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Immunotherapy Plus Stereotactic Radiosurgery or Fractionated Stereotactic Radiotherapy in Patients with Brain Metastases

Amin S, Baine M and Lin C*

Radiation Oncology, University of Nebraska Medical Center, Omaha, NE, USA

***Corresponding author:**

Chi Lin MD,
Department of Radiation Oncology, University of Nebraska Medical Center, 986861 Nebraska Medical Center, Omaha, NE, 68198-6861, USA

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1. Abstract

1.1. Aim: To investigate the association of stereotactic radiosurgery (SRS) plus immunotherapy with overall survival (OS) compared to 3-5 fractions of stereotactic radiation therapy (SRT) plus immunotherapy in patients with brain metastases (BMs) from breast cancer, non-small cell lung cancer (NSCLC), and melanoma.

1.2. Methods: Cancer patients with brain metastases were identified from the National Cancer Database.

1.3. Results: Among the 6,215 patients, 508 (8.17%) received immunotherapy (391 SRS plus immunotherapy, and 117 SRT plus immunotherapy). In the multivariable Cox regression analysis, SRT plus immunotherapy was not associated with improved OS compared to SRS plus immunotherapy (HR: 0.951, CI: 0.728-1.241; p=0.71).

1.4. Conclusions: There was no difference in the OS of patients who received SRT plus immunotherapy and those who received SRS plus immunotherapy.

2. Background

Each year more than 170,000 patients are diagnosed with brain metastases (BMs) in the United States [1]. Approximately 20% to 40% of all patients with cancer develop BMs. The most common primary tumors associated with BMs are lung cancer (40%-50%), breast cancer (15%-30%), and melanoma (5%-20%) [2]. Patients with BMs are treated with surgery, whole-brain radiation therapy (WBRT), or stereotactic radiotherapy (SRT) [3-5]. BMs patients' overall survival (OS) is dismal, despite improvement in surgical and radiation techniques over the last few decades6. The median survival of BMs patients is between 4 to 16 months, depending on the primary cancer site [6-8].

The role of cytotoxic chemotherapy in the survival of BMs is not clear as drugs that have shown excellent efficacy in the treatment of extracranial cancers have shown little or no efficacy in the brain due to the poor permeability of these drugs through the blood-brain barrier (BBB). Immunotherapy has revolutionized the treatment landscape of cancer patients and has been approved for many cancers in various settings [9]. The brain was long considered an immune-privileged organ, and it was thought that immunotherapy would not elicit a robust response in the brain even if it crosses the BBB [9,10]. Recent preclinical and clinical research suggests that T cells and tumor-infiltrating lymphocytes traffic to the brain and their presence could improve the response to immunotherapy [11-13].

The RT dose and fractionation scheme can influence the immune system and produce different immune responses [14]. A high-dose radiation therapy (RT) may elicit a favorable immune response as its shorter delivery time minimizes lymphocytes' eradication [14]. SRT disrupts the BBB within hours after administration, allowing immune cells and other substances to easily cross into the CNS for a few weeks [15]. However, it is not clear if one fraction SRT (brain stereotactic radiosurgery (SRS)) or 3-5 fractions (brain SRT) produce the same immune response. Combining immunotherapy with SRS or SRT (3-5 fractions) may induce a different synergistic immune response in BMs patients if SRS's immune stimulation differs from 3-5 fractions SRT.

Ongoing clinical trials and a few retrospective immunotherapy studies have reported improved intracranial response and median OS in BMs patients diagnosed with melanoma [16-20]. However, these studies included only patients with BMs from melanoma, focused on a single drug, ipilimumab, and had a small number of patients [16-20]. More importantly, these studies only compared stereotactic radiosurgery (SRS) plus ipilimumab with SRS alone [16-20]. To the best of our knowledge, no study has compared SRS plus immunotherapy vs. SRT plus immunotherapy using an extensive database such as the National Cancer Database (NCDB). This study aims to investigate the association of SRS plus immunotherapy compared to 3-5 fractions SRT plus immunotherapy in patients with BMs from melanoma, non-small cell lung cancer (NSCLC), and breast cancer.

3. Materials and Methods

3.1. Data Source

The data for the current study were extracted from the NCDB, a joint program of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The NCDB is a nationwide oncology outcomes database for more than 1500 Commission on Cancer–accredited cancer programs in the United States and Puerto Rico. It captures 70% or more of newly diagnosed malignant neoplasms in the United States annually, and as of 2021, it contains information about more than 34 million cancer cases. The NCDB is not a publicly available data. Data is only available to the participating institutions after the submission of a research proposal and access application.

3.2. Study Population

The study consisted of patients aged ≥18 years who were diagnosed with the primary cancer of NSCLC, breast cancer, or melanoma between 2010 and 2015 and had BMs at the time of primary cancer diagnosis. The NCDB started collecting information about brain metastases at the time of primary cancer diagnosis in 2010.

Patients who received definitive surgery of the primary site were excluded because their survival is different from patients who did not receive surgery of the primary site, as reported in our previous paper [21]. Patients who receive surgery of the primary site are different from patients who do not receive surgery of the primary cancer site. Patients who received RT to areas other than the brain and patients who received WBRT were excluded. Patients missing information about brain RT, chemotherapy, surgery to the primary, and immunotherapy were also excluded. Patients diagnosed with small-cell lung cancer, colorectal cancer, and kidney cancer were excluded due to a small number of patients who received immunotherapy. We included those with radiation to the brain and defined SRS as a dose of 1,500-2,400 (1 fraction), and SRT as a dose of 2,100-3,000 (3 fractions), and a dose of 2,500-3,250 (5 fractions).

3.3. Outcome Variable

The OS was the primary outcome of this study, which was calculated from the date of diagnosis of BMs to the date of death. Patients who were alive or lost to follow-up were censored. The secondary outcome was to identify the factors associated with receiving immunotherapy, for which the odds ratios (OR) from the multivariable logistic regression analysis were calculated.

3.4. Explanatory Variables

The main explanatory variables were SRS, SRT 3-5 fractions, immunotherapy plus SRS, and immunotherapy plus SRT 3-5 fractions. Other variables included age at diagnosis, sex, race, education level, income level, residential area, treatment facility type, insurance status, Charlson-Deyo comorbidity score, year of diagnosis, and primary tumor type.

3.5. Statistical Analysis

Descriptive statistics for continuous and categorical variables are reported. Median and range were reported for continuous variables, while proportions were reported for categorical variables for patients who received immunotherapy and those who did not. A univariable and multivariable logistic regression analysis was used to report the predictors of immunotherapy, and the corresponding OR was reported as the measure of association with the likelihood of using immunotherapy. Survival time was measured in months from the date of diagnosis to the date of death. Kaplan-Meier curves were used to report the median OS, and the Log-rank test was used to determine the difference in OS between the treatment groups.

Cox proportional hazard regression analysis was used to report the impact of different variables on the OS of patients. The hazard ratio (HR) and associated 95% confidence interval (CI) were reported. Variables with a $p<0.15$ in the univariable analyses were selected for the multivariable analysis. The backward elimination was used to develop the final multivariable model with only variables with $p<0.10$ remaining in the final model. We used the P-value of 0.05 to define statistical significance, and all tests were 2-tailed. We performed all statistical analyses in SAS version 9.4 (SAS Institute).

3.6. Ethical approval

The data is de-identified and holds no identifying patient information, and therefore, written informed consent was not needed for this study. The institutional review board (IRB) was also not required for the study. All methods were carried out in accordance with relevant guidelines and regulations.

4. Results

Characteristics of the study participants. A total of 6,215 patients met the inclusion criteria, among whom 4,854 (78.20%) received SRS, 1361 (21.90%) received SRT, 508 (8.17%) received immunotherapy. 391 (76.97%) received SRS plus immunotherapy

among those who received immunotherapy, and 117 (23.03%) received SRT plus immunotherapy.

The median age of the study population was 65 years, with a range of 21 to 90 years. Most patients were white, living in urban areas, residing in high-income and high-education level areas, had health insurance, received chemotherapy, had primary cancer of NSCLC, and had a Charlson/Deyo Score of zero. The baseline characteristics of the study participants by immunotherapy group are shown in Table 1.

Logistic regression analysis. In the multivariable logistic regression analysis, younger age at diagnosis, receiving chemotherapy, primary cancer type of breast, or NSCLC (compared to melanoma), and diagnosis in 2014 or after were positively associated with the use of immunotherapy. The ORs of receiving immunotherapy for the variables of interest are provided in Table 2.

Survival analysis (Kaplan–Meier method and Cox proportional hazards regression). There was no difference in the median OS of patients who received SRS plus immunotherapy and patients who received SRT 3-5 fractions plus immunotherapy (17.38 [95% CI: 15.01-19.48] months vs. 18.4 [95% CI: 14.78-21.49] months; P=0.78) (Figure 1a). However, patients who received SRS plus immunotherapy had better median OS compared with those who received SRS without immunotherapy, with an absolute median OS benefit of 6.5 months (17.38 [95% CI: 15.01-19.48] months vs. 10.91 [95% CI: 10.45-11.37] months; P<0.001) (Figure 1b). Patients who received SRT plus immunotherapy had better median OS compared with those who received SRT without immunotherapy, with an absolute median OS benefit of 7.2 months (18.4 [95% CI: 14.78-21.49] months vs. 11.24 [10.22-12.39] months; P<0.001) (Figure 1c). Patients who received SRS plus immunotherapy had better median OS compared with those who received SRT without immunotherapy, with an absolute median OS benefit of 6.5 months (6.14 [95% CI: 15.01-19.48] months vs. 11.24 [95% CI: 10.22-12.39] months; P<0.001) (Figure 2a). Patients who received SRT plus immunotherapy had better median OS compared with those who received SRS without immunotherapy, with an absolute median OS benefit of 7.49 months (18.4 [95% CI: 14.78-21.49] months vs. 10.91 [10.45-11.37] months; P<0.001) (Figure 2b). There was no difference in the median OS of patients who received SRS and patients who received SRT (10.91 [95% CI: 10.45-11.37] months vs. 11.24 [10.22-12.39] months; P=0.37) (Figure 2c).

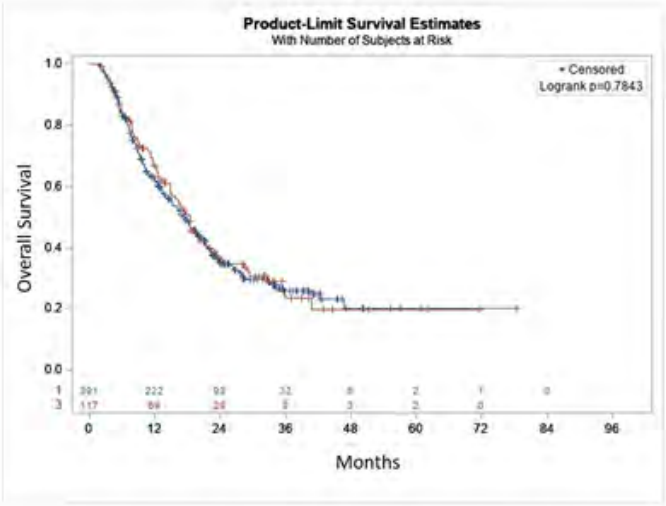
In the univariable Cox proportional hazard analysis, there was no difference in the OS of patients who received SRS plus immunotherapy and patients who received SRT plus immunotherapy (HR: 0.962, CI: 0.742-1.246; P= 0.77) (Table 2). However, SRS without immunotherapy and SRT without immunotherapy were associated with worse OS compared to SRS plus immunotherapy (HR: 1.483, CI: 1.306-1.685; P<0.001) and (HR: 1.436, CI: 1.250-1.649; P<0.001). SRS without immunotherapy and SRT without immunotherapy were also associated with worse OS compared to SRT plus immunotherapy (HR: 1.542, CI: 1.225-1.941; P<0.001) and (HR: 1.493, CI: 1.178-1.891; P<0.001).

Other factors associated with improved OS in the univariable Cox analysis included young age, female sex, non-Black non-White race, living in an area with an annual income of $35,000 or greater, living in area with <13% people with no high school degree, receiving treatment in an academic facility, Charlson-Deyo comorbidity score of zero or 1, receiving chemotherapy, year of diagnosis between 2014 and 2015, and tumor type of NSCLC (compared to melanoma).

In the multivariable Cox regression analysis, there was no difference in the OS of patients who received SRT plus immunotherapy compared to SRS plus immunotherapy (HR: 0.951, CI: 0.728-1.241; P=0.71). SRS without immunotherapy and SRT without immunotherapy were associated with worse OS compared to SRS plus immunotherapy (HR: 1.309, CI: 1.142-1.500; P<0.001) and (HR: 1.229, CI: 1.063-1.422; P<0.001). SRS without immunotherapy and SRT without immunotherapy were associated with worse OS compared to SRT plus immunotherapy (HR: 1.377, CI: 1.081-1.754; P<0.001) and (HR: 1.293, CI: 1.010-1.656; P<0.001). Other factors associated with improved OS in the multivariable analysis were younger age, female sex, Black race, non-black-non-white, living in an area with income level >$35,000, receiving treatment at an academic center, Charlson/Deyo Score of zero or one, diagnosis in 2014 or after, receiving chemotherapy, and primary cancer type of breast or NSCLC (compared to melanoma).

In the subset analysis stratified by primary tumor site, there was no difference in the OS of patients who received SRT plus immunotherapy compared to SRS plus immunotherapy (HR: 1.093, CI: 0.789-1.513; P=0.59) in patients diagnosed with NSCLC and in patients who had melanoma (HR: 0.774, CI: 0.450-1.331; P=0.35). We did not perform analysis for breast cancer as primary cancer as there were only very few patients (N=11) who received immunotherapy.

An RT dose >=8 Gray per fraction was associated with improved OS compared to a dose of <8 Gray per fraction (HR: 0.637, CI: 0.604-0.673; P<0.001). There was no difference in the OS of patients receiving an RT dose >=8 Gray per fraction plus immunotherapy and an RT dose<8 Gray per fraction plus immunotherapy (HR: 1.062, CI: 0.739-1.524; P=0.75). Although we excluded patients who received surgery of the primary site, the results did not change when those patients were included in an exploratory analysis (HR: 0.959, CI: 0.737-1.249; P=0.76).



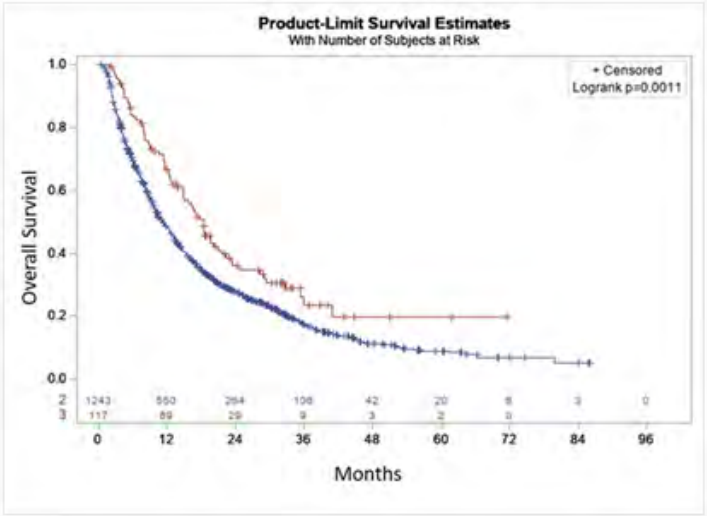
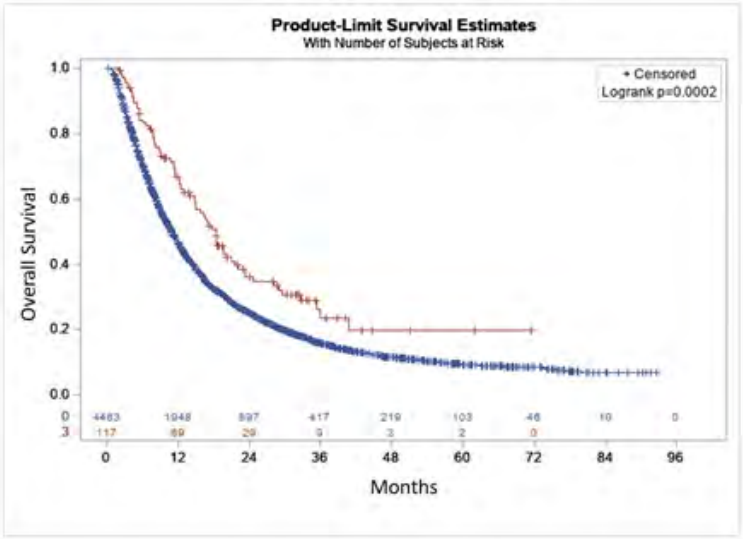


Figure 1: Overall survival of patients: (a) SRS plus immunotherapy (Blue), SRT plus immunotherapy (Red); (b) SRS (Blue), SRS plus immunotherapy (Red); (c) SRT (Blue), SRT plus immunotherapy (Red).



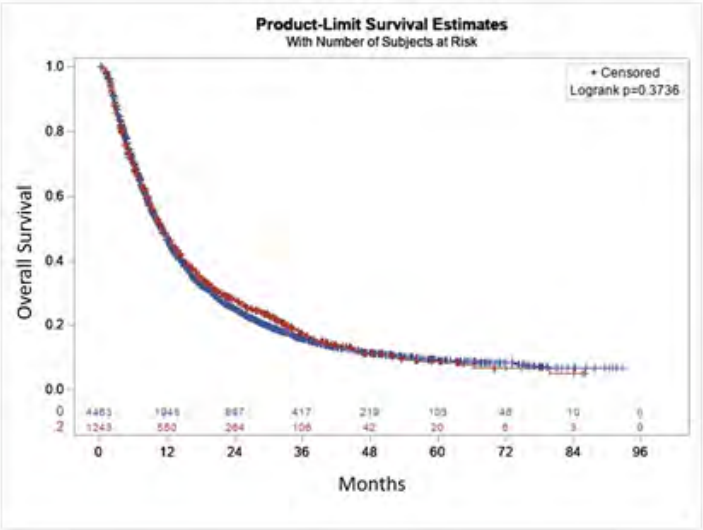


Figure 2: Overall survival of patients: (a)SRS plus immunotherapy (Blue), SRT (Red); (b) SRS (Blue), SRT plus immunotherapy (Red); (c) SRS (Blue), SRT (Red).

Table 1: Baseline characteristics of the study participants by immunotherapy

Variable		Immunotherapy 508 (8.17%)	No Immunotherapy 5,707 (91.83%)	Total 6,215
Age at diagnosis, Median (range)		62.0 (25-90)	65.0 (21-90)	65.0 (21-90)
Brain RT	SRS	391 (76.97)	4,463 (78.20)	4,854 (78.20)
	SRT	117 (23.03)	1,244 (21.80)	1,361 (21.90)
Sex	Male	257 (50.59)	2,824 (49.48)	3081 (49.57)
	Female	251 (49.41)	2,883 (50.52)	3,134 (50.43)
Race	White	448 (88.71)	4,786 (84.66)	5,234 (85.00)
	Black	44 (8.71)	629 (11.13)	673 (10.93)
	Other	13 (2.57)	238 (4.21)	251 (4.08)
	Unknown	3	54	57
Education	>=13% NHD	193 (38.07)	2,324 (40.81)	2,517 (40.59)
	<13% NHD	314 (61.93)	3,370 (59.19)	3,684 (59.41)
	Unknown	1	13	14
Income	>=$35,000	328 (64.69)	3,477 (61.09)	3,805 (61.38)
	<35,000	179 (35.31)	2,215 (38.91)	2,394 (38.62)
	Unknown	1	15	16
Place of Living	Urban	492 (98.99)	5,458 (98.38)	5,950 (98.43)
	Rural	5 (1.01)	90 (1.61)	95 (1.57)
	Unknown	11	159	170
Hospital Type	Academic	226 (46.69)	2,635 (46.76)	2,861 (46.76)
	Community	258 (53.31)	3,000 (53.24)	3,258 (53.24)
	Unknown	24	72	96
Insurance Status	Insured	487 (97.01)	5,470 (96.92)	5,957 (96.92)
	Not insured	15 (2.99)	174 (3.08)	189 (3.08)
	Unknown	6	63	69
Charlson/Deyo Score	0	374 (73.62)	3,809 (66.74)	4,183 (67.30)
	1	98 (19.29)	1,303 (22.83)	1,401 (22.54)
	>=2	36 (7.09)	595 (10.43)	631 (10.15)
Chemotherapy	Yes	349 (68.70)	4,165 (72.90)	4,514 (72.63)
	No	159 (31.30)	1,542 (27.02)	1,701 (27.37)
Cancer Type	Breast	38 (7.48)	133 (2.33)	171 (2.75)
	NSCLC	325 (63.98)	5,270 (92.34)	5,595 (90.02)
	Melanoma	145 (28.54)	304 (5.33)	449 (7.22)
Year of Diagnosis	2010-2013	139 (27.36)	3,107 (54.44)	3,246 (52.23)
	2014-2015	369 (72.64)	2,600 (45.56)	2,969 (47.77)

NHD=no high school degree

Table 2: Univariable and multivariable logistic regression analysis for the factors associated with receiving immunotherapy

Variables		Univariable Analysis	P-value	Multivariable Analysis	P-value
		OR (95% CI)		OR (95% CI)	
Age		0.975 (0.967-0.983)	0.001	0.984 (0.976-0.993)	0.003
Brain RT	SRT	Ref		Ref	
	SRS	0.932 (0.751-1.156)	0.52	1.179 (0.933-1.490)	0.17
Sex	Male	Ref		Ref	
	Female	0.957 (0.798-1.147)	0.63	…	
Race	White	Ref		Ref	
	Black	0.747 (0.542-1.030)	0.08	0.913 (0.648-1.288)	0.6
	Other	0.584 (0.331-1.028)	0.06	0.630 (0.351-1.132)	0.12
Education	>=13% NHD	0.891 (0.739-1.074)	0.23	…	
	<13% NHD	Ref		Ref	
Income	>=$35,000	Ref		Ref	
	<35,000	0.857 (0.709-1.036)	0.11	0.881 (0.716-1.083)	0.23
Place of Living	Urban	Ref		Ref	
	Rural	0.616 (0.249-1.524)	0.29	…	
Hospital Type	Academic	Ref		Ref	
	Community	1.003 (0.832-1.208)	0.98	…	
Insurance Status	Insured	Ref		Ref	
	Not insured	0.969 (0.567-1.655)	0.91	…	
Charlson/Deyo Score	0	Ref		Ref	
	1	0.766 (0.608-0.965)	0.02	0.898 (0.702-1.148)	0.39
	>=2	0.616 (0.433-0.877)	0.007	0.737 (0.508-1.069)	0.11
Chemotherapy	Yes	Ref		Ref	
	No	1.231 (1.011-1.498)	0.04	0.759 (0.597-0.964)	0.02
Primary Cancer	Breast	0.599 (0.397-0.904)	0.01	0.416 (0.266-0.649)	
	NSCLC	0.129 (0.103-0.162)	0.001	0.103 (0.078-0.135)	0.001
	Melanoma	Ref		Ref	0.001
Year of Diagnosis	2010-2013	0.315 (0.258-0.386)	0.001	0.269 (0.217-0.333)	0.001
	2014-2015	Ref		Ref	

NHD=no high school degree …. The variable was not included in the multivariable analysis due to having p>0.15 in the univariable analysis

Table 3: Univariable and Multivariable Cox Proportional Analysis of BMs patients with immunotherapy.

Variables		Univariable Analysis	P-value	Multivariable Analysis	P-value
		HR (95% CI)		HR (95% CI)	
Age		1.020 (1.018-1.023)	0.001	1.016 (1.013-1.018)	0.001
Treatment Combinations	SRS	1.483 (1.306-1.685)	0.001	1.309 (1.142-1.500)	0.001
	SRS +immunotherapy	Ref		Ref	
	SRT	1.436 (1.250-1.649)	0.001	1.229 (1.063-1.422)	0.005
	SRT + immunotherapy	0.962 (0.742-1.246)	0.77	0.951 (0.728-1.241)	0.71
Sex	Male	Ref		Ref	
	Female	0.777 (0.735-0.822)	0.001	0.798 (0.753-0.846)	0.001

Race	White	Ref		Ref	
	Black	0.953 (0.870-1.044)	0.3	0.899 (0.816-0.990)	0.03
	Other	0.724 (0.622-0.844)	0.001	0.737 (0.631-0.861)	0.001
Education	>=13% NHD	1.093 (1.032-1.157)	0.002	1.067 (0.996-1.143)	0.06
	<13% NHD	Ref		Ref	
Income	>=$35,000	Ref		Ref	
	<35,000	1.121 (1.058-1.187)	0.001	1.084 (1.012-1.161)	0.02
Place of Living	Urban	Ref		Ref	
	Rural	1.099 (0.876-1.378)	0.42	…	
Hospital Type	Academic	Ref		Ref	
	Community	1.128 (1.066-1.194)	0.001	1.076 (1.016-1.140)	0.01
Insurance Status	Insured	Ref		Ref	
	Not insured	1.010 (0.857-1.191)	0.91	…	
Charlson/Score	0	Ref		Ref	
	1	1.232 (1.152-1.318)	0.001	1.148 (1.072-1.229)	0.001
	>=2	1.413 (1.288-1.549)	0.001	1.215 (1.107-1.334)	0.001
Chemotherapy	Yes	Ref		Ref	
	No	1.656 (1.557-1.762)	0.001	1.723 (1.611-1.842)	0.001
Primary Cancer	Breast	0.873 (0.710-1.073)	0.19	1.332 (1.065-1.666)	0.01
	NSCLC	1.257 (1.121-1.409)	0.001	1.604 (1.407-1.829)	0.001
	Melanoma	Ref		Ref	
Year of Diagnosis	2010-2013	1.099 (1.038-1.164)	0.001	1.068 (1.007-1.134)	0.03
	2014-2015	Ref		Ref	

NHD=no high school degree

5. Discussion

The analysis of the current study demonstrates no difference in the OS of BMs patients who received SRS plus immunotherapy compared to 3-5 fractions SRT. SRS plus immunotherapy was associated with improved OS compared to SRS without immunotherapy and 3-5 fractions SRT without immunotherapy. SRT plus immunotherapy was associated with improved OS compared to SRT without immunotherapy and SRS without immunotherapy.

The median OS reported in our study for SRS plus immunotherapy and SRT plus immunotherapy is similar to the median OS reported in previous studies of BMs from melanoma. SRS plus immunotherapy improved OS by 5.1 months (17.0 (10.7–23.2) vs. 11.9 (9.8–14.0; P <0.001) compared to SRS alone in BMs from melanoma [22]. SRT plus immunotherapy was associated with improved OS compared to SRT alone in BMs from NSCLC [23]. The 1-year and 2-year OS was 68% and 62% in the SRT plus immunotherapy group compared to 64% and 35% in the SRT alone group (log-rank p = 0.023). In our study, SRS plus immunotherapy was associated with improved OS compared to SRS alone in BMs patients with melanoma (HR: 0.693, CI: 0.490-0.980; P=0.03) and NSCLC (HR: 0.998, CI: 0.741-1.344; P=0.99).

Immunotherapy may improve the survival of BMs patients either via controlling the extracranial disease or via controlling the intracranial tumor without or with the minimal extracranial disease. The control of intracranial disease may be influenced by the drug permeability through BBB, and SRT and SRS before immunotherapy may enhance such permeability. No difference in the OS of SRS plus immunotherapy and SRT plus immunotherapy is an indication that if immunotherapy has any impact on controlling the intracranial disease, SRS and SRT have the same effect on BBB permeability. If the impact is via controlling the extracranial disease, the systemic immune response produced by SRS or SRT is also the same.

The improved OS associated with SRS plus immunotherapy compared to SRS alone or SRT plus immunotherapy compared to SRT alone may be due to the additive or synergistic interaction of immunotherapy with SRS and SRT. Radiation therapy causes the release of neoantigens, upregulation of inflammatory cytokines, and the release of cellular danger-associated molecular patterns from irradiated tumor cells, all of which increase tumor cells' immunogenicity and make the tumor cells better target for the immune system [24-29].

To our knowledge, this study is the first and largest study that has compared SRS plus immunotherapy and 3-5 fractions SRT plus immunotherapy in BMs patients from breast cancer, NSCLC, and

melanoma. The findings are important in the context of our hypothesis that SRS and 3-5 fractions SRT may generate a different immune stimulatory response, which could be associated with a difference in the synergistic effect of combining immunotherapy with any of these treatments. The findings also indicate that the synergistic effect of both SRS and SRT with immunotherapy produces enough immune stimulation that they provide the same survival benefits in BMs patients. Besides, the better OS of SRS and SRT combined with immunotherapy compared to SRS and SRT without immunotherapy could be due to the better extracranial control of the disease by the combination treatments irrespective of immune stimulation. The findings are crucial as the decision to recommend SRS or SRT depends on various factors such as the number of metastases, the size of the intracranial tumor, and the location of the tumor. Since the addition of immunotherapy to SRS or SRT deliver the same survival benefit, immunotherapy could be combined with SRS or SRT while also not compromising the candidacy of patients for SRS or SRT. No difference in the OS of an RT dose >=8 Gray per fraction plus immunotherapy and an RT dose <8 Gray per fraction plus immunotherapy is an indication that a lower RT dose also produces immune response enough for the synergistic interaction of immunotherapy that could be matched with a higher dose RT combined with immunotherapy.

Our study has several limitations inherent to the NCDB, which do not provide information about the type of immunotherapy, cause of death, and surgery to the brain. In addition, we do not have information about the number of brain metastases, the volume of intracranial disease, extracranial disease burden, and performance status, all of which have roles in the decision of receiving SRS or SRT. Patients who received SRT are likely to have a larger brain tumor size compared to patients who received SRS. Patients who received immunotherapy may represent a unique cohort of BMs patients with characteristics that we could not adjust for in the database. There also could be some additional residual confounding.

The current study is the most comprehensive retrospective study investigating the association of SRS plus immunotherapy compared to 3-5 fractions SRT plus immunotherapy in BMs patients from breast cancer, NSCLC, and melanoma. We found no difference in the OS of patients who received SRS plus immunotherapy compared to SRT plus immunotherapy. SRS plus immunotherapy was associated with improved OS compared to SRS alone, and SRT plus immunotherapy was associated with improved OS compared to SRT alone.

6. Summary Points

• There was no difference in the OS of patients who received SRT plus immunotherapy and those who received SRS plus immunotherapy. SRS and SRT without immunotherapy were associated with worse OS compared to SRS plus immunotherapy

• SRS without immunotherapy and SRT without immunotherapy were associated with worse OS compared to SRS plus immunotherapy

• SRS without immunotherapy and SRT without immunotherapy were associated with worse OS compared to SRT plus immunotherapy

• There was no difference in the OS of patients receiving an RT dose >=8 Gray per fraction plus immunotherapy and an RT dose<8 Gray per fraction plus immunotherapy

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