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CLINICAL STUDY

Time from stereotactic radiosurgery to immunotherapy in patients with melanoma brain metastases and impact on outcome

Rodney E. Wegner[1] · Stephen Abel[1] · Randy S. D'Amico[2] · Gautam U. Mehta[3] · Jason Sheehan[4]

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Abstract

Background The role of immunotherapy for metastatic melanoma has expanded over the past decade triggering questions regarding the combination and timing of immunotherapy and radiation for brain metastases. We used the National Cancer Database (NCDB) to see if the time from radiation to immunotherapy in patients with melanoma brain metastases had an impact on survival.

Methods We queried the NCDB from 2010 to 2015 for patients with melanoma brain metastases treated with immunotherapy and stereotactic radiosurgery (SRS). Receiver operator characteristic (ROC) curve analysis was done to determine a timepoint associated with outcome. Cox regression was used to identify predictors of survival. Propensity matching was done to account for indication bias.

Results We identified 247 patients meeting the above criteria. The median patient age was 62 years (27–90) and the vast majority were Caucasian (99%). The median SRS dose was 22 Gy (18–24 Gy).The median time to SRS was 39 days (0–344) and the median time to immunotherapy was 56 days (6–454). The ROC analysis revealed 8 days from SRS to immunotherapy as associated with outcome. Fifty-six patients had immunotherapy prior to SRS, 30 patients had immunotherapy within 0–7 days of SRS, and the remaining 161 had immunotherapy greater than 7 days from SRS. Three year survival rates were 21%, 55%, and 35% for those timeframes, respectively ($p=0.0153$). Propensity matching of the 0–7 day and > 7 day groups yielded 28 pairs and Kaplan Meier analysis showed 3 year overall survival of 55% and 35%, in favor of immunotherapy within 7 days of SRS ($p=0.0357$). Multivariable Cox regression identified lack of extracranial disease, more recent year of treatment, and time from SRS to immunotherapy of 0–7 days as predictors of improved survival.

Conclusions Immunotherapy within 7 days of SRS shows a possible association with improve outcomes in patients with brain metastases from melanoma.

Keywords Radiosurgery · Melanoma · Brain metastases · Immunotherapy

Introduction

Melanoma remains one of the most common malignancies to metastasize intracranially, affecting 20–25% of patients with the diagnosis [1]. The treatment for brain metastases from melanoma continues to evolve and ranges from surgical resection, whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), a combination thereof, or even targeted/immunotherapy alone [2–4]. With advances in technology and imaging, SRS is increasingly used in patients that have multiple brain metastases (> 5–10). Considering the relatively radioresistant nature of melanoma, SRS permits delivery of higher effective doses to the tumor while simultaneously sparing adjacent uninvolved brain parenchyma, thus mitigating the neurocognitive dysfunction associated with

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✉ Rodney E. Wegner
rodney.wegner@ahn.org

[1] Division of Radiation Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, USA

[2] Department of Neurosurgery, Lenox Hill Hospital/Donald and Barbara Zucker School of Medicine at Hofstra, New York, USA

[3] Division of Neurosurgery, House Ear Institute, Los Angeles, USA

[4] Department of Neurosurgery, University of Virginia School of Medicine, Charlottesville, USA

WBRT [5–8]. With enhanced central nervous system penetration of targeted and immunotherapeutic agents, there has been increased interest in the utility of combination treatment with SRS and immunotherapy. Additionally, there are emerging data suggesting synergy between higher doses of radiation (as delivered with SRS) and the immune system [9, 10]. However, the optimal timing and sequencing of SRS with targeted and/or immunotherapy remains to be determined. As such, we sought to use the National Cancer Database (NCDB) to examine the interval from SRS to immunotherapy in this patient population and attempt to identify an optimal timeframe that may correlate with outcome.

Methods and materials

We queried the NCDB from 2010 to 2015 for patients with melanoma and brain metastases at time of diagnosis. Patients had to be treated with immunotherapy and brain-directed SRS to be included in the final cohort. Immunotherapy is coded for in the NCDB but the agents used and number of cycles administered are not documented. Radiation related variables/parameters coded for by the NCDB include: technique, anatomic target location, dose, and fraction pattern. We excluded any patients with less than 1 month of follow up to account for immortal time bias. Of note, the only outcome recorded in the NCDB is overall survival. In addition, follow up and survival are calculated as time from diagnosis to death or last known follow up. There is no available data on local failure, distant failure, toxicity, or salvage therapy.

The NCDB is a national cancer registry maintained by the American College of Surgeons and Commission on Cancer. It spans over 1500 cancer centers across the United States and documents up front staging and treatment information on approximately 70% of all newly diagnosed malignancies each year. As is required, we must state that the American College of Surgeons (ACS) and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator. Given the de-identified nature of the dataset, institutional review board approval was not required.

The NCDB began documenting brain metastases present at diagnosis in 2010, as well as liver metastases, lung metastases, and bone metastases. Patients with metastases in one of these sites were recorded as having extracranial disease. In addition, the NCDB records socioeconomic data points by zip code including education level as percentage of people without a high school diploma and average income. Race was simplified into Caucasian, African American, or other. The well-known Charlson-Deyo comorbidity score was used to quantify comorbid conditions. Insurance was listed as uninsured, governmental (Medicare/Medicaid), or private. Facility type was classified by ACS definition including community cancer program, comprehensive community cancer program, or academic/research program.

Medcalc Version 18 (Ostend, Belgium) was used for all statistical analyses. Baseline clinicopathologic and demographic characteristics were tabulated for all included patients. A receiver operator characteristic (ROC) curve analysis was performed to determine days from SRS to immunotherapy that correlated with outcome, ultimately revealing the criteria as 8 days (Supplemental Fig. 1). A multivariable logistic regression analysis was performed to identify baseline predictors of treatment with immunotherapy between 0 and 7 days from SRS. Univariable Cox regression was used to identify significant predictors of survival, which were then entered into a Multivariable Cox regression model using an enter method. Kaplan Meier analysis was used to compare survival across treatment groups. Propensity matching was performed using the above logistic regression to generate a propensity score indicating the likelihood of treatment between 0 and 7 days based on all baseline factors. A matched cohort was then created including patients treated at 0–7 days and > 7 days using an exact match on the propensity score. This yielded 28 pairs, which were then compared using a Kaplan Meier analysis. To support the assumption of balance, the propensity score was validated by splitting the cohorts into quartiles by score, showing differences in average score by quartile of less than 0.01.

Results

We identified 247 patients between 2010 and 2015 with melanoma brain metastases treated with immunotherapy and SRS. Full selection details are in Fig. 1. The median age was 62 years (27–90) and 45% of patients were male. Sixty-six percent of patients had extracranial metastatic disease. Fifty-six patients (23%) were treated with immunotherapy prior to SRS. Of the remaining 191 patients, 30 patients were treated with SRS at 0–7 days prior to immunotherapy. Please see Table 1 for a full set of baseline characteristics. The median time from diagnosis of melanoma to SRS was 39 days (0–344) and the median time to immunotherapy from diagnosis of melanoma was 56 days (6–454). The median SRS dose was 22 Gy (18–24 Gy). As described in the methods, a ROC analysis revealed 8 days from SRS to immunotherapy as criterion for survival. Multivariable logistic regression did not identify any predictors of treatment within 0–7 days. See Table 2 for a comprehensive list of odds ratios generated from that analysis.

The median follow up was 14 months (2–74) and the median survival for all patients was 20 months. Kaplan Meier analysis for patients treated with immunotherapy

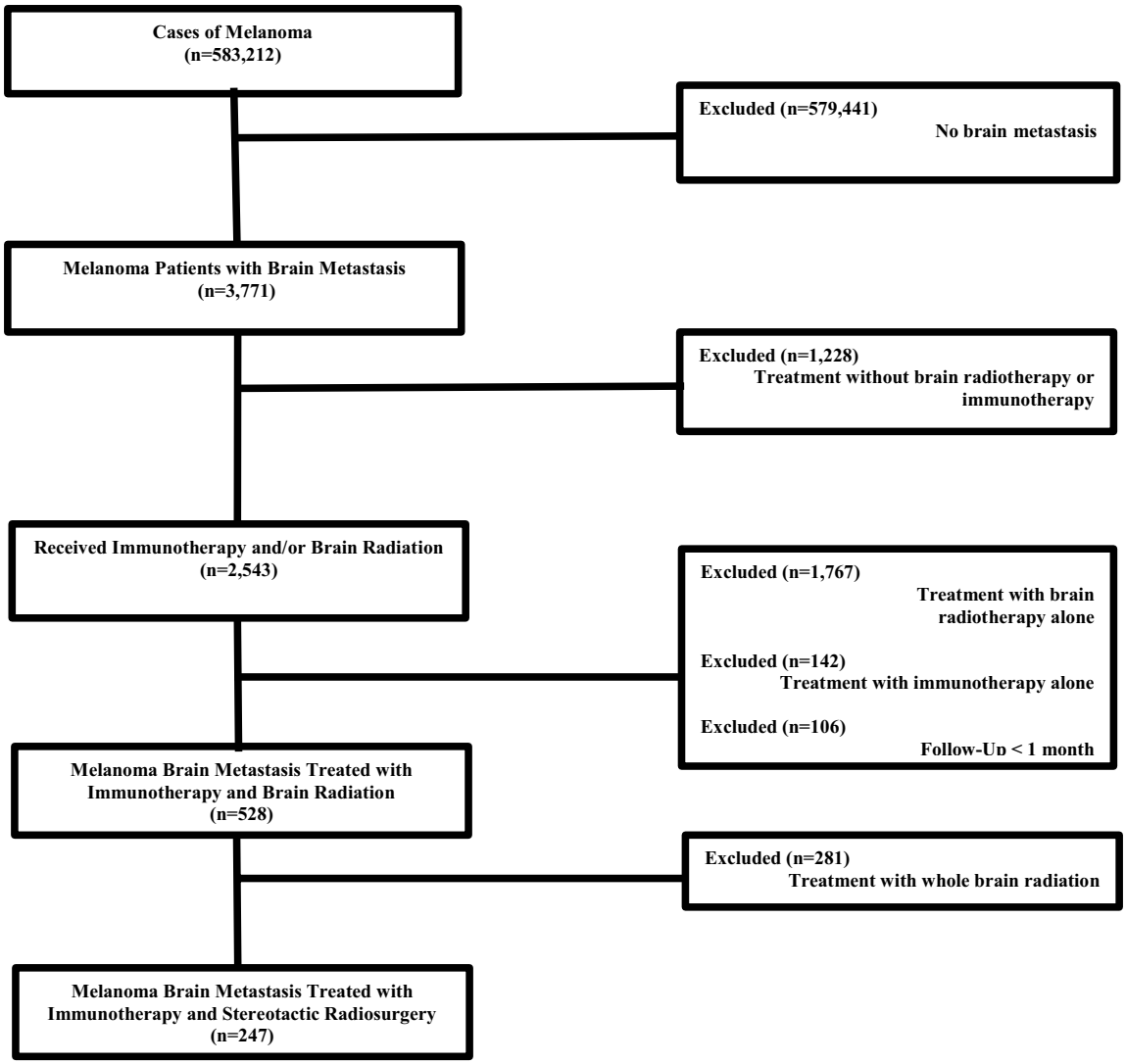

Fig. 1 CONSORT diagram. Patients with melanoma-related brain metastasis treated with immunotherapy and stereotactic radiosurgery

before SRS, 0–7 days after SRS, and > 7 days from SRS was associated with median survival outcomes of 13.4 months, median survival not reached, and 19.0 months ($p = 0.0153$) respectively. The corresponding 3 year survival rates for those cohorts were 21%, 55%, and 35%, respectively (Fig. 2). Multivariable Cox regression identified lack of extracranial disease, treatment with SRS 0–7 days prior to immunotherapy, and more recent year of diagnosis as predictive of better survival (Table 3). Creating a matched set using the propensity score generated by the multivariable logistic regression, yielded 28 matched pairs (of a potential 30) that were treated with SRS 0–7 days before immunotherapy and > 7 days. Kaplan Meier analysis on the matched cohorts showed 3 year overall survival rates of 55% and 35%, in favor of immunotherapy within 7 days of SRS ($p = 0.0357$). (Fig. 3).

Discussion

The results presented here lend further support to the notion that high dose radiation should be coupled with immunotherapy in patients with metastatic melanoma; ideally prior to and within close proximity of systemic therapy delivery. These findings help corroborate theoretical evidence that time is likely required for immune recognition following radiation-mediated antigen release and prior to the anti-tumor immune response. Not surprisingly, presence of extracranial metastatic disease predicted for worse outcomes, likely signifying increased burden of disease. It was interesting to note that year of treatment also predicted for better survival, likely owing to the FDA approval of multiple new immunotherapies and targeted agents over that

Table 1 Baseline patient characteristics (n = 247)

Treatment groups, time from SRS to immunotherapy (%)				
Characteristics	< 0 days (n = 56)	0–7 days (n = 30)	> 7 days (n = 161)	All (n = 247)
Sex				
Male	42 (75)	18 (60)	112 (70)	172 (70)
Female	12 (25)	12 (40)	49 (30)	75 (30)
Race				
Caucasian	55 (98)	30 (100)	160 (99)	245 (99)
African American	1 (2)	0 (0)	0 (0)	1 (0.5)
Other	0 (0)	0 (0)	1 (1)	1 (0.5)
Comorbidity score				
0	42 (75)	25 (83)	137 (85)	204 (83)
1	12 (21)	5 (17)	23 (15)	41 (16)
≥ 2	2 (4)	0 (0)	0 (0)	2 (1)
Insurance				
Not insured	1 (2)	1 (4)	4 (3)	6 (2)
Private payer	36 (64)	16 (53)	82 (51)	134 (54)
Government	19 (34)	13 (43)	74 (46)	106 (43)
Unrecorded	0 (0)	0 (0)	1 (< 1)	1 (1)
Education %				
≥ 29	7 (13)	3 (10)	12 (7)	22 (8)
20 to 28.9	14 (25)	6 (20)	34 (21)	54 (22)
14 to 19.9	12 (21)	8 (27)	58 (36)	78 (32)
< 14	23 (41)	12 (40)	57 (35)	92 (37)
Not recorded	0 (0)	1 (3)	0 (0)	1 (1)
Treatment facility type				
Community cancer program	4 (7)	0 (0)	3 (2)	7 (3)
Comprehensive community cancer program	14 (25)	6 (20)	32 (20)	52 (21)
Academic/research program	34 (68)	24 (80)	126 (78)	188 (76)
Treatment facility location				
Metro	48 (85)	26 (87)	146 (91)	214 (87)
Urban	7 (13)	4 (13)	13 (8)	25 (10)
Rural	1 (2)	0 (0)	2 (1)	8 (3)
Income, US dollars				
< 30,000	10 (18)	4 (13)	10 (8)	24 (10)
30,000 to 35,000	9 (16)	6 (20)	19 (10)	34 (14)
35,000 to 45,999	9 (16)	7 (23)	49 (30)	65 (26)
> 46,000	28 (50)	13 (44)	83 (52)	124 (50)
Distance to treatment facility, miles				
≤ 14 miles	27 (48)	14 (47)	74 (46)	115 (47)
> 14 miles	29 (52)	16 (53)	87 (54)	132 (53)
Age distribution, years				
≤ 62	35 (63)	19 (63)	81 (50)	135 (55)
> 62	21 (37)	11 (37)	80 (50)	112 (45)
Year of diagnosis				
2010	1 (2)	1 (3)	7 (2)	9 (3)
2011	8 (14)	0 (0)	14 (9)	22 (9)
2012	5 (9)	2 (7)	15 (9)	23 (9)
2013	10 (18)	4 (13)	30 (19)	44 (18)
2014	9 (16)	8 (27)	45 (30)	62 (25)
2015	23 (41)	15 (50)	50 (31)	88 (36)

Table 1 (continued)

Treatment groups, time from SRS to immunotherapy (%)				
Characteristics	< 0 days (n = 56)	0–7 days (n = 30)	> 7 days (n = 161)	All (n = 247)
Extracranial disease				
No	19 (34)	12 (40)	53 (33)	84 (34)
Yes	37 (66)	18 (60)	108 (67)	163 (66)
Chemotherapy				
No	48 (86)	28 (93)	144 (89)	220 (90)
Yes	8 (14)	2 (7)	17 (11)	27 (10)

time frame which are better tolerated and have drastically improved outcomes in patients with metastatic melanoma.

The issue of combining SRS and immunotherapy has been investigated in recent years. These investigations have mainly been triggered by the thought that combining immunotherapy and radiation promotes antigen exposure, thus improving he efficacy of immunotherapy [11, 12]. In addition, there is preclinical data suggesting that higher, ablative doses of radiation may produce increased tumor immunogenicity [13]. A NCDB analysis from Washington University in St. Louis compared patients treated with SRS for brain metastases with or without immunotherapy [9]. In that study, overall survival was nearly doubled (11 months vs 6 months), in patients treated with both SRS and immunotherapy compared to those treated with radiation alone. Similarly, a recently published NCDB analysis looked at the opposite scenario: patients treated with immunotherapy with or without cranial radiation [14]. In that study, patients treated with both SRS and immunotherapy had improved outcomes compared to those treated with immunotherapy alone or in combination with WBRT.

Several other retrospective series have examined the combination of SRS and immunotherapy, including one from Massachusetts General Hospital [15]. In that study the investigators reviewed the records of 74 patients treated with SRS and immunotherapy either concurrently (defined as within 30 days) or separately. Patients treated concurrently were more likely to attain durable intracranial control with no increase in radionecrosis. A group from Italy has also reported on outcomes in 80 patients treated with ipilimumab or nivolumab and SRS for melanoma brain metastases [10]. The drugs were typically administered within 48–72 h after SRS for patients within this study. Local control ranged from 70 to 85% at 1 year depending on the drug used. The rate of radionecrosis was slightly higher (15%), however, compared to historical controls.

The more specific issue of timing between targeted/immunotherapy and SRS has been examined before, mostly in a retrospective fashion. A cohort of 46 patients with melanoma brain metastases treated at the University of Virginia were analyzed, 32 of which had SRS prior to ipilimumab [16]. The group receiving SRS prior to ipilimumab had a median local recurrence free progression of 19 months compared to 3 months in those receiving SRS after ($p = 0.002$). Perilesional edema was more frequent in the patients with up front SRS (31% vs. 15%), with an overall radionecrosis rate of 16.4% across all patients. This phenomenon has been studied in other disease sites as well. A study on patients with stage IV non-small cell lung cancer (NSCLC) showed a benefit when there was a slight delay to immunotherapy administration. This particular study showed that patients treated with SRS or stereotactic body radiotherapy to a metastatic site from NSCLC had improved outcomes if immunotherapy was delivered > 21 days later (19 months vs 14 months, $p = 0.03$) [17]. Prospective studies are ongoing examining the interaction between high dose radiation and immunotherapy in stage IV melanoma. An open phase II study at Johns Hopkins is examining the use of SBRT to any single extracranial metastatic site (on day 1–14) along with nivolumab every 4 weeks until progression (NCT04042506). The investigators are attempting to characterize the theoretical abscopal effect, as well as, assess for clonal expansion of melanoma specific T cells.

As is the case with most retrospective series and especially those utilizing the NCDB, there is a significant amount of selection bias which can impact the interpretation of results presented here. In addition, whether patients were symptomatic and the number/size of lesions are not recorded, which could influence treatment recommendations. The types and combinations of immunotherapies (dual agent versus single agent) are not reflected in the database, and, since the study period, immunotherapy agents and protocols have become refined. BRAF status is also not recorded within the NCDB, which could further impact results and type of systemic therapy. It should also be mentioned that multiple immunotherapies were approved

Table 2 Multivariable logistic regression for odds ratios of IMT within 0–7 days after SRS

Variable	Odds ratio (95% CI)	P
Age		
≤ 62	Reference	
> 62	0.26 (0.06–1.06)	0.06
Chemotherapy		
No	Reference	
Yes	0.28 (0.03–2.44)	0.25
Comorbidity score		
0	Reference	
1	0.85 (0.25–2.89)	0.79
2	0.71 (0.03–15.22)	0.83
Distance from treating facility		
≤ 14 miles	Reference	
> 14 miles	0.92 (0.37–2.27)	0.85
Extracranial disease		
No	Reference	
Yes	0.66 (0.25–1.72)	0.39
Facility type		
Community cancer program	Reference	
Comprehensive community program	0.48 (0.02–9.37)	0.63
Academic program	0.45 (0.02–8.07)	0.58
Education level, % without high school diploma		
≥ 29	Reference	
20–28.9	0.86 (0.15–4.98)	0.87
14–19.9	1.17 (0.20–6.86)	0.86
< 14	2.47 (0.39–15.41)	0.33
Average household income, USD		
< 30,000	Reference	
30,000–35,000	0.49 (0.08–2.98)	0.44
35,001–45,999	0.37 (0.06–2.26)	0.28
≥ 46,000	0.22 (0.04–1.33)	0.09
Insurance type		
None	Reference	
Private	0.72 (0.06–8.28)	0.79
Government (medicare/medicaid)	1.77 (0.11–27.5)	0.68
Location		
Metropolitan	Reference	
Urban	1.13 (0.23–5.64)	0.88
Rural	0.99 (0.05–19.59)	0.99
Race		
Caucasian	Reference	
African American	0.42 (0.02–10.66)	0.60
Other	0.42 (0.02–10.66	0.60
Sex		
Male	Reference	
Female	1.83 (0.73–4.60)	0.19
Year of diagnosis		
2010	Reference	
2011	7.94 (0.29–214.56)	0.22
2012	0.21 (0.01–5.02)	0.34
2013	0.73 (0.06–8.64)	0.80
2014	1.20 (0.11–12.73)	0.88

Table 2 (continued)

Variable	Odds ratio (95% CI)	P
2015	1.42 (0.14–14.49)	0.77

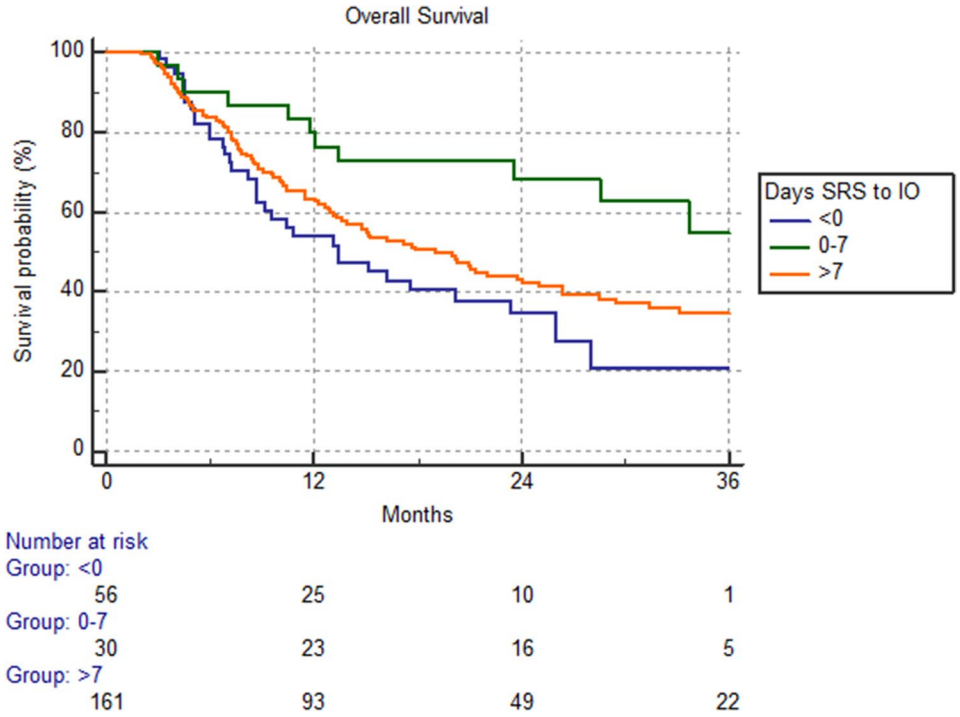

Fig. 2 Kaplan Meier curves for patients treated with immunotherapy prior to SRS, 0–7 days after SRS, and > 7 days from SRS. The median survival was 13.4 months, not reached, and 19.0 months for each group, respectively (p = 0.0153). Corresponding 3 year survival rates were 21%, 55%, and 35%

Table 3 Multivariable cox regression to identify predictors of survival

Characteristic	HR (95% CI)	P
Extracranial disease		
No	Reference	
Yes	1.95 (1.32–2.87)	**0.0007**
Time from SRS to IMT		
< 0 days	Reference	
0–7 days	0.36 (0.18–0.72)	**0.0041**
> 7 days	0.73 (0.48–1.10)	0.1353
Year of diagnosis		
2010–2015	0.84 (0.76–0.94)	**0.0067**

Bold values indicate statistical significance, p < 0.05

in 2014, and given their better tolerated toxicity profiles, could influence the results seen here. Furthermore, there is no available information regarding whether any intracranial lesions were resected, which would further influence the timing of radiation and systemic therapies. Importantly, local failure and distant failure are not captured within the NCDB, as well as, any salvage therapies, all of which could influence the outcomes in patients with melanoma brain metastases. As discussed above, there is some evidence that combined therapy may increase toxicity in the form of edema and/or radionecrosis, which is likewise not recorded but important to consider when it comes to timing treatment in these patients.

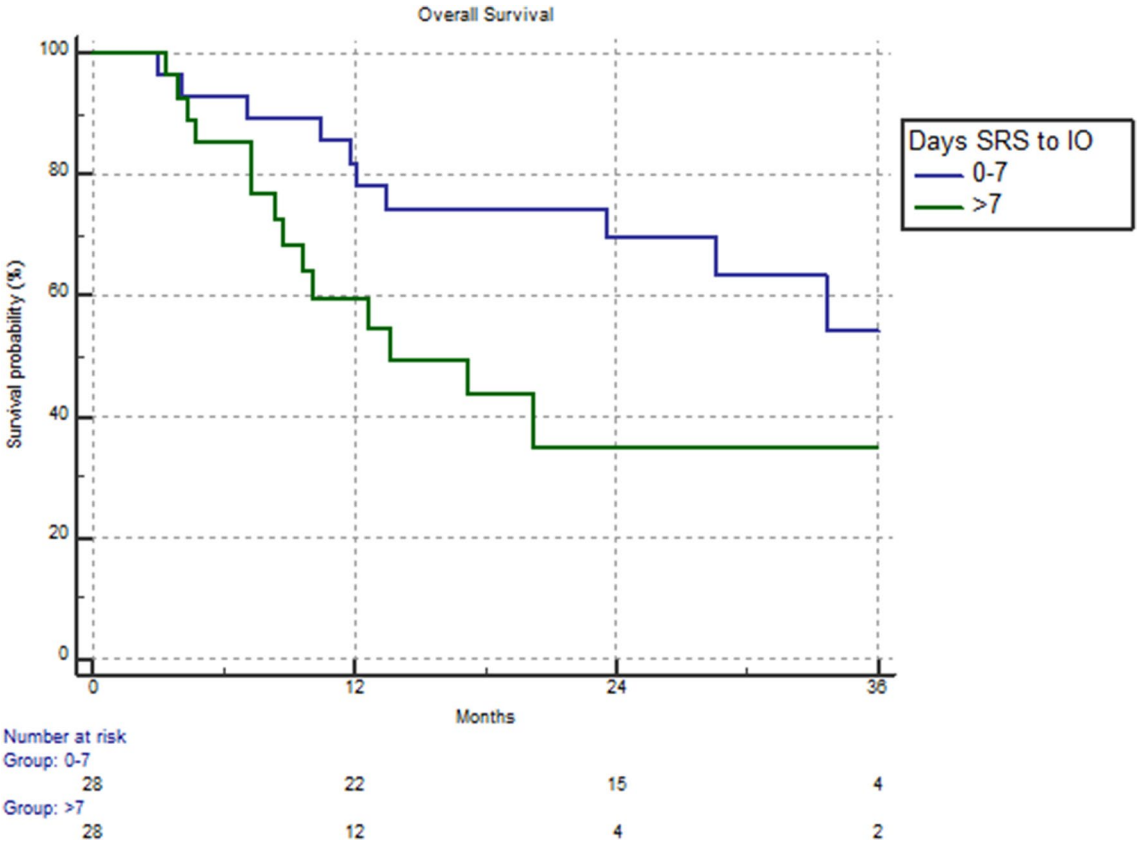

Fig. 3 After propensity matching there were 28 pairs of patients that were treated with immunotherapy 0–7 days from SRS and > 7 days from SRS. Median survival was not reached for those treated within 7 days of SRS and was 13.6 months for those treated later than 7 days ($p = 0.0357$). The 3 year survival rates were 55% and 35%, in favor of immunotherapy within 7 days of SRS

Conclusions

Immunotherapy delivered within 7 days of SRS treatment shows a possible association with improved outcomes in patients with brain metastases from melanoma. Ongoing trials will help further elucidate the best timeframe and sequencing of these therapies.

Author contributions REW: Project conception and design, statistical analysis, manuscript preparation; SA: Statistical analysis, manuscript editing; RSD: Manuscript Editing; GUM: Manuscript editing; JS: Manuscript Editing, final approval.

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Data availability This study was based on the NCDB registry data. The authors do not own these data and hence are not permitted to share them in the original form.

Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interest.

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