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Real World Outcomes of Melanoma Brain Metastases Treated with Immunotherapy with or without Stereotactic Radiosurgery

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Real World Outcomes of Melanoma Brain Metastases Treated with Immunotherapy with or without Stereotactic Radiosurgery

By

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B.S., Georgia Institute of Technology, 2017

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Abstract

Real World Outcomes of Melanoma Brain Metastases Treated with Immunotherapy with or without Stereotactic Radiosurgery

By Troy Kleber

Background:
Immunotherapies (IT) are effective for melanoma with extracranial metastases based on multiple phase 3 clinical trials. For patients with melanoma brain metastases (MBM), however, the role of IT is less clear. We hypothesized that treatment of MBM with IT and SRS in combination results in longer patient survival compared to IT alone.

Methods:
Using the National Cancer Database, we identified 775 adult patients diagnosed with MBM between 2010 and 2017 treated with IT. We excluded those who received whole-brain radiotherapy. We then compared receipt of both IT and SRS (IT/SRS) vs. IT alone (IT/noSRS). Our primary endpoint was overall survival (OS). As a subset analysis on the IT/SRS cohort, we assessed the association between the relative timing of therapies and OS. This involved multiple statistical analyses using different definitions for relative timing: days from start of SRS to IT, proximity of therapies (IT started ≤ 28 vs. > 28 days from SRS), and sequence of therapies (IT started after vs. before SRS). Adjusted hazard ratios (aHR) were calculated using multivariable Cox regression modeling and reported with 95% confidence intervals (CI). Significance level was set as 0.05.

Results:
Of the 775 adult patients with MBM treated with IT, 546 (70.5%) were male, 759 (98.3%) were white, and 654 (84.4%) were diagnosed in 2014-2017. Those with lung, liver, and bone metastasis numbered 275 (56.9%), 100 (20.6%), and 84 (17.4%), respectively. 492 (63.5%) patients were treated with IT/SRS, and 283 (36.5%) received IT/noSRS. The median OS was 29.5 months (95% CI: 22.3 - 44.8 mo) for IT/SRS and 11.9 months (95% CI: 9.2 - 17.2 mo) for IT/noSRS with an aHR of 0.70 (95% CI: 0.56-0.88, $p < 0.01$). For the IT/SRS cohort, there was no significant association between the relative timing of therapies and OS.

Conclusions:
Patients with MBM treated with both IT and SRS appear to have longer survival compared to IT without intracranial radiation. This finding demonstrates the benefits of local therapy for brain metastases when prescribed in combination with IT.

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Introduction

The brain is an unfortunately common site of metastasis for melanoma and a frequent cause of death for advanced melanoma patients. Brain metastases are present in 40-50% of patients with stage IV melanoma, and the prognosis of patients with melanoma brain metastases (MBM) is poor.[1] Median overall survival for MBM is 7-9 months.[2] Because traditional chemotherapies are ineffective at crossing the blood-brain barrier, the management of MBM has historically relied on brain-directed therapies—intracranial radiation and/or surgery—often given concurrently with systemic therapies.

Currently, one of the recommended first-line treatment regimens for MBM is the combination of stereotactic radiosurgery (SRS) and immunotherapy (IT), based on guidelines from the National Comprehensive Cancer Network.[3] SRS is a form of intracranial radiation that precisely directs the radiation beam to one or more sites of brain lesions. IT is a systemic therapy that activates the body's anti-tumoral immune response. Currently, the most effective IT agents for metastatic melanoma belong to a subclass called checkpoint inhibitors, which target surface proteins on immune cells. Checkpoint inhibitors have been proven to effectively control extracranial sites of metastatic melanoma based on multiple phase 3 clinical trials.[4, 5]

Interestingly, recent studies have questioned the need for upfront brain-directed therapy, such as SRS, for patients with MBM. These clinical trials investigated the use of IT alone for MBM and reported modest rates of intracranial efficacy.[6-9] However, it remains unclear how this novel regimen of IT alone compares to the more established regimen of IT and SRS in combination. Herein, we report our findings on this comparison, which utilized patient records contained within the National Cancer Database (NCDB).

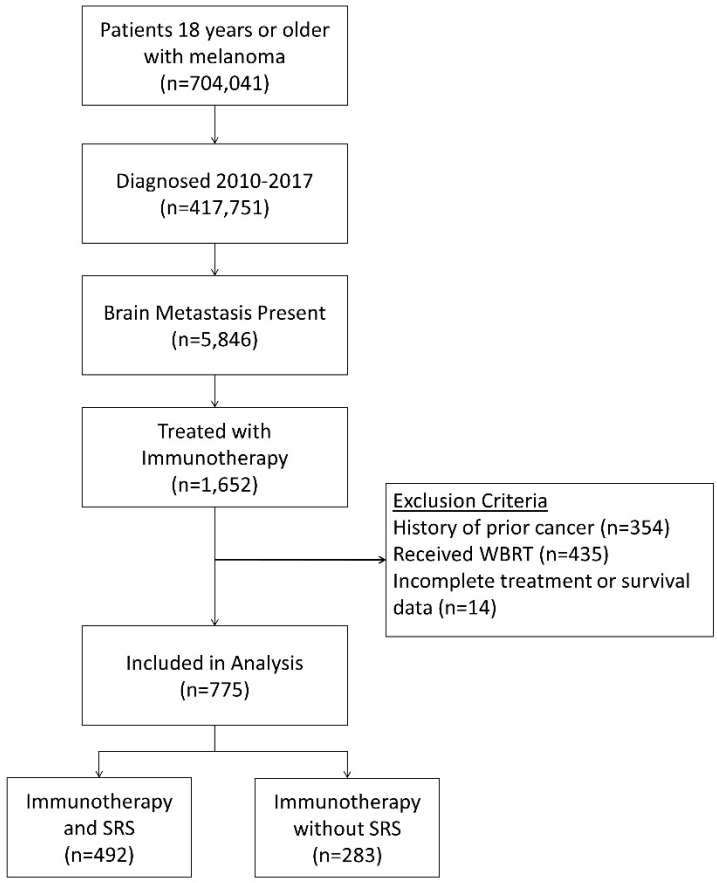
Methods

The NCDB contains diagnostic, staging, treatment, and outcomes information for patients diagnosed with cancer in the United States. This database is overseen by the Commission on Cancer (CoC), a program of the American College of Surgeons, and records are submitted by the more than 1,500 CoC-accredited facilities.[10] The NCDB has been shown to capture 52% of cases of newly diagnosed melanoma in the country.[11] Because the NCDB is a de-identified dataset, this study was exempt from requiring approval from an institutional review board.

We queried the NCDB to identify all adult patients diagnosed with MBM between 2010 and 2017 and treated with IT. 2010 was the first year in the NCDB to include brain metastases as a variable, and 2017 is the latest year published with complete patient survival data. We then excluded patients who had a history of a prior diagnosis of cancer, received whole brain radiotherapy for MBM, or had missing radiation or survival data. Figure 1 illustrates our inclusion and exclusion criteria.

Regarding treatment details, this study only considered a patient's first course of treatment following the diagnosis of MBM, defined as "all methods of treatment recorded in the treatment plan and administered to the patient before disease progression or recurrence" per the Standards for Oncology Registry Entry.[12] Radiotherapy details recorded in the NCDB include modality, dose, location, and start day. IT and chemotherapy details include start day, but specific agents and number of cycles are not reported. The NCDB also records whether a patient received a metastasectomy but does not provide details on the location of metastasectomy.

Figure 1
Inclusion and Exclusion Criteria



WBRT – Whole Brain Radiotherapy; SRS – Stereotactic Radiosurgery.

Of the dozens of variables reported by the NCDB, 17 covariates were deemed relevant to this study and assessed for associations with the intervention and outcome variables in our primary and secondary analyses. Community income quartile represents the median household income for each patient's zip code categorized into quartiles with the cut-points $40,227, $50,354, and $63,333. Community education quartile represents the percentage of high school graduates in each patient's zip code categorized into quartiles with the cut-points 82.4%, 89.1%, and 93.7%. The NCDB obtains income and education data from the 2016 American Community Survey. Distance from facility is calculated as the straight-line distance (i.e. "crowfly" distance)

between the patient and the diagnosing facility. The NCDB reports the Charlson-Deyo score as a surrogate for a patient's number and severity of comorbidities.[10]

As our primary analysis, we compared overall survival (OS) between those treated with both IT and SRS (IT/SRS) versus IT without SRS (IT/noSRS). OS was defined as the number of months between diagnosis of MBM and last known follow-up or death. Patients alive at the end of follow-up were censored at last follow-up date.

We conducted a sensitivity analysis to address the potential for immortal time bias. This analysis was conducted using a different definition of overall survival—number of months from treatment initiation to last known follow-up or death. For the IT/SRS cohort, the second modality started was considered to be the day of treatment initiation.

We also conducted a sensitivity analysis to assess the robustness of statistical significance. This adjusted analysis was conducted using an inverse probability weighted Cox proportional hazards model with propensity scores calculated through multivariable logistic regression.

All covariates were assessed for statistical interaction with treatment regimen (IT/SRS vs. IT/noSRS) within the multivariable Cox proportional hazards model. Only community education quartile was found to have significant interaction. Thus, a post-hoc stratified analysis was conducted to demonstrate this interaction effect. Within each strata for community education quartile, the association between treatment regimen and OS was evaluated.

Lastly, as a subset analysis on the IT/SRS cohort, we assessed the association between the relative timing of therapies and OS. This involved multiple statistical analyses using different definitions for relative timing: days from initiation of SRS to IT, days between initiation of SRS

and IT (positive values only), proximity of therapies (IT started ≤ 28 vs. > 28 days from SRS), and sequence of therapies (IT started same day or after vs. before SRS).

P-values less than 0.05 indicated statistical significance. 95% confidence intervals (CI) were calculated using Greenwood's formula for survival probabilities and the Brookmeyer-Crowley method for median survival times. All unadjusted and adjusted hazard ratios (HR) were calculated using univariate and multivariable Cox proportional hazards models, respectively, unless otherwise specified. Covariates that were included in each multivariable model were found to be associated with either the intervention or outcome variable by a significance level of 0.1. All analysis was completed in SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

We identified 775 adult patients with MBM diagnosed between 2010 and 2017 and treated with IT with or without SRS, according to our eligibility criteria. Patient demographics are displayed in Table 1. Of these patients, 492 (63.5%) were treated with IT/SRS, and 283 (36.5%) received IT/noSRS. 546 (70.5%) were male, 759 (98.3%) were white, and 654 (84.4%) were diagnosed between 2014 and 2017. Mean age at diagnosis was 59.6 (range 18-90). Those with lung, liver, and bone metastasis numbered 275 (56.9%), 100 (20.6%), and 84 (17.4%), respectively. 83 (10.8%) patients received chemotherapy and 258 (35.3%) received metastasectomy also as part of their first course of treatment. Mean time from diagnosis to IT start was 63.7 days (standard deviation: 45.8) with no significant difference between cohorts. For the IT/SRS cohort, median SRS dose was 22 Gray (Interquartile Range (IQR): 18-25), and median number of fractions of SRS was 1 (IQR: 1-3).

Of the covariates assessed, community education quartile, insurance status, presence of liver metastasis, presence of bone metastasis, and receipt of metastasectomy were all individually associated with treatment regimen received. Patient age, year of diagnosis, facility type, insurance status, presence of lung metastasis, presence of liver metastasis, presence of bone metastasis, receipt of chemotherapy, and receipt of metastasectomy were all individually associated with overall survival. These associations are demonstrated in Tables 1 and 2.

Table 1
Patient Demographics by Treatment Regimen

	Total (N=775)	**IT/SRS (N=492)**	**IT/noSRS (N=283)**	***P*-value**
Age at Diagnosis (years)				0.93
Mean (SD)	59.6 (14.06)	59.6 (13.78)	59.5 (14.57)	
Sex				0.21
Male	546 (70.5%)	339 (68.9%)	207 (73.1%)	
Female	229 (29.5%)	153 (31.1%)	76 (26.9%)	
Race				0.78
White	759 (98.3%)	482 (98.2%)	277 (98.6%)	
Not White	13 (1.7%)	9 (1.8%)	4 (1.4%)	
Ethnicity				0.48
Hispanic	18 (2.3%)	10 (2.0%)	8 (2.9%)	
Non-Hispanic	750 (97.7%)	478 (98.0%)	272 (97.1%)	
Year of Diagnosis				0.39
2014 - 2017	654 (84.4%)	411 (83.5%)	243 (85.9%)	
2010 - 2013	121 (15.6%)	81 (16.5%)	40 (14.1%)	
Type of Facility				0.59
Community-Based Program	204 (29.2%)	133 (29.9%)	71 (28.0%)	
Integrated/Academic	495 (70.8%)	312 (70.1%)	183 (72.0%)	
Location of Facility				0.85
Metropolitan	622 (82.8%)	396 (83.0%)	226 (82.5%)	
Non-Metropolitan	129 (17.2%)	81 (17.0%)	48 (17.5%)	
Distance from Facility				0.94
≥ 50 miles	135 (17.4%)	84 (17.1%)	51 (18.0%)	
12.5-49.99 miles	344 (44.4%)	219 (44.5%)	125 (44.2%)	
< 12.5 miles	296 (38.2%)	189 (38.4%)	107 (37.8%)	
Community Income Quartile*				0.78
Lowest	74 (11.0%)	46 (10.8%)	28 (11.2%)	
Second	141 (20.9%)	84 (19.8%)	57 (22.9%)	
Third	170 (25.2%)	110 (25.9%)	60 (24.1%)	
Highest	289 (42.9%)	185 (43.5%)	104 (41.8%)	
Community Education Quartile**				**0.04**
Lowest	82 (12.1%)	48 (11.3%)	34 (13.7%)	
Second	174 (25.8%)	108 (25.4%)	66 (26.5%)	
Third	219 (32.4%)	128 (30.0%)	91 (36.5%)	
Highest	200 (29.6%)	142 (33.3%)	58 (23.3%)	
Insurance Status				0.09
Uninsured	19 (2.5%)	8 (1.6%)	11 (3.9%)	

Medicare/Medicaid/Government	363 (47.1%)	227 (46.2%)	136 (48.7%)	
Private Payer	388 (50.4%)	256 (52.1%)	132 (47.3%)	
Charlson-Deyo Score				0.69
≥ 2	51 (6.6%)	35 (7.1%)	16 (5.7%)	
1	91 (11.7%)	59 (12.0%)	32 (11.3%)	
0	633 (81.7%)	398 (80.9%)	235 (83.0%)	
Presence of Lung Metastasis				0.30
Yes	444 (58.3%)	169 (60.8%)	275 (56.9%)	
No	317 (41.7%)	109 (39.2%)	208 (43.1%)	
Presence of Liver Metastasis				**< 0.01**
Yes	189 (24.6%)	89 (31.4%)	100 (20.6%)	
No	580 (75.4%)	194 (68.6%)	386 (79.4%)	
Presence of Bone Metastasis				**< 0.01**
Yes	175 (22.8%)	91 (32.3%)	84 (17.4%)	
No	591 (77.2%)	191 (67.7%)	400 (82.6%)	
Received Chemotherapy				0.66
Yes	83 (10.8%)	51 (10.4%)	32 (11.4%)	
No	687 (89.2%)	439 (89.6%)	248 (88.6%)	
Received Metastectomy				**< 0.01**
Yes	258 (35.3%)	188 (40.6%)	70 (26.2%)	
No	472 (64.7%)	275 (59.4%)	197 (73.8%)	

IT/SRS – Immunotherapy with Stereotactic Radiosurgery; IT/noSRS – Immunotherapy without Stereotactic Radiosurgery.
P-values calculated by two-sample t-test, Chi-square test, or Fisher's exact test. Missing values excluded from column counts, percentages, and calculations for *P*-values.
*This variable represents the percentage of adults (25 or older) in the patient's zip code who have a high school degree, categorized by quartiles.
**This variable represents the median income of households in the patient's zip code, categorized by quartiles.

Table 2
Associations between patient details and overall survival

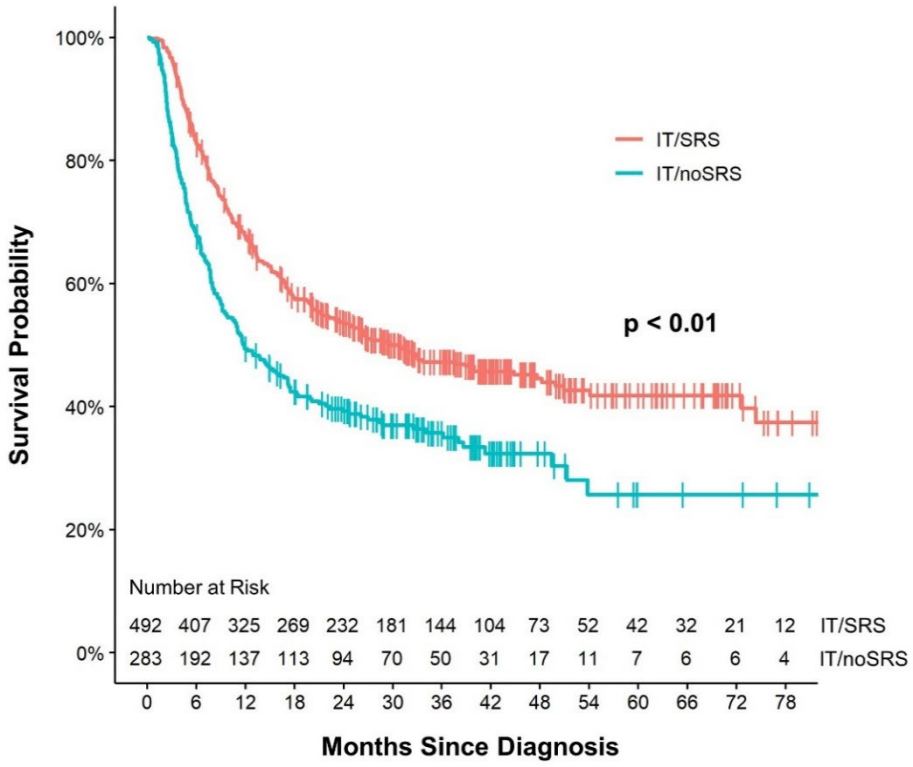
	HR (95% CI)	***P*-value**
Age at Diagnosis (years)	1.02 (1.01-1.02)	**< 0.01**
Sex		
Male	1.18 (0.96-1.46)	0.12
Female	ref	
Race		
White	1.42 (0.64-3.18)	0.39
Not White	ref	
Ethnicity		
Hispanic	0.65 (0.31-1.36)	0.25
Non-Hispanic	ref	
Year of Diagnosis		
2014 - 2017	0.77 (0.61-0.98)	**0.03**
2010 - 2013	ref	
Type of Facility		
Community-Based Program	1.26 (1.02-1.55)	**0.03**
Integrated/Academic	ref	
Location of Facility		
Metropolitan	0.89 (0.69-1.14)	0.36
Non-Metropolitan	ref	
Distance from Facility		
≥ 50 miles	0.98 (0.74-1.28)	0.85
12.5-49.99 miles	0.99 (0.80-1.21)	0.89
< 12.5 miles	ref	
Community Income Quartiles*		
Lowest	1.20 (0.86-1.68)	0.28
Second	1.09 (0.84-1.42)	0.52
Third	1.04 (0.82-1.33)	0.74
Highest	ref	
Community Education Quartiles**		
Lowest	1.23 (0.88-1.71)	0.22
Second	0.90 (0.69-1.18)	0.45
Third	1.13 (0.88-1.44)	0.35
Highest	ref	
Insurance Status		
Uninsured	0.72 (0.34-1.52)	0.38
Medicare, Medicaid, Government	1.39 (1.15-1.68)	**< 0.01**
Private Payer	ref	

Charlson-Deyo Score		
2+	1.18 (0.82-1.71)	0.37
1	1.00 (0.75-1.34)	0.98
0	ref	
Presence of Lung Metastasis		
Yes	1.60 (1.32-1.95)	**< 0.01**
No	ref	
Presence of Liver Metastasis		
Yes	1.94 (1.58-2.37)	**< 0.01**
No	ref	
Presence of Bone Metastasis		
Yes	1.98 (1.61-2.43)	**< 0.01**
No	ref	
Received Chemotherapy		
Yes	1.34 (1.01-1.77)	**0.04**
No	ref	
Received Metastasectomy		
Yes	0.50 (0.40-0.62)	**< 0.01**
No	ref	

HR – Hazard Ratio; CI – Confidence Interval; ref – Reference Level.
Hazard ratios and *P*-values calculated by univariate Cox proportional hazards models with the endpoint of overall survival.
*This variable represents the percentage of adults (25 or older) in the patient's zip code who have a high school degree, categorized by quartiles.
**This variable represents the median income of households in the patient's zip code, categorized by quartiles.

Treatment with IT/SRS was associated with significantly improved OS compared to IT/noSRS. Median OS was 29.5 months (95% CI: 22.3-44.8 mo) for IT/SRS and 11.9 months (95% CI: 9.2-17.2 mo) for IT/noSRS. Six-month survival probability was 83.1% (95% CI: 79.5-86.1%) for IT/SRS and 68.4% (95% CI: 62.6-73.5%) for IT/noSRS. The unadjusted HR was 0.64 (95% CI: 0.53-0.77, $P < 0.01$) and the adjusted HR (aHR) was 0.70 (95% CI: 0.56-0.88, $P < 0.01$). These findings are illustrated in Figure 2 and Table 3. The association between IT/SRS and improved OS remained significant through both sensitivity analyses, as demonstrated in Table 4.

Figure 2
Kaplan-Meier Plot of Overall Survival by Treatment Regimen



For the IT/SRS cohort, 6-month and 12-month survival rates were 83.1% (95% CI: 79.5-86.1%) and 67.8% (95% CI: 63.5-71.8%), respectively. For the IT/noSRS cohort, 6-month and 12-month survival rates were 68.4% (95% CI: 62.6-73.5%) and 49.4% (43.4-55.1%), respectively. Vertical lines indicate censored data. *P*-value calculated through log-rank test. IT/SRS – Immunotherapy with Stereotactic Radiosurgery; IT/noSRS – Immunotherapy without Stereotactic Radiosurgery; CI – Confidence Interval.

Table 3
Patient Overall Survival by Treatment Regimen

		Unadjusted		Adjusted*	
	Median OS (95% CI)	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
IT/SRS (n = 492)	29.5 months (22.3-44.8 mo)	0.64 (0.53-0.77)	**< 0.01**	0.70 (0.56-0.88)	**< 0.01**
IT/noSRS (n = 283)	11.9 months (9.2-17.2 mo)				

IT/SRS – Immunotherapy with Stereotactic Radiosurgery; IT/noSRS – Immunotherapy without Stereotactic Radiosurgery; OS – Overall Survival; HR – Hazard Ratio; CI – Confidence Interval.
*Adjusted for patient's age, diagnosis year, insurance, facility type, community education quartile, presence of lung metastasis, presence of liver metastasis, presence of bone metastasis, receipt of chemotherapy, and receipt of metastasectomy.

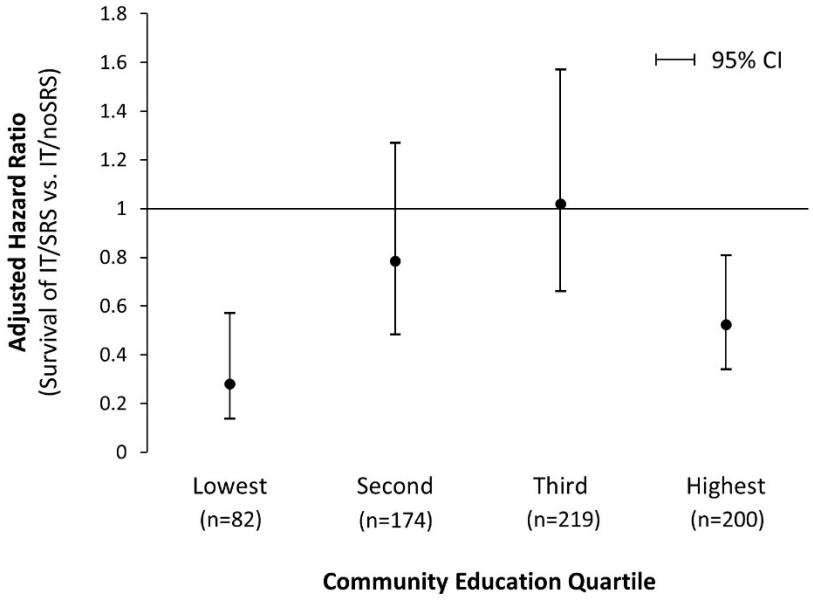
Table 4
Sensitivity Analyses for Association of Treatment Regimen and Survival

	Sensitivity Analysis 1				Sensitivity Analysis 2	
	Unadjusted		Adjusted*		Adjusted*	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
IT/SRS vs. IT/noSRS	0.65 (0.54-0.79)	**< 0.01**	0.72 (0.57-0.90)	< 0.01	0.72 (0.58-0.90)	**< 0.01**

IT/SRS – Immunotherapy with Stereotactic Radiosurgery; IT/noSRS – Immunotherapy without Stereotactic Radiosurgery; HR – Hazard Ratio; CI – Confidence Interval.
For sensitivity analysis 1, the comparative analysis was conducted using a different definition of overall survival—the number of days from treatment initiation to last known follow-up or death. For sensitivity analysis 2, the comparative analysis was conducted using a different adjustment strategy—inverse probability weighted Cox proportional hazards model.
*Adjusted for patient's age, diagnosis year, insurance, facility type, community education quartile, presence of lung metastasis, presence of liver metastasis, presence of bone metastasis, receipt of chemotherapy, and receipt of metastasectomy.

Community education quartile was found to have significant statistical interaction with treatment regimen received ($P = 0.03$). Amongst those in the lowest quartile for community education, the association between IT/SRS and improved OS was significant (aHR: 0.28, 95% CI: 0.14-0.57, $P < 0.01$). The association between IT/SRS and improved OS was also significant amongst those in the highest quartile for community education (aHR: 0.53, 95% CI: 0.34-0.81, $P < 0.01$). However, for those in the middle two quartiles for community education, the association between treatment regimen and OS was not significant (aHR in second quartile: 0.79, 95% CI: 0.49-1.27, $P = 0.32$; aHR in third quartile: 1.02, 95% CI: 0.66-1.57, $P = 0.93$). These results are illustrated in Figure 3.

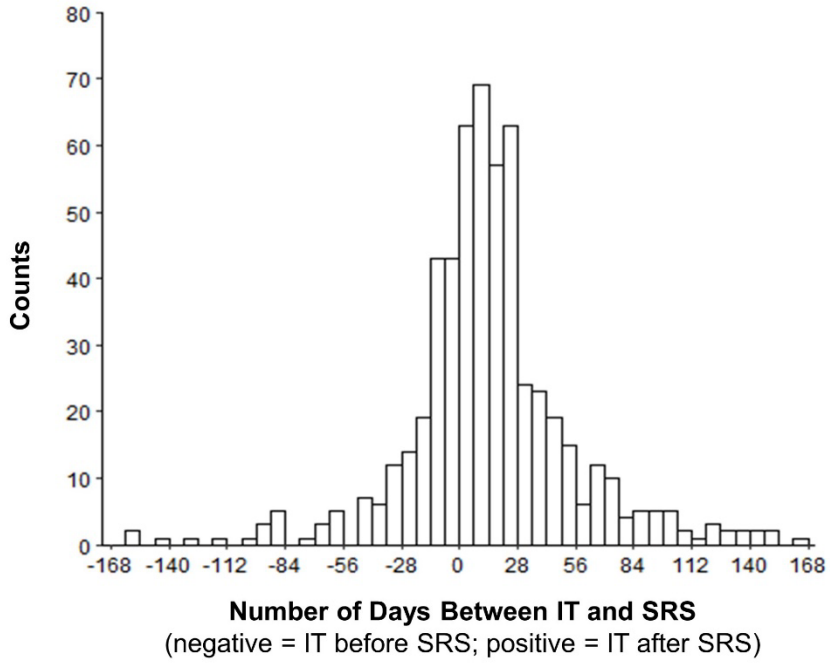
Figure 3
Interaction Effect of Community Education Quartile and Treatment Regimen



This figure illustrates the association between treatment regimen and overall survival, stratified by community education quartile. Community education quartile represents the percentage of adults (25 or older) in the patient's zip code who have a high school degree, categorized by quartiles. Hazard ratios were adjusted for patient's age, diagnosis year, insurance, facility type, community education quartile, presence of lung metastasis, presence of liver metastasis, presence of bone metastasis, receipt of chemotherapy, and receipt of metastasectomy. IT/SRS – Immunotherapy with Stereotactic Radiosurgery; IT/noSRS – Immunotherapy without Stereotactic Radiosurgery; CI – Confidence Interval.

Amongst the subset of patients who received IT/SRS (n = 492), IT was initiated on average 14.6 days after SRS (standard deviation: 46.5 days). The distribution of number of days between starting IT and SRS for this subset is illustrated in Figure 4. There was no significant association between timing of therapies and OS using any of the following definitions of timing: days from initiation of SRS to IT (aHR: 1.001, 95% CI: 0.998-1.004, $P = 0.47$), days between initiation of SRS and IT (aHR: 1.000, 95% CI: 0.996-1.003, $P = 0.84$), IT started ≤ 28 vs. > 28 days from SRS (aHR: 0.99, 95% CI: 0.73-1.35, $P = 0.94$), and IT started same day or after vs. before SRS (aHR: 1.03, 95% CI: 0.74-1.43, $P = 0.88$). These results are outlined in Table 5.

Figure 4
Histogram of Days Between IT and SRS



On average, IT was started 14.6 days after SRS with a standard deviation of 46.5 days. IT – Immunotherapy; SRS – Stereotactic Radiosurgery.

Table 5
Association of Relative Timing of Therapies and Overall Survival

		Unadjusted		Adjusted*	
	Levels	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Days from Start of SRS to IT	Continuous variable	1.000 (0.997-1.003)	0.99	1.001 (0.998-1.004)	0.47
Days between Start of SRS and IT	Continuous variable (positive values only)	1.000 (0.996-1.003)	0.79	1.000 (0.996-1.003)	0.84
Proximity of Therapies	IT started ≤ 28 vs. >28 days from SRS	1.04 (0.80-1.34)	0.79	0.99 (0.73-1.35)	0.94
Sequence of Therapies	IT started same day or after vs. before SRS	0.94 (0.71-1.24)	0.65	1.03 (0.74-1.43)	0.88

IT – Immunotherapy; SRS – Stereotactic Radiosurgery; HR – Hazard Ratio; CI – Confidence Interval.
*Adjusted for patient's age, sex, diagnosis year, insurance, facility type, community education quartile, presence of lung metastasis, presence of liver metastasis, presence of bone metastasis, and receipt of metastasectomy

Discussion

The results of our study show that the treatment of MBM with a combination of IT and SRS leads to improved overall survival compared to treatment with IT without intracranial radiation. Median overall survival for the IT/SRS cohort (29.5 months) was more than double that of the IT/noSRS cohort (11.9 months). This difference remained significant following adjustment for covariates and sensitivity analyses. Interestingly, the benefit of IT/SRS over IT/noSRS was strongest amongst those in the lowest and highest quartiles for community education level. For patients with MBM treated with IT/SRS, there was no specific proximity or sequence of therapies associated with any significant improvement in overall survival.

The Evolution of Treatment Paradigms for MBM

SRS has been a mainstay of treatment of MBM since its rapid acceptance in the 1990s.[13] Although initially prescribed only for those with few brain lesions, the indications for SRS have expanded over time. Studies have demonstrated the clinical benefit of SRS without any additional brain-directed therapy in cases of up to 10 brain metastases, and SRS has been shown to be beneficial as an adjuvant therapy following intracranial surgery.[14, 15]

SRS is generally given in combination with one or more systemic therapies, due to the high likelihood of extracranial disease in patients with MBM.[16] Currently, the category 1 recommended first-line systemic therapies for metastatic melanoma are single-agent checkpoint inhibitors (i.e. pembrolizumab, nivolumab), dual-agent checkpoint inhibitors (i.e. ipilimumab/nivolumab), and combination targeted regimens (i.e. dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib; only for those with a BRAF V600-activating mutation), per the National Comprehensive Cancer Network.[3]

The combination of SRS and checkpoint inhibitors for MBM has become particularly popular based on a suspected synergy in their mechanisms of action. Radiation has been shown to cause immunogenic cell death, whereby there is a release of cancer cell components that activate an anti-tumoral immune response.[17] Markers of this process have been upregulated by the addition of checkpoint inhibitors, as demonstrated in mouse experiments.[18] Furthermore, intracranial radiation is known to impair the integrity of the blood-brain barrier, potentially providing an avenue for intracranial infiltration by checkpoint inhibitors.[19] Multiple retrospective clinical studies have demonstrated that the addition of checkpoint inhibitors leads to significantly improved overall survival for patients with MBM treated with SRS.[20-22]

The use of checkpoint inhibitors as the sole initial treatment modality for MBM is a relatively new management strategy that has gained popularity due to several clinical trials published in the last decade (Table 6). These trials demonstrated that checkpoint inhibitors can stimulate control of intracranial lesions with decent rates of radiographic response without the use of any brain-directed therapies.[6-9] The most impressive results came from Tawbi et al., where 57% of the 101 participants treated with dual-agent checkpoint inhibitors—ipilimumab/nivolumab—achieved intracranial clinical benefit.[9]

These clinical trials, however, had notable limitations. The samples were relatively small, and none included a control group of patients with MBM treated with upfront checkpoint inhibitors and SRS concurrently. Additionally, it is known that some participants received brain-directed therapy around the time of starting the checkpoint inhibitor regimen, potentially inflating the clinical outcomes. For the trial of pembrolizumab for MBM reported by Kluger et al.,[8] it was subsequently reported that 13 out of 23 participants (57%) received SRS, intracranial surgery, or laser interstitial thermal therapy soon before or after initiating pembrolizumab.[23] It is

unclear whether participants in the other trials listed in Table 6 experienced similarly high rates of brain-directed therapy since this data was not reported.

Table 6
Clinical Trials of Checkpoint Inhibitors for Melanoma Brain Metastases

	Regimen	ICBR*	6-month OS	n
Margolin et al., 2012 [6]	Ipilimumab	24%	55%	51
Long et al., 2018 [7]	Nivolumab	20%	68%	25
	Ipilimumab/Nivolumab	57%	78%	35
Kluger et al., 2019 [8]	Pembrolizumab	30%	74%	23
Tawbi et al., 2018 [9]	Ipilimumab/Nivolumab	57%	92%	101

ICBR – Intracranial Clinical Benefit Rate; OS – Overall Survival.
*Intracranial clinical benefit rate represents the percentage of patients with complete response, partial response, or stable disease ≥ 6 months for intracranial lesions.

Combination Therapy vs. Immunotherapy Alone for MBM

Our study found that the treatment of MBM with IT without intracranial radiation led to significantly worse overall survival compared to the more established regimen of IT and SRS. This study complements the findings of previous retrospective studies that have addressed similar questions. Amaral et al. identified 380 patients with MBM treated at German Skin Cancer Centers between 2015 and 2018 with ipilimumab/nivolumab. This study found that the addition of local intracranial therapy (either SRS or surgery) was associated with significantly improved overall survival.[24]

White et al. utilized the NCDB to assess patients with MBM treated with IT between 2010 and 2015. Using propensity score matching, this study compared those treated with or without intracranial radiation (either SRS or whole brain radiotherapy) and initially found no

significant difference in overall survival between cohorts. However, when patients treated with whole brain radiotherapy were excluded from the sample, the difference became significant; the regimen of IT and SRS produced better overall survival compared to IT without intracranial radiation.[25] Because this study produced similar results to ours despite employing different statistical methods, this further supports the robustness of these findings.

Relationship between Patient Education and Treatment Outcomes

Interestingly, our study identified a significant interaction between community education level and treatment regimen received. For those living in the most or least educated communities (i.e. bottom or top quartiles for percentage of high school graduates), the survival benefit of SRS in combination with IT was strongest. Furthermore, the association between treatment regimen and overall survival was non-significant for patients characterized by the second or third community education quartiles. To the authors' knowledge, this parabolic-like interaction between education and treatment outcomes has never been previously reported.

One possible explanation for this finding is that there is a similarly parabolic relationship between a patient's health literacy and their adherence to therapy protocols. That is, adherence is strongest in those with the highest or lowest health literacy and poorest in those with moderate health literacy. Adherence to therapy protocols and follow-up visits is crucial to experience optimal benefit from treatment regimens, especially for patients with cancer,[26] and it is well established that high health literacy is associated with strong adherence.[27] Interestingly, it has also been shown that those with low health literacy have higher preferences for physician-directed rather than patient-involved decision making,[28] suggesting a heightened trust and stronger adherence to medical recommendations amongst this demographic group. It is therefore

logical that patients with intermediate health literacy would have the lowest rates of adherence as they may be characterized by both a desire for patient-involved decision making and a lack of sufficient understanding of complex cancer treatments. Of course, this explanation relies on several assumptions, including that a patient's community education level is associated with their individual health literacy. Future work is needed to test these hypotheses.

Impact of Therapy Timing on Clinical Outcomes

Our study was unable to demonstrate that a particular timing, proximity, or sequence of IT and SRS led to any significant change in patient survival. This question has been investigated often during retrospective studies of patients with brain metastases, and results have been mixed. Some studies have found that starting therapies in close proximity is associated with significantly better clinical outcomes compared to non-concurrent administration.[29-31] Others have found no difference in outcomes between concurrent and non-concurrent regimens.[22]

The lack of a clear association between IT/SRS timing and clinical outcomes may inform the mechanism of action of this combination regimen. There is a suspected synergy between IT and SRS, but the molecular basis for this synergy have been a topic of much debate. One proposed mechanism is that radiation releases neo-antigens that work in concert with IT to "reinvigorate exhausted intratumoral CD8 T-cells." Buchwald et al. argues that if this is the dominant mechanism, the relative timing of therapies would not be expected to influence their efficacy.[17]

Study Limitations

The NCDB has a number of shortcomings, which limit interpretations of our study. The dataset lacks information on certain treatment details, including the specific IT agent used, number of cycles of IT, and location of metastasectomy. There are also no details regarding patient symptomatology or radiographic findings, which would have been helpful for secondary endpoints. The NCDB has been shown to have poor representation of certain racial groups, including Asian/Pacific Islanders and American Indian/Alaskan Natives, potentially limiting the generalizability of our findings.[11] Additionally, as a retrospective study, it is impossible to account for all possible confounders and biases. An ongoing prospective study randomizing patients with MBM to receive ipilimumab/nivolumab with or without SRS will be valuable to further guide clinical practice (ClinicalTrials.gov, NCT03340129).

Conclusion

Our study is the largest known retrospective analysis examining patients with MBM treated with IT with or without SRS. We found that patients treated with both IT and SRS appear to have longer survival compared to IT without intracranial radiation. Additional studies are needed to clarify the relationship between patient education level and treatment outcomes for multi-modal oncologic treatments and to understand whether there is a particular sequence or proximity of IT and SRS that will optimize clinical outcomes.

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