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Scientific Article

Determinants of Symptomatic Intracranial Progression After an Initial Stereotactic Radiosurgery Course

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Purpose: Clinical and imaging surveillance of patients with brain metastases is important after stereotactic radiosurgery (SRS) because many will experience intracranial progression (ITCP) requiring multidisciplinary management. The prognostic significance of neurologic symptoms at the time of ITCP is poorly understood.

Methods and Materials: This was a multi-institutional, retrospective cohort study from 2015 to 2020, including all patients with brain metastases completing an initial course of SRS. The primary outcome was overall survival (OS) by presence of neurologic symptoms at ITCP. OS, freedom from ITCP (FF-ITCP), and freedom from symptomatic ITCP (FF-SITCP) were assessed via Kaplan-Meier method. Cox proportional hazard models tested parameters impacting FF-ITCP and FF-SITCP.

Results: Among 1383 patients, median age was 63.4 years, 55% were female, and common primaries were non-small cell lung (49%), breast (15%), and melanoma (9%). At a median follow-up of 8.72 months, asymptomatic and symptomatic ITCP were observed in 504 (36%) and 194 (14%) patients, respectively. The majority of ITCP were distant ITCP (79.5%). OS was worse with SITCP (median, 10.2 vs 17.9 months, $P < .001$). SITCP was associated with clinical factors including total treatment volume ($P = .012$), melanoma histology ($P = .001$), prior whole brain radiation therapy ($P = .003$), number of brain metastases ($P < .001$), interval of 1 to 2 years from primary and brain metastasis diagnosis ($P = .012$), controlled extracranial disease ($P = .042$), and receipt of pre-SRS chemotherapy ($P = .015$). Patients who were younger and received post-SRS chemotherapy ($P = .001$), immunotherapy ($P < .001$), and targeted or small-molecule inhibitor therapy ($P < .026$) had better FF-SITCP.

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Conclusions: In this cohort study of patients with brain metastases completing SRS, neurologic symptoms at ITCP is prognostic for OS. This data informs post-SRS surveillance in clinical practice as well as future prospective studies needed in the modern management of brain metastases.

Introduction

Brain metastases are the most commonly occurring intracranial malignancy in adults, and up to 40% of patients with solid tumors will develop brain metastases in their clinical course.[1,2] Treatment with surgical resection and/or stereotactic radiosurgery (SRS) is the standard of care for most patients with limited brain metastases.[3-5] For patients with limited brain metastases, SRS is the preferred radiation therapy technique due to lower rates of neurocognitive decline compared with whole brain radiation therapy.[6] With advances in SRS technologies as well as systemic therapies with intracranial penetrance, overall survival (OS) of patients with brain metastasis has significantly improved, and prognostication in this population has become nuanced in guiding individualized treatment courses.[7-9] After SRS, monitoring of neurologic symptoms and imaging with magnetic resonance imaging (MRI) is essential for identifying intracranial progression (ITCP) and to direct further treatment.[10] To this end, our prior work identified patients at high risk for ITCP[11,12] as well as the degree to which ITCP correlates to OS.[13] However, the incidence, prognostic significance, and clinical parameters associated with neurologic symptoms at post-SRS ITCP remain poorly characterized.

Although local control of treated metastases with SRS is approximately 80% to 90%,[14] overall intracranial control is only ~50% at 1 year, due to the development of new brain metastases distant from treated locations.[15] Many progressing patients have associated neurologic symptoms, including focal deficits, headaches, and seizures.[16] Although it is known that symptomatic progression impacts quality of life, little is known regarding the prognostic significance of neurologic symptoms at progression after treatment of brain metastases, and characteristics of patients who will present with symptomatic ITCP. This is especially important as recent clinical trials increasingly include patients with brain metastases who are not symptomatic.[17,18] Therefore, in this multi-institutional cohort of patients with brain metastases completing SRS, we address several points which remain largely undefined: 1) the prognostic significance of neurologic symptoms at the time of intracranial progression; 2) which patients are at the highest risk for symptomatic intracranial progression; and 3) whether the presence of neurologic symptoms is associated with a longer time interval from SRS completion to subsequent intracranial progression.

Methods and Materials

For this institutional review board-approved retrospective cohort study, consecutive adult patients completing an initial SRS course for brain metastases were identified across 2 institutions between January 2015 and December 2020. The same cohort of patients were used for prior studies of other prespecified clinical endpoints.[12,13] Informed consent waiver was granted because de-identified data were used. Exclusion criteria included age <18 years at time of SRS as well as prior SRS. Single- and multifraction SRS cases were included, as were those with prior whole brain radiation therapy (WBRT) or surgical resection of brain metastases. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Demographic and clinical parameters included year of SRS completion, age, sex, race, Karnofsky performance status (KPS), primary tumor site, and sites of extracranial metastatic disease at time of SRS. Oligometastatic disease burden was defined as 1 to 5 metastases (ie, nonlocoregional) present across all anatomic locations, including intracranial disease, at time of SRS.[19]

Across both institutions, post-SRS surveillance included follow-up with brain MRIs every 2 to 3 months. The exact duration between scans was left to the discretion of the multidisciplinary care team, as was consideration of surveillance intervals >3 months after 1 to 3 years without ITCP. ITCP was defined as any clinical concern for distant and/or recurrent intracranial progression per multidisciplinary review of MR brain images.[18] Symptomatic ITCP (SITCP) was defined as ITCP with concurrent new or progressive neurologic symptoms correlating to the specific intracranial region of progression. Two-sided t tests and χ^2 tests were used to evaluate differences in baseline demographic characteristics. OS, freedom from ITCP (FF-ITCP), and freedom from symptomatic ITCP (FF-SITCP) were assessed via Kaplan-Meier method. The log-rank test was used to compare OS between groups. Cumulative incidence rates of SITCP accounted for asymptomatic ITCP and death as competing risks. For the FF-ITCP analysis, patients were censored at time of death. For FF-SITCP analysis, patients were censored at time of death or at time of asymptomatic ITCP. Assessment of parameters impacting FF-ITCP and FF-SITCP was performed with univariable Cox proportional hazard models. Proportional hazards

assumption was assessed via Schoenfeld residual testing, and for continuous variables, nonlinearity was assessed via Martingale residuals. Missing data were excluded from analysis and no correction for multiple comparisons was performed in this retrospective analysis. All analyses were performed using R Statistical Software (version 4.1.2; R Foundation for Statistical Computing).

Results

We identified 1383 patients comprising our study cohort (Table 1). At the time of SRS, the median age was 64.3 years (IQR, 55.4-72.1 years). There were 758 women (55%) and 625 men (45%). In terms of performance status, 631 patients (46%) had a KPS score of 90 or greater, and 598 (43%) had a KPS of 70 to 80. A total of 283 patients (20%) were Black, 1032 (75%) were White, and 68 (5%) were of other races and ethnicities. The most common primary tumor site was non-small cell lung cancer (NSCLC), where 537 (39%) had a nondriver mutation and 137 (10%) had a driver mutant. Other common primaries included breast (203 [15%]) and melanoma (118 [9%]). Prior therapies before SRS included surgical resection in 361 (26%) of patients, WBRT in 142 (10%), chemotherapy (CHT) in 693 (50%), immunotherapy (IT) in 327 (24%), and targeted or small-molecule inhibitor therapy (TT) in 304 (22%). At the time of SRS, 648 patients (47%) had oligometastatic disease and 470 (34%) had controlled extracranial disease. Multiple brain metastases were treated with SRS in 738 patients (53%) overall, where 247 (18%) were treated for 2, 308 (22%) were treated for 3 to 5, and 183 (13%) were treated for ≥6 brain metastases. The median (IQR) planning target volume (PTV) was 6.6 (1.7-23) ccs for all treated brain metastases and 4.9 (1.2-17.7) ccs for the largest single brain metastasis in a single patient. After SRS, 436 patients (32%) were treated with CHT, 378 (27%) with IT, and 293 (21%) with TT. The median time to MRI after SRS was 3.1 months (IQR, 2.0-6.0 months). Patients in the SITCP cohort had fewer lines of post-SRS chemotherapy ($P < .001$) and larger PTVs in terms of the largest lesion ($P = .003$) and the total PTV ($P = .03$), compared with those with asymptomatic ITCP.

At a median follow-up of 8.72 months (IQR, 3.25-19.68 months), intracranial progression was observed in 698 patients (50%), preceding 492 of 1000 observed deaths (49%). For 143 of the 698 patients (20.5%) who experienced progression, initial concern for progression was limited to one or more previously irradiated brain metastases. These events were determined to be radionecrosis in 96 cases (67%) and local progression in 47 (33%) by multidisciplinary review of clinical and imaging characteristics. For the remainder 555 patients (79.5%), ITCP involved distant intracranial metastasis (eg, new brain metastases seen on surveillance). Symptomatic intracranial progression was observed in 194 (14%) of patients, and asymptomatic intracranial progression in 504 (36%). The cumulative incidence of SITCP for all patients at 3, 6, and 12 months was 5.9% (95% CI, 4.8-7.3%), 10% (95% CI, 8.8-12%), and 13% (95% CI, 11-15%) respectively (Table E1). Overall survival of patients who experienced ITCP stratified by the presence of neurologic symptoms at the time of progression is presented in Fig. 1. Patients with neurologic symptoms at ITCP had significantly worse OS compared with those who were asymptomatic ($P < .0001$), with a median OS of 10.2 months (95% CI, 7.7-12.9 months) compared with a median OS of 17.9 months (95% CI, 16.0-21.2 months) for those with asymptomatic ITCP.

FF-ITCP stratified by the presence of neurologic symptoms for patients with documented post-SRS intracranial progression is presented in Fig. 2. Patients with neurologic symptoms at ITCP had a shorter FF-ITCP compared with those who were asymptomatic ($P = .00019$), with a median time to ITCP of 3.4 months (95% CI, 3.0-4.1 months) for patients with symptoms compared with a median of 4.7 months (95% CI, 3.8-5.7 months) for those who were asymptomatic.

For all patients in the cohort, factors associated with experiencing neurologic symptoms at ITCP were analyzed in Table 2. Assumption testing via Schoenfeld residuals and Martingale residual plots are provided in Table E2 and Fig. E1, respectively; the proportional hazards assumption was not met for KPS ($P = .029$) and receipt of post-SRS chemotherapy ($P = .005$). On univariable Cox regression, symptomatic ITCP was associated with melanoma histology (hazard ratio [HR], 2.09 [95% CI, 1.35-3.24], $P = .001$), controlled extracranial disease (HR, 1.34 [95% CI, 1.01-1.78], $P = .042$), receipt of pre-SRS chemotherapy (HR, 1.42 [95% CI, 1.07-1.89], $P = .015$), interval of >1 year and ≤2 years from primary diagnosis to brain metastases (HR, 1.72 [95% CI, 1.13-2.61], $P = .012$), prior WBRT (HR, 1.87 [95% CI, 1.24-2.81], $P = .003$), and number of brain metastases in terms of 2 versus 3 to 5 (HR, 2.08 [95% CI, 1.47-2.95], $P < .001$), or in terms of 3 to 5 versus ≥6 (HR, 1.89 [95% CI, 1.23-2.90], $P = .004$), and total PTV (per cc, HR, 1.01 [95% CI, 1.00-1.01], $P = .012$). Symptomatic ITCP was not associated with single versus 2 brain metastases, prior surgical resection, year of SRS, and PTV of largest lesion treated ($P = .103$, 0.619, 0.743, and 0.250, respectively). Younger age (per year, HR, 0.99 [95% CI, 0.99-1.00], $P = .007$) and receipt of any post-SRS systemic therapy were associated with a lower probability of experiencing symptomatic ITCP, including chemotherapy (HR, 0.58 [95% CI, 0.42-0.81], $P = .001$), immunotherapy (HR, 0.55 [95% CI, 0.39-0.77], $P < .001$), and targeted or small-molecule inhibitor therapy (HR, 0.67 [95% CI, 0.47-0.95], $P = .026$). Factors associated with FF-ITCP overall in the cohort is presented in Table E3.

Table 1 Demographic, clinical, and treatment parameters across all patients, those with asymptomatic post-SRS intracranial progression, and those with symptomatic intracranial progression

Parameter	All Pts (n = 1383) N (%)	Pts with Asx ITCP (n = 504) N (%)	Pts with SITCP (n = 194) N (%)	*P* value
Year SRS				.6
2015-2017	592 (42.8)	228 (45.2)	83 (42.8)	
2018-2020	791 (57.2)	276 (54.8)	111 (57.2)	
Median age (IQR)	64.3 (55.4-72.1)	62.3 (53.4-69.5)	61.73 (52.08-70.60)	.72
Male sex	625 (45.2)	212 (42.1)	73 (37.6)	
Race				.9
White	1032 (74.6)	381 (75.6)	150 (77.3)	
Black	283 (20.5)	99 (19.6)	36 (18.6)	
Other	68 (4.9)	24 (4.8)	8 (4.1)	
KPS				.07
90-100	631 (45.6)	281 (55.8)	90 (46.4)	
70-80	598 (43.2)	196 (38.9)	89 (45.9)	
≤60	154 (11.1)	27 (5.4)	45 (23.2)	
Primary tumor type				.078
NSCLC, nondriver mutant	537 (38.8)	183 (36.3)	69 (35.6)	
NSCLC, driver mutant	137 (9.9)	68 (13.5)	15 (7.7)	
Breast	203 (14.7)	88 (17.5)	36 (18.6)	
Melanoma	118 (8.5)	44 (8.7)	28 (14.4)	
Other	338 (24.4)	121 (24)	46 (23.7)	
Oligometastatic disease at time of SRS	648 (46.9)	249 (49.4)	102 (52.6)	.5
Controlled extracranial disease at SRS	470 (34)	187 (37.1)	86 (44.3)	.08
Interval from primary dx to brain mets				.11
≤30 d	441 (31.9)	171 (33.9)	52 (26.8)	
>30 d, ≤1 y	269 (19.5)	93 (18.5)	34 (17.5)	
>1 y, ≤2 y	201 (14.5)	67 (13.3)	38 (19.6)	
>2 y	472 (34.1)	173 (34.3)	70 (36.1)	
Lines of pre-SRS chemotherapy				.8
0	690 (49.9)	249 (49.4)	89 (45.9)	
1	406 (29.4)	154 (30.6)	60 (30.9)	
2	167 (12.1)	60 (11.9)	27 (13.9)	
≥3	120 (8.7)	41 (8.1)	18 (9.3)	
Lines of pre-SRS immunotherapy				.4
0	1056 (76.4)	389 (77.2)	147 (75.8)	
1	242 (17.5)	86 (17.1)	29 (14.9)	
2	71 (5.1)	22 (4.4)	14 (7.2)	
≥3	14 (1)	7 (1.4)	4 (2.1)	
Lines of pre-SRS targeted therapy				.5
0	1079 (78)	382 (75.8)	156 (80.4)	
1	166 (12)	65 (12.9)	20 (10.3)	

(*continued on next page*)

Table 1 (*Continued*)

Parameter	All Pts (n = 1383) N (%)	Pts with Asx ITCP (n = 504) N (%)	Pts with SITCP (n = 194) N (%)	*P* value
2	86 (6.2)	36 (7.1)	13 (6.7)	
≥3	52 (3.8)	21 (4.2)	5 (2.6)	
Lines of post-SRS chemotherapy†				<.001*
0	947 (68.5)	296 (58.7)	145 (74.7)	
1	331 (23.9)	170 (33.7)	37 (19.1)	
2	91 (6.6)	33 (6.5)	9 (4.6)	
3+	14 (1)	5 (1)	3 (1.5)	
Lines of post-SRS immunotherapy†				.1
0	1005 (72.7)	349 (69.2)	149 (76.8)	
1	347 (25.1)	141 (28)	43 (22.2)	
2	30 (2.2)	14 (2.8)	2 (1)	
3+	1 (0.1)	0 (0)	0 (0)	
Lines of post-SRS targeted therapy†				.5
0	1090 (78.8)	378 (75)	154 (79.4)	
1	248 (17.9)	105 (20.8)	36 (18.6)	
2	37 (2.7)	17 (3.4)	3 (1.5)	
3+	8 (0.6)	4 (0.8)	1 (0.5)	
Prior whole brain radiotherapy	142 (10.3)	49 (9.7)	27 (13.9)	.11
Surgical resection	361 (26.1)	138 (27.4)	58 (29.9)	.5
No. of brain metastases				.4
1	645 (46.6)	214 (42.5)	79 (40.7)	
2	247 (17.9)	104 (20.6)	32 (16.5)	
3-5	308 (22.3)	117 (23.2)	54 (27.8)	
≥6	183 (13.2)	69 (13.7)	29 (14.9)	
PTV of largest lesion (cc; median, IQR)	4.87 (1.18-17.71)	3.19 (0.88-15.09)	6.80 (2.00-21.19)	.003*
PTV total (cc; median, IQR)	6.62 (1.74-22.97)	4.71 (1.13-20.42)	10.58 (2.68-30.22)	.03*

Abbreviations: Asx = asymptomatic; dx = diagnosis; ITCP = intracranial progression; KPS = Karnofsky performance status; NSCLC = non-small cell lung cancer; Pts = patients; PTV = planning target volume; SITCP = symptomatic intracranial progression; SRS = stereotactic radiosurgery.
*Statistically significant.
†From SRS completion to initial post-SRS intracranial progression or last follow-up.

Discussion

In this large, multi-institutional cohort of patients with brain metastases treated with contemporary therapies, the presence of neurologic symptoms at ITCP was associated with inferior OS after an initial course of SRS. We also identified that symptomatic ITCP occurred earlier than asymptomatic ITCP and clinical and treatment characteristics associated with a higher risk of SITCP. These findings are important as more and more patients are being treated with radiosurgery to multiple brain metastases where progression in untreated locations is common. These data suggest an association of specific clinical factors with SITCP and characterizing the negative prognostic implications of SITCP in terms of survival.

Although the association between ITCP and neurologic decline is understood, it is not well characterized in the literature in relation to patient and treatment characteristics. In contemporary practice, clinical monitoring and regular brain imaging is especially important after SRS as approximately 50% of patients will develop intracranial progression (especially distant intracranial progression in terms of new metastases) within the first year after treatment. Given that high local control and neurocognitive preservation are major reasons for SRS instead of WBRT in many patients, identifying clinical

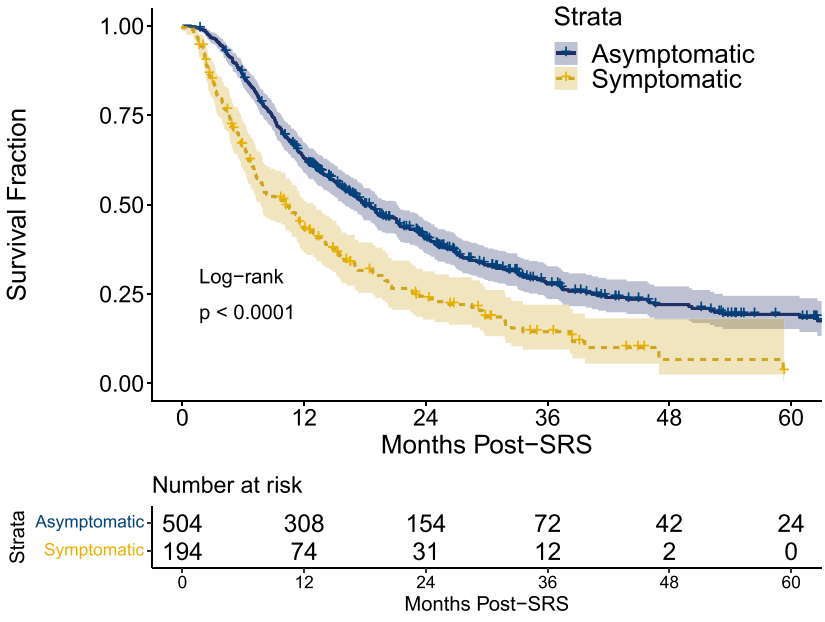

Figure 1 Overall survival, with 95% CI, is shown for all patients with documented post stereotactic radiosurgery intracranial progression, stratified by presence of neurologic symptoms at time of progression. *Abbreviation*: SRS = stereotactic radiosurgery.

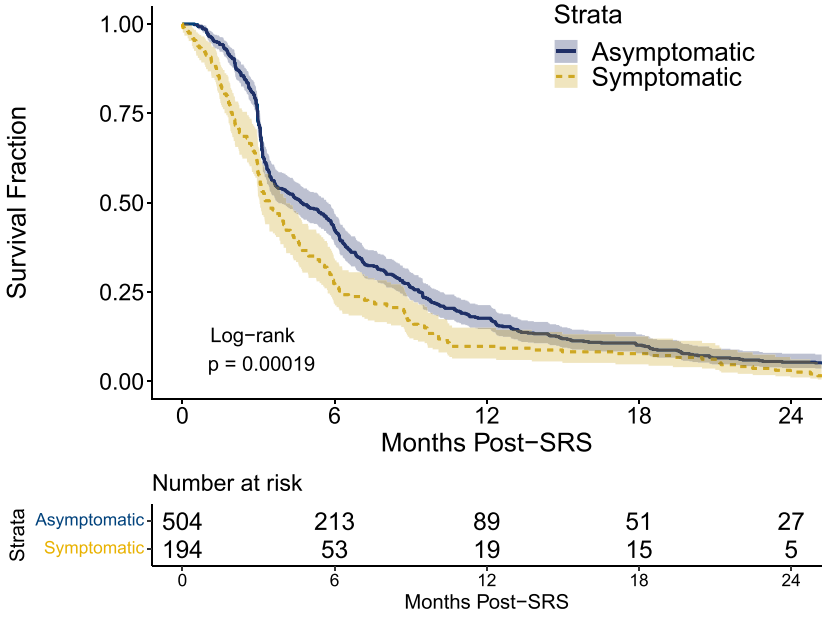

Figure 2 Freedom from intracranial progression, with 95% CI, is shown for all patients with documented post stereotactic radiosurgery intracranial progression, stratified by presence of neurologic symptoms at time of progression. *Abbreviation*: SRS = stereotactic radiosurgery.

parameters specifically associated with symptomatic progression after SRS may help to identify higher risk patients and guide their multidisciplinary management. This data provide support for the use of symptomatic ITCP as a defined clinical endpoint in patient care.

Indeed, we found that most intracranial events in this study were driven by distant intracranial progression with new brain metastases at a median follow-up of 8.72 months. Local events of radionecrosis and local progression of treated metastases were a minority in the overall cohort. In this analysis, the 96 cases of radionecrosis (13.8%) identified were included as ITCP events (698 in total) in the context of prognostication, as it is often difficult to distinguish between radionecrosis and local

Table 2 Univariate analysis of freedom from symptomatic intracranial progression for all patients

Parameter	HR (95% CI)	*P* value
Year SRS		
2015-2017	Ref	
2018-2020	1.049 (0.788-1.395)	.743
Age, per year	0.985 (0.974-0.996)	.007*
Male sex	0.793 (0.593-1.06)	.117
Race		
White	Ref	
Black	0.811 (0.563-1.166)	.258
Other	0.807 (0.396-1.643)	.554
KPS		
90-100	Ref	
70-80	1.291 (0.962-1.731)	.088
≤60	1.139 (0.659-1.971)	.641
Primary tumor type		
NSCLC, nondriver mutant	Ref	
NSCLC, driver mutant	0.715 (0.409-1.249)	.238
Breast	1.348 (0.901-2.017)	.147
Melanoma	2.090 (1.347-3.244)	.001*
Other	1.082 (0.744-1.572)	.681
Oligometastatic disease	0.947 (0.714-1.257)	.706
Controlled extracranial disease	1.343 (1.011-1.783)	.042*
Receipt of pre-SRS chemotherapy	1.422 (1.072-1.888)	.015*
Receipt of pre-SRS immunotherapy	1.333 (0.959-1.853)	.087
Receipt of pre-SRS targeted therapy	0.867 (0.608-1.236)	.431
Receipt of post-SRS chemotherapy	0.584 (0.422-0.807)	.001*
Receipt of post-SRS immunotherapy	0.550 (0.393-0.769)	<.001*
Receipt of post-SRS targeted therapy	0.672 (0.474-0.952)	.026*
Interval from primary to brain dx		
≤30 d	Ref	
>30 d, ≤1 y	1.339 (0.868-2.064)	.186
>1 y, ≤2 y	1.715 (1.129-2.607)	.012*
>2 y	1.387 (0.968-1.986)	.075
Prior whole brain radiotherapy	1.868 (1.241-2.813)	.003*
Surgical resection	0.925 (0.679-1.259)	.619
No. of brain metastases		
1	Ref	
2	1.409 (0.933-2.126)	.103
3-5	2.081 (1.469-2.948)	<.001*
≥6	1.886 (1.228-2.895)	.004*
PTV of largest lesion (cc)	1.004 (0.996-1.011)	.250
PTV total (cc)	1.008 (1.002-1.013)	.012*

Abbreviations: dx = diagnosis; HR = hazard ratio; ICP = intracranial progression; KPS = Karnofsky performance status; NSCLC = non-small cell lung cancer; PTV = planning target volume; SRS = stereotactic radiosurgery.
*Statistically significant.

progression at the time of the initial surveillance MRI without information from subsequent clinical, radiographic, and potentially surgical follow-up that can take place over months. Regardless of the mechanism of progression, the cumulative rate for symptomatic progression was 8.9% by 6 months and 12% by 1 year, and these patients had worse overall survival compared with those who experience intracranial progression without neurologic symptoms. We identified distinct clinical and treatment characteristics that are associated with a high risk of SITCP. These factors included melanoma histology, larger total PTV, greater number of brain metastases, controlled extracranial disease at SRS, prior WBRT, interval of 1 to 2 years between primary and brain metastases diagnosis, and receipt of pre-SRS chemotherapy. Although the association of PTV with worse local control is studied in the literature,[20,21] here it was associated with higher risk for symptomatic intracranial progression overall and future studies examining treatment volume thresholds for predicting SITCP can potentially provide actionable information in the treatment planning process. Receipt of post-SRS systemic therapy was associated with lower probabilities of experiencing SITCP. In melanoma, a recent study of long-term intracranial outcomes after SRS and dual immune checkpoint blockade demonstrated improved intracranial control.[22] These studies reflect the increasing use of systemic therapies with effective intracranial activity over time, which play complimentary roles with SRS for intracranial control.[23] Potential trends in systemic therapy use was broadly captured in this study in terms of the year of treatment. Future prospective studies should record these trends in more granular detail, for example in NSCLC with the use of third-generation epidermal growth factor receptor tyrosine kinase inhibitors that demonstrate greater intracranial control.[24,25] Finally, although risk for SITCP closely approximates the risk for any ITCP (Table E3), one specific difference is the number of brain metastases treated with ≥ 3 rather than ≥ 2 as a cutoff. Together, our findings here provide a rigorous characterization of symptomatic intracranial progression after SRS, which can significantly impact patient quality of life and direct ongoing oncologic care in terms of surveillance, treatment, and supportive care.[26]

Optimal post-SRS surveillance is not well defined in terms of patient and treatment characteristics. Historic studies have focused on salvage WBRT after SRS, which has little clinical utility in contemporary practice as patients are frequently treated with further courses of SRS for intracranial progression.[27,28] Here, we found that SITCP occurred earlier than asymptomatic ITCP (median, 3.4 vs 4.7 months). This suggests that symptomatic intracranial progression is happening not because of missed scans and appointments, but because current surveillance intervals are insufficient to detect disease at a timepoint before symptom onset. Prior studies have attempted to personalize post-SRS imaging intervals to detect ITCP before the onset of neurologic symptoms,[11,29] and require further validation to optimize imaging strategy in this population.

Intracranial response assessment has become increasingly important as patients with brain metastases who are not symptomatic are being included in clinical trials.[17] OS as an outcome measure has the distinct advantage of being a direct measure of meaningful clinical benefit. However, in the brain metastases population, high rates of competing risks are likely to dilute the impact on local control, and larger sample sizes are required to uncover direct impacts on overall survival.[17,18] In this study, SITCP was prognostic for OS and further supports the use of ITCP endpoints as surrogates in oncologic trials. As intracranial progression-free survival become increasingly used in oncology trials, including those with brain metastases,[30] this data also provide relevant context in terms of patient symptoms at the time of ITCP.

Strengths and limitations

The strengths of this study include its large, multi-institutional nature, which allowed for robust analyses of our endpoints of interest. Limitations include the generalizability of the results outside of institutions with the availability of multidisciplinary management for brain metastases. Results here reflect outcomes after an initial course of SRS and is not generalizable to subsequent courses of intracranially directed therapy after SRS. This retrospective review did not capture neurologic symptoms at baseline, which should be stratified in future studies. Additionally, the rate of leptomeningeal disease, although generally low in the SRS setting, were not specifically captured here. Because SITCP events require both clinical and imaging assessment, a proportion of patients who died in the context of undocumented progression were not accounted for in the analyses. In the context of comparing asymptomatic ITCP and SITCP (both requiring imaging documentation), this is less relevant compared with our prior work.[13] Overall, this retrospective study offers an exploratory and hypothesis-generating analysis and should be interpreted with caution until validated by future prospective cohort studies in the modern SRS setting.

Conclusion

This cohort study of patients completing an initial course of SRS for brain metastases suggest that neurologic symptoms at ITCP is prognostic for inferior OS, and is associated with melanoma histology, lack of adjuvant systemic therapy, and greater number of brain metastases.

These exploratory and hypothesis-generating data require further validation in prospective cohorts and may inform surveillance after SRS and design of clinical trials that include patients with brain metastases.

Disclosures

John P. Kirkpatrick reported receiving grants from Varian Medical Systems and BioMimetix SBR, receiving personal fees from Monteris Medical, and owning ClearSight LLC outside the submitted work. Julian C. Hong reported receiving research funding from Roche outside the submitted work. Zachary J. Reitman reported having intellectual property managed by Duke University related to brain tumor genomic profiling tests outside the submitted work. Peter E. Fecci reported receiving consulting fees and grant funding from Monteris Medical outside the submitted work.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101475.

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