated. Survival curves were compared using the log rank test and Gehan's Wilcoxon test. Those analyses were performed to compare the efficacy of WBRT and SRS. A *p*-value less than 0.05 was considered statistically significant.

Propensity score matching method was used to select 50 patients from the SRS group so that they differed as little as possible from patients in the WBRT group. The propensity score was calculated using a logistic regression model built based on age, Zubrod's scale, GPA scale, and C34 diagnosis. The closest neighbor method was used, which involved selecting for each person in the WBRT group the person from the SRS group with the closest propensity score value. There were no statistically significant differences in age (p=0.557, Mann–Whitney test), GPA scale (p=0.366, Mann–Whitney test), and diagnosis C34 (p=0.548, chi-squared test) between the WBRT group and the selected SRS group. The median Zubrod score in the SRS and WBRT group was 2 (p=0.017, Mann–Whitney test).

Results

General Characteristics and OS: Training Cohort

The clinicopathological characteristics are presented in Table 3. The median follow-up for the SRS training cohort was 9.5 months (range: 148–536 days), median survival was 6.7 months, and 48% of patients were still alive at the time of analysis. Lung adenocarcinoma was the most common metastasis. Fifty-seven percent of patients were treatment-naïve at the time of BM diagnosis. 44 patients

Table 4 Overall Survival Analysis with Respect to Risk Factors in the Training Cohort

	3 Months Survival YES		3 Months Survival NO		*p*	OR	95%CI
GPA	<2 n (%)	≥2 n (%)	<2 n (%)	≥2 n (%)			
	18 (28)	46 (72)	12 (67)	6 (33)	0.003	5.11	1.67–15.69
<3 extracranial metastases and sum of diameters <3 cm	No n (%)	Yes n (%)	No n (%)	Yes n (%)			
	35 (55)	29 (45)	16 (89)	2 (11)	0.008	6.60	1.41–31.25
First line of systemic therapy ("no" if next line)	No n (%)	Yes n (%)	No n (%)	Yes n (%)			
	41 (64)	23 (36)	12 (67)	6 (33)	0.838	–	–
Known beneficial biological status	No n (%)	Yes n (%)	No n (%)	Yes n (%)			
	57 (89)	7 (11)	15 (83)	3 (17)	0.683	–	–
Good neurological status	No n (%)	Yes n (%)	No n (%)	Yes n (%)			
	18 (28)	46 (72)	13 (72)	5 (28)	0.001	6.60	2.07–21.34
Mass effect on MRI	Yes n (%)	No n (%)	Yes n (%)	No n (%)			
	9 (14)	55 (86)	2 (11)	16 (89)	<1	–	–
Age (≥65)	Yes n (%)	No n (%)	Yes n (%)	No n (%)			
	28 (44)	36 (56)	8 (44)	10 (56)	0.958		
Sum of unfavorable factors >3	Yes n (%)	No n (%)	Yes n (%)	No n (%)			
	23 (36)	41 (64)	0 (0)	18 (100)	0.003	21.00	1.21–364.00
Number of targets >1	Yes n (%)	No n (%)	Yes n (%)	No n (%)			
	34 (53)	30 (47)	5 (28)	13 (72)	0.057	–	–
Total volume >10 cm^3	Yes n (%)	No n (%)	Yes n (%)	No n (%)			
	39 (62)	24 (38)	10 (56)	8 (44)	0.627	–	–

Abbreviations: GPA, Graded Prognostic Assessment; MRI, magnetic resonance imaging.

had available molecular results such as *EGFR, BRAF*, or *KRAS* mutation status, *ALK* rearrangements, or PD-L1 expression. Anti-PD-1 immunotherapy was administered to seven patients after SRS and targeted therapy (gefitinib, erlotinib, or dabrafenib and trametinib) to four patients. Eighteen patients (22%) treated with SRS alone died within three months, and 11 patients (17%) had intracranial progression during follow-up.

Survival was significantly different according to neurological deficits, sum of unfavorable factors >3, and number of BM (Table 4). The three-month survival probability for patients with serious neurological symptoms was >50%. Other factors related to longer survival included number of metastases (single vs >1 brain metastasis) and sum of unfavorable factors (>3 vs less).

SRS vs WBRT

In the WBRT group, 54% (n=27) of patients died within three months; three patients had a longer survival than the longest observation in the SRS group. In log-rank survival comparisons, survival was limited to the longest observation time in the SRS group. 46%Forty-six percent of patients in the WBRT group had a GPA of ≥2. Age (61 SRS; 59 WBRT) and GPA (<2 and ≥2) were similar in the SRS and WBRT groups (χ^2 p=0.082). In the low GPA group (<2), the median survival was 58 days for WBRT (IQR: days after treatment) and 128 days for SRS (p=0.007; HR=2.3, 95%CI: 1.2–4.2; Figure 1A). The median survival of the WBRT and SRS groups was 86 days (IQR: 38–172) and 201 days, respectively (p<0.0001; HR=2.57, 95%CI: 1.7–3.87; Figure 1B).

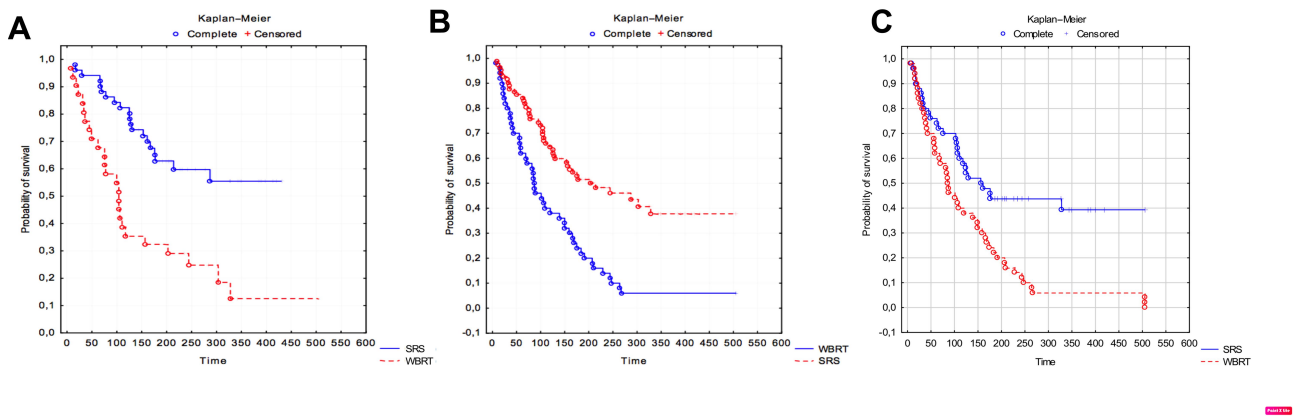

Figure 1 (**A**) Kaplan–Meier survival curves for all patients treated with WBRT or SRS alone. (**B**) Kaplan–Meier survival curves for patients with GPA <2 treated with WBRT or SRS alone. (**C**) Kaplan–Meier survival curves for patients with NSCLC diagnosis treated with WBRT or SRS alone matched according to unfavorable factors (propensity score matching).

Overall survival after SRS and WBRT also differed when patients were adjusted according primary tumors (NSCLC), age, GPA, and Zubrod scale by propensity score matching 50 patients treated with WBRT with 50 similar patients treated with SRS. There were no significant differences in age and GPA but there were significant differences in survival (log-rank p=0.00058, Gehana– Wilcoxon test p=0.01744; Figure 1C).

Risk of Early Death: Training Cohort Treated with SRS

In univariable analysis, a GPA score of <2 was related to risk of early death (χ^2 p=0.003; OR: 5.1, 95%CI: 1.7–15.7). Nevertheless, 18/30 (60%) patients with a GPA score ≤1.5 survived for over three months, with the longest survivor still alive more than 10 months after SRS at analysis. The median volume of intracranial disease in low GPA patients was 6.8 cm^3 (mean 12 cm^3) treated with a median dose of 18 Gy, with an average of three lesions per patient.

In terms of other factors affecting three-month survival, extensive extracranial disease or serious neurological deficits were also related to early death (χ^2 p=0.008; OR: 6.6, 95%CI: 1.4–31.2 and χ^2 p=0.001; OR: 6.6, 95%CI: 2.1–21.34, respectively).

A GPA score of <2 in addition to serious neurological deficits and extensive extracranial disease were related to the greatest risk of early death (χ^2 p=0.001; OR: 9.44: 95% CI: 2.564–34.752). Number or volume of BM, age, line of systemic therapy, unfavorable biological profile, or tumor mass effect were not related to risk of early death.

In multivariable logistic regression, two independent logistic models were specified: in the first GPA (p=0.001; OR: 0.44, 95%CI: 0.21–0.95) and in the second extensive extracranial disease (p=0.013; OR: 0.13, 95%CI: 0.02–0.66) and serious neurological deficits (p=0.001; OR: 0.13, 95%

Table 5 Multivariable Analysis of Factors Associated with Risk of Early Death

Model	*p*-value of Model	OR of Model	Parameter (*p*-value Wald Chi-squared)	OR	95%CI for OR	Classification
I	0.025	–	GPA (p=0.034)	0.443	0.206–0.952	Percent correctly classified: 78 Sensitivity: 0% Specificity: 100%
II	<0.001	14	Extensive extracranial disease (p=0.013) Serious neurological deficits (p=0.001)	0.125 0.130	0.024–0.661 0.037–0.459	Percent correctly classified: 83 Sensitivity: 66.67% Specificity: 87.50%

Abbreviation: GPA, Graded Prognostic Assessment.

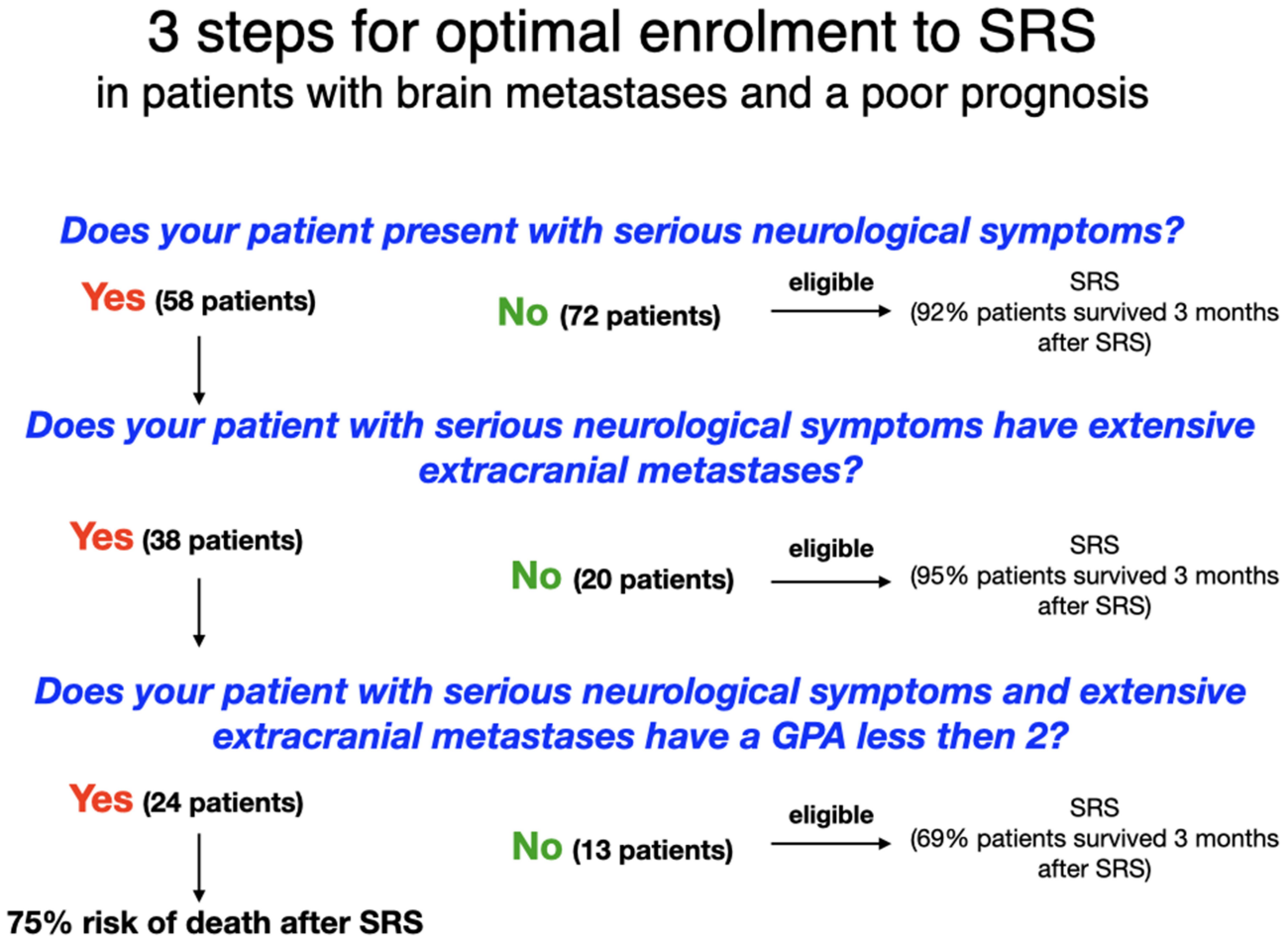

Figure 2 Diagram presenting three steps for optimal enrollment to SRS in patients with brain metastases and unfavorable factors.

CI: 0.03–0.45) were associated with risk of early death (Table 5). The GPA model correctly classified 78% of cases (specificity 100%, sensitivity 0%) and the second model 83% of cases. The OR of the model was 14, ie, 14-times more cases were classified correctly than incorrectly, with a sensitivity of 67.0% and a specificity of 87.5%. The AUC was 0.675 for the GPA model and 0.802 for the second model (p=0.024 and p<0.001, respectively).

Table 6 Neurological Deteriorations After SRS in the Training Cohort

Symptom	Improvement	Deterioration	Stable
Aphasia	2	0	3
Consciousness	1	2	0
Headache	6	1	13
Imbalance	11	4	5
Numbness	5	6	3
Paresis	6	8	5
Visual field	0	1	6

ROC Analysis

A greater risk of death within three months was predicted by a GPA <2 with a sensitivity and specificity of 71.9% and 66.7%, respectively (AUC: 0.675; p=0.023). A GPA <2 with serious neurological deficits and extensive extracranial disease was associated with a high risk of death within three months, with a sensitivity of 44.4% and specificity of 92.2% (AUC: 0.822).

Risk of Early Death: Validation Cohort Treated with SRS

Early death occurred in 12/48 (25%) of validation cohort patients. In univariable analysis, a GPA score <2 was associated with risk of early death (χ^2 p=0.003; OR: 38.5, 95%CI: 4.30–345.13). GPA score <2 together with serious neurological deficits and extensive extracranial disease were associated with the highest risk of early death (χ^2 p=0.001; OR: 385, 95%CI: 22.179–6683.2) and was 105 times higher than in patients with a GPA <2.

GPA, serious neurological deficits, and extensive extracranial disease best selected patients ineligible for SRS with an AUC of 0.932 (sensitivity 90.9%, specificity 97.2%); only 9% of patients with these three unfavorable factors survived 3 months. In the case of low GPA, 42% of patients survived more than three months (91.7% sensitivity, 77.8% specificity; AUC: 0.925). If one of GPA, neurological status, or extension of extracranial disease was favorable, 73% (16/22) of the training cohort and 100% (13/13) of the validation cohort survived three months.

In all studied groups, 24 patients presented with serious neurological deficits with extensive extracranial disease and GPA <2. The probability of three months survival after SRS in this case was only 25%. SRS of the remaining 105 patients resulted 89% probability of three months survival. Based on our experience diagram supporting optimal enrollment to SRS is presented in Figure 2.

Risk of Neurological Deterioration After SRS: Training Cohort

Twenty-four patients (29%) improved and 27 (33%) were neurologically stable after treatment. In 15 patients (18%), neurological status decreased. In 16 patients, adequate data were not available to assess neurological status. Improvements were mainly noted for imbalance, headache, and paresis (Table 6).

Discussion

SRS of patients with low GPA scores remains controversial. Relatively new SRS techniques such as volumetric modulated arc therapy (VMAT) and single isocenter dynamic conformal arc (DCA) therapy allow multiple brain metastases to be treated in minutes. This prompted us to investigate the benefits of SRS in patients with unfavorable prognostic factors. Moreover, we defined patients with a very high risk of death within three months after SRS in whom management must be carefully considered to avoid possible overtreatment.

WBRT does not appear to provide a survival benefit compared to supportive care in patients with GPA scores lower then 2.5, ie, at least 50% of patients encountered in everyday clinical practice.[4] We found a survival benefit in treating patients with SRS alone when compared to WBRT. This benefit was also apparent in a propensity score matching analysis and when restricted to low GPA. The combination of WBRT and SRS is no longer recommended due to an increased risk of cognitive deterioration without survival benefit.[11] Cognitive deterioration may occur four to six weeks post therapy so may be important even in patients with low GPAs and a prognosis of a few months.[12,13] A recent expert opinion study infrequently recommended WBRT for patients with unfavorable prognostic factors. Even in patients with adverse prognostic features raising the prospect of an increased risk of futile treatment near the end of life, SRS/SFRT was more often recommended than optimal supportive care unless a patient decided to forego active treatment.[14] Our data adds value to these recommendations because, to our best knowledge, there is a lack of data from prospective trials evaluating WBRT vs SRS in patients with low GPA. In a retrospective analysis of an elderly population, Chen et al found that median overall survival (OS) from BM diagnosis in patients treated with WBRT (n=82) vs SRS (n=37) was 4.3 vs 14.4 months, respectively (p<0.0001, HR: 3.7, 95%CI: 1.9–7.0).[13] While WBRT patients had a worse performance status, more intracranial metastases, and uncontrolled extracranial disease, the main finding was increased rates of treatment-related toxicity compared to patients treated with SRS.

Overall, SRS was associated with a 22–25% risk of early death. This is similar to a previously published series of surgical patients (23% risk of early death)[15] and slightly higher than a recent retrospective study of SRS (19–23% risk),[16,17] probably due to the inclusion of more high-risk patients in our series. Bennett et al[16] reported an increase in risk of death within three months with additional factors from 5% in the most favorable group to 39% in the unfavorable group.

Our data are strengthened by the simplicity and accuracy of defining patients at risk of death in the three months after SRS. We divided patients according to GPA, neurological status, and extensive extracranial disease, all of which are easily clinically defined. When all three factors were unfavorable, the risk of death increased to >90%, and the risk was significantly reduced when at least one of these factors was favorable (100% survived three months in validation cohort). Other nomograms have been proposed and introduced. For example, the accuracy of prediction of early death (<3 months) in NSCLC patients with up to four BM[18] outperformed other nomograms such as the Golden grading system (GGS), disease-specific graded prognostic assessment (DS-GPA), score index for radiosurgery in BM (SIR), and[19] as assessed by ROC analysis (AUC: 0.70 and AUC: 0.79). Our AUC of

0.822 in the training cohort and 0.932 in the validation cohort was therefore competitive and, moreover, our study was not limited to NSCLC and four brain lesions.

GPA is an easy to use and well-validated tool for defining the prognosis of BM patients.[6–8,20,21] Nevertheless, we established that it has some limitations in defining candidates for SRS. First, even the worst patient subgroups had median survival times of >3 months. Second, the same GPA result can have a different prognosis depending on the primary site. For example, a breast cancer patient with a GPA of 0 (>60 years, KPS 40, triple-negative disease, seven BM, and extracranial disease) could be considered a good candidate for SRS due to a six-month probability of survival. However, in practice, the chance of survival was less than 10% due to poor neurological status and extensive extracranial disease. Third, GPA depends on BM number, and our current data and recent studies have demonstrated that BM number is not of prognostic significance when patients are treated with SRS.[5,22,23] The accurate and simple prognostic index known as BS-BM[24] also combines three features (controlled primary disease, extracranial disease, and KPS). However, good specificity is limited by the low sensitivity and, in BS-BM, oligometastatic patients are classified into the same group as patients with extensive extracranial disease.

The most important unfavorable prognostic features other than GPA were poor neurological status and extensive (non-oligometastatic) disease outside the brain. In our study, 8% of neurologically asymptomatic patients died in the three months after SRS. Therefore, asymptomatic patients should be treated with SRS independently of other factors. Nevertheless, the efficacy of intracranial therapy is limited by poorly controlled extracranial disease or a lack of systemic treatment.[15,22] In recent study of patients with asymptomatic BM, performance status was related to risk of early death. Both KPS and severe neurological symptoms routinely exclude patients from systemic therapies. This may explain why serious neurological deterioration limited the value of SRS.

Moreover, we also found that some symptomatic patients may benefit from SRS, but only when other clinical prognostic factors are favorable. Extracranial disease status should be carefully analyzed in patients with neurological symptoms. Our results confirmed that risk of early death is related to oligometastatic status in patients with neurological symptoms. Patients with three to five extracranial tumors, routinely defined as oligometastatic disease,[25] have a better prognosis and additional treatment options like stereotactic body radiotherapy (SBRT). Controlled BM disease depends on effective extracranial therapy.[9] Further studies could focus on combined intracranial SRS and extracranial SBRT for oligometastatic patients disqualified from effective systemic therapies.

SRS of patients with extensive disease and neurological symptoms could also provide benefit in terms of neurological improvement. More than 50% of our symptomatic patients were stable or improved in three months. The relief or stabilization of symptoms found in the majority of patients should be considered an important indication for SRS in this group. With supportive care, patients with brain metastases are not expected to improve or stabilize neurologically over three to six months follow-up. However, to select proper candidates for such an approach, GPA should be analyzed in these cases. Almost 70% of patients with serious neurological symptoms and extensive extracranial disease are expected to survive three months after SRS when their GPA is at least two and this decreased when the GPA was lower. In case by case analyses, we have found examples of additional benefit in terms of eligibility for systemic therapy when performance status improves after SRS.

A tumor mass effect was not related to outcomes, probably due to a small number of patients experiencing this complication as a result of good cooperation with our neurosurgery department; most BM showing a mass effect are referred for surgery. The molecular biology of the tumor is another important factor that determines long-term survival of metastatic patients.[20] Nevertheless, we did not detect an association between molecular factors and risk of early death. This may have been due to the relatively small number of patients treated with targeted therapies or immunotherapies, partly because the excessive risk in many patients excluded those treatments and there was a low frequency of predictive molecular aberrations.

The study has limitations. First, the training, validation, and WBRT cohorts might be subject to bias given that they relate to two different time periods in the same institution. However, only a minority of patients in the SRS group were treated with systemic therapies unavailable to patients treated with WBRT. We only studied a small number of patients treated with targeted therapy or immunotherapy, which may decrease early risk of death and we consequently excluded patients treated with those

therapies from propensity score analysis. Other limitations are the relatively small number of NSCLC, non-breast primary sites and small amount of molecular data, limiting the analysis of molecular data as a prognostic factor. Nevertheless, the analyses were based on data from a prospective registry, in a heterogeneous population, and were validated.

Conclusion

SRS alone is a viable treatment option for patients with poor prognosis defined as GPA <2. Good neurological status, extracranial oligometastatic disease, or GPA ≥2 should be present to justify SRS in patients with brain metastases. Our results suggest no survival benefit for patients with GPA <2 concomitant with serious neurological symptoms and extensive extracranial disease. Further investigations should focus on this very high-risk group in relation to molecular characteristics and systemic therapy options.

Disclosure

The authors report no conflicts of interest in this work.

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