

Radiation Necrosis in Stereotactic Radiosurgery and Checkpoint Inhibitors for Brain Metastases from Lung Adenocarcinoma

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Abstract

- Concurrent therapy with stereotactic radiosurgery (SRS) and immune checkpoint inhibitors (ICI) is increasingly common for brain metastases from lung adenocarcinoma
- Rates and timing of radiation necrosis (RN) with SRS in the setting of ICIs is an ongoing area of research.
- We investigated rates and timing of RN in 39 patients with brain metastases from lung adenocarcinoma treated with SRS with or without concurrent ICIs
- No statistical difference was found between rates of RN in patients treated with SRS and ICI (SRS-ICI) and rates of RN in patients treated with SRS alone
- Patients treated with SRS alone were found to have a statistically shorter length of time ($p=0.01$) from initial SRS treatment to symptomatic RN than patients treated with SRS-ICI

Introduction

- Lung adenocarcinoma is associated with brain metastases in up to 25% of patients
- SRS or fractionated stereotactic radiation therapy (SRT) is a first-line treatment for brain metastases that provides excellent local control
- Radiation necrosis (RN) is a known risk of SRS and may occur in up to 25% of patients who undergo treatment
- RN may cause significant neurological impairment, cognitive dysfunction, unnecessary retreatment, and lower quality of life
- ICIs are an increasingly common therapy for brain metastases, and are often used concurrently with SRS
- Rates and timing of RN after SRS-ICI treatment for lung adenocarcinoma may differ from rates and timing of RN after SRS alone and is an ongoing area of interest

Methods

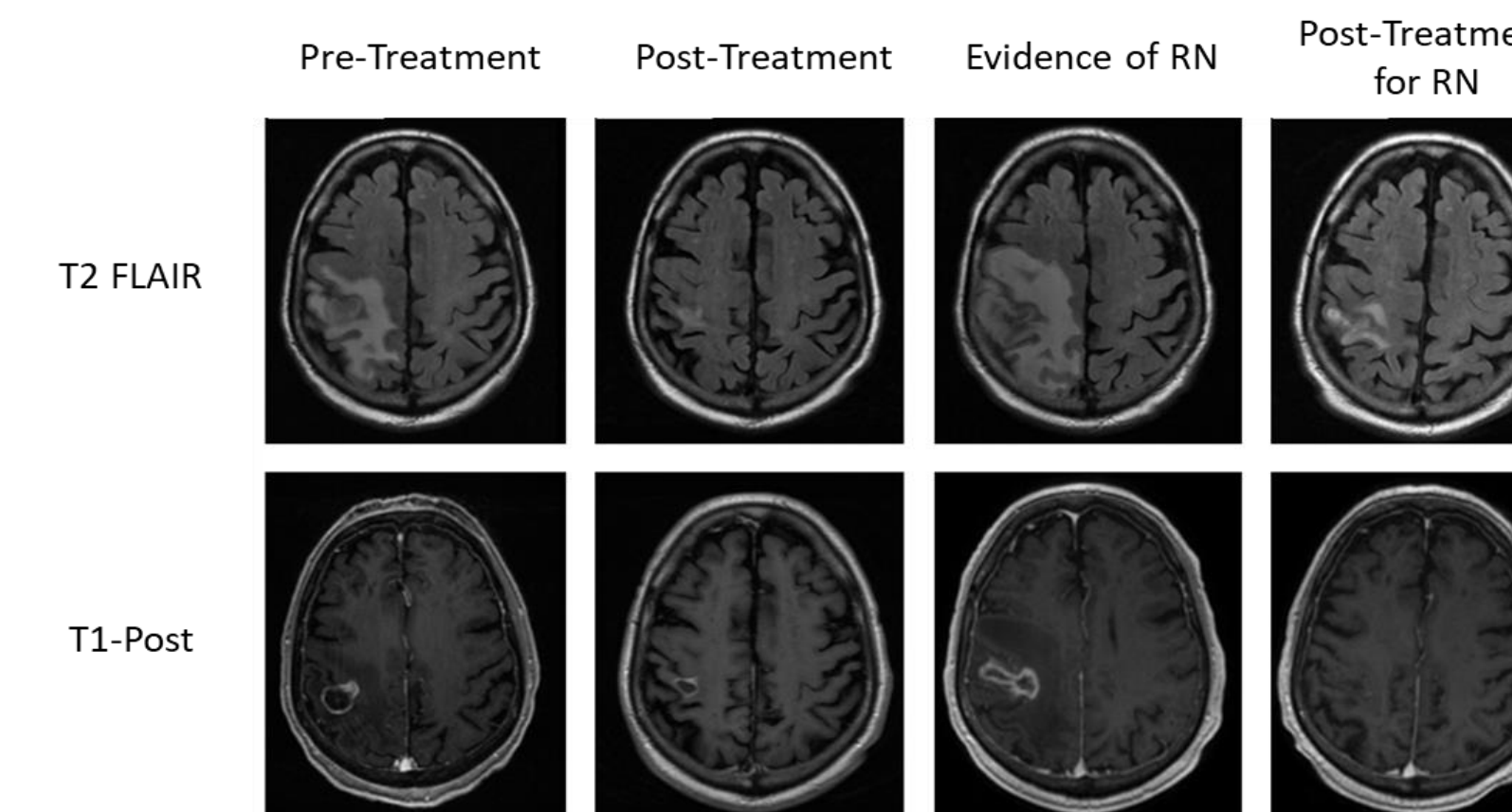
- We analyzed retrospective data from patients undergoing SRS for lung adenocarcinoma with BM at our institution from 2015 to 2018
- 39 patients were eligible for evaluation: 20 patients received SRS-ICI and 19 received SRS without ICI
- Other inclusion criteria were: 3 or more MRIs of the brain from initial diagnosis of brain metastases, and a minimum 3 months survival from initial treatment for assessment of RN
- Only patients receiving PD-1 or PD-L1 inhibitors were included
- Diagnosis of RN was made either histologically or clinically based on MRI scans with enhanced FLAIR signal after SRS that subsequently resolved with treatment for RN.

Patient Characteristics and Evaluation

Table 1: Baseline Patient Characteristics at Time of Diagnosis with Brain Metastases

Baseline Characteristics		SRS-ICI n=20	SRS n=19
Gender (n)	Male	12	10
	Female	8	9
Age Group (years)	<50	0	2
	50-59	5	5
	60-69	7	10
	70-79	6	2
	80+	2	0
Extracranial Metastases (n)	No	11	8
	Yes	9	11
Brain Metastases (n)	1 to 4	9	16
	5 to 8	8	3
	9+	3	0
ECOG (n)	1	9	8
	2	9	4
	3	2	7
Other Systemic Therapies	Yes	15	15
	No	5	4

Figure 1: Example of Radiation Necrosis on MRI



Development of Radiation Necrosis

Table 2: Characteristics, Treatment, and Survival of Patients with Radiation Necrosis

Patient	Sex	Age of Diagnosis	Tumor Volume (ccm)	SRS Dose to BM	ICI (no. doses) at time of diagnosis of RN	ECOG Performance Status at time of SRS	Treatment for RN	Overall Survival (months)
1	Male	54	5.16	20Gy	8 cycles of Nivolumab	1	Dexamethasone, Bevacizumab	37.07
2	Male	70	6.92	18Gy	17 cycles of Nivolumab	2	Dexamethasone, Bevacizumab	40.53
3	Female	55	3.72	20Gy	22 cycles of Atezolizumab	2	Dexamethasone	45.9
4	Female	55	41.05	40Gy/5fx	None	1	Dexamethasone, Bevacizumab	29.47
5	Male	72	40.08	(1)20Gy (2)30Gy/5fx	None	2	Dexamethasone, Bevacizumab	19.2
6	Female	58	18.19	32.5Gy/5fx	None	2	Dexamethasone	8.37

Patient	Sex	Age of Diagnosis	Tumor Volume (ccm)	SRS Dose to BM	ICI (no. doses) at time of diagnosis of RN	ECOG Performance Status at time of SRS	Treatment for RN	Overall Survival (months)
7	Male	68	1.79	20Gy	None	1	Dexamethasone	10.43
8	Male	68	2.91	20Gy	None	1	Dexamethasone, Bevacizumab	14.4
9	Male	69	5.05	20Gy	4 cycles of Pembrolizumab 2 cycles of Nivolumab	1	Dexamethasone, Bevacizumab	15.13
10	Male	55	2.98	18Gy	Nivolumab Unknown no. of cycles	2	Dexamethasone, Bevacizumab	21.8
11	Female	68	19.68	30Gy/5fx	None	3	Dexamethasone	4.9

Timing and Rates of Radiation Necrosis in Patients Treated with SRS-ICI Vs. SRS

Graph 1: Time from SRS to Radiation Necrosis

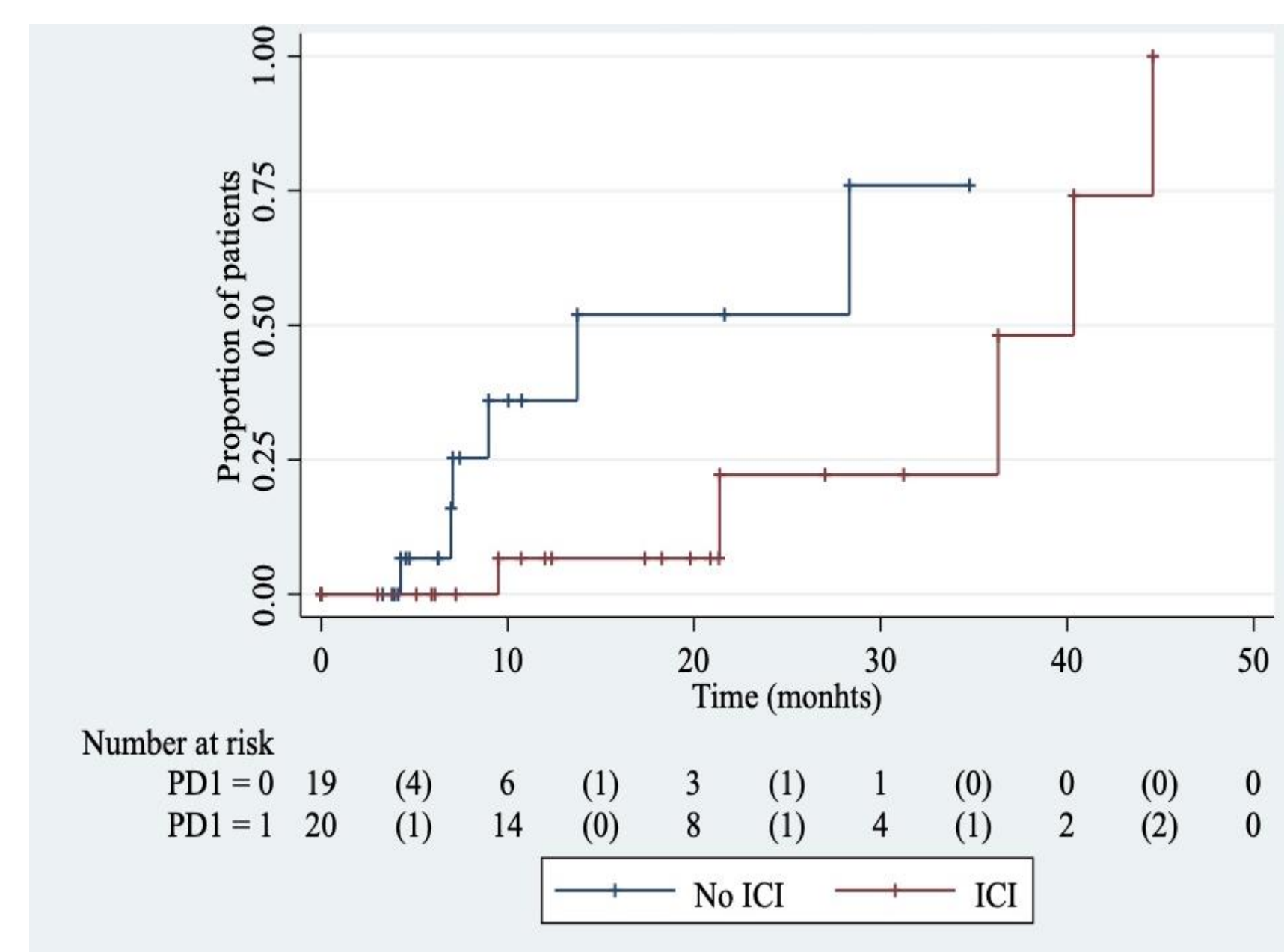


Table 3: Univariate and Multivariate Analysis of Risk Factors for Radiation Necrosis

Risk Factor	Reference Value	Univariate Analysis		Multivariate Analysis	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Age	40Y (OR per each increase of 10)	3.26 (0.11-65.93)	0.53	N/A	N/A
Sex	Male	0.66 (0.16-2.77)	0.72	N/A	N/A
CT	None	4.00 (0.44-36.58)	0.34	N/A	N/A
ICI	None	0.72 (0.17-2.93)	0.65	N/A	N/A
ECOG	1 (OR per each increased unit)	1.99 (1.33-33.33)	0.05	1.11 (0.53-53.03)	0.10
Resection	None	1.21 (0.28-5.21)	0.80	N/A	N/A
# Lesions Treated	1 (OR per each increased unit)	2.00 (0.34-45.32)	0.86	N/A	N/A
Volume Treated	1cc (OR per each increased 1cc)	1.02 (1.01-4.01)	0.02	1.11 (0.60-1.23)	0.48
EGFR/ALK+	Negative	1.38 (0.27-6.84)	0.70	N/A	N/A

Summary

- 39 patients with 171 brain metastases were included in the study: 20 patients received SRS-ICI and 19 received SRS without ICI
- 11 patients (28%) developed RN: five patients from the SRS-ICI group and six patients from the SRS group
- Patients treated with SRS-ICI were found to have a longer period from SRS to development of RN than patients treated with SRS alone ($p=0.01$)
- Lower ECOG status and volume treated were associated with decreased rates of RN on univariate analysis although statistical significance was not reached on multivariate analysis
- On multivariate analysis, no statistical difference was found in rates of RN based on ICI treatment, chemotherapy, number of lesions treated, or previous resection of metastases

Conclusions

- Treatment with ICI may affect the length of time from SRS to development of RN when compared to treatment with SRS alone.
- In our study, length of time from SRS to development of RN was statistically longer in patients treated with SRS-ICI when compared to SRS alone ($p=0.01$)
- Given the small sample size of patients with RN, further evaluation regarding timing of RN with SRS-ICI vs. SRS is warranted
- No difference in rates of RN was found between patients treated with SRS-ICI vs. SRS. This is consistent with recently published studies.
- ECOG level and volume treated were found to affect rates of RN, although this finding did not hold on multivariate analysis
- Future directions include expanding the number of patients in the study to obtain a more robust analysis

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