ORIGINAL ARTICLE

Safety of Combined PD-1 Pathway Inhibition and Intracranial Radiation Therapy in Non–Small Cell Lung Cancer

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ABSTRACT

Introduction: Intracranial metastases are a common cause of morbidity and mortality in patients with advanced NSCLC, and are frequently managed with radiation therapy (RT). The safety of cranial RT in the setting of treatment with immune checkpoint inhibitors (ICIs) has not been established.

Methods: We identified patients with advanced NSCLC with brain metastases who received cranial RT and were treated with or without programmed cell death 1/programmed death ligand 1 inhibitors between August 2013 and September 2016. RT-related adverse events (AEs) were retrospectively evaluated and analyzed according to ICI treatment status, cranial RT type, and timing of RT with respect to ICI.

Results: Of 163 patients, 50 (31%) received ICIs, whereas 113 (69%) were ICI naive. Overall, 94 (58%), 28 (17%), and 101 (62%) patients received stereotactic radiosurgery, partial brain irradiation, and/or whole brain RT, respectively. Fifty percent of patients received more than one radiation course. We observed no significant difference in rates of all-grade AEs and grade 3 or higher AEs between the ICI-naive and ICI-treated patients across different cranial RT types (grade $\geq$3 AEs in 8% of ICI-naive patients versus in 9% of ICI-treated patients for stereotactic radiosurgery [$p = 1.00$] and in 8% of ICI-naive patients versus in 10% of ICI-treated patients for whole brain RT [$p = 0.71$]). Additionally, there was no difference in AE rates on the basis of timing of ICI administration with respect to RT.

Conclusions: Treatment with an ICI and cranial RT was not associated with a significant increase in RT-related AEs, suggesting that use of programmed cell death 1/programmed death ligand 1 inhibitors in patients receiving cranial RT may have an acceptable safety profile. Nonetheless, additional studies are needed to validate this approach.

Keywords: NSCLC; Radiation; Immunotherapy; PD-1 inhibitor; Brain metastases

Introduction

Intracranial metastases are a common and devastating complication of lung cancer.[1] Intracranial metastases will develop in approximately 40% of patients with advanced

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NSCLC during their disease course, with most (approximately 70%) going on to receive intracranial radiation therapy (RT).[2] Recently, multiple immune checkpoint inhibitors (ICIs) targeting the programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) axis have entered the clinic and have quickly reshaped management strategies for patients with advanced NSCLC.[3–5] Within this evolving treatment paradigm, patients with brain metastases are increasingly being considered for combined treatment using a systemic ICI and cranial RT; yet, there are limited data regarding the safety of this approach.[6]

Preclinical findings suggest that the immune activity of RT and ICIs is nonredundant and may in fact be synergistic.[7–9] Radiation has been shown to liberate neoantigens yet also lead to upregulation of PD-1 and PD-L1 on immune and tumor cells, respectively, resulting in immune escape.[10–14] PD-1 inhibition can in turn reverse T-cell exhaustion in this setting, enabling neoantigen recognition.[15] These findings raise concerns that combined RT and ICIs—although synergistic—may potentially also increase toxicity.

Clinical data evaluating combined ICI and RT have thus far been limited in NSCLC, particularly in patients with brain metastases. Indeed, patients with active brain metastases have traditionally been excluded from prospective trials of ICIs.[3,4] Case reports have described radiographic pseudoprogression after treatment with cranial RT and ICI therapy, and pathologic examination in such cases has demonstrated reactive astrocytosis and T-cell infiltrates. However, retrospective evidence has been contradictory, with select studies demonstrating a significant increase in intracranial inflammation and related toxicity after combined cranial RT and ICI therapy that was not observed in other studies.[16–18] Furthermore, the sequence and timing of cranial RT and ICI therapy is a theoretical modifier of the extent of potential immune synergy and therefore may have implications for both efficacy and toxicity.[19] However, the optimal timing of combined therapy has not been established.

To investigate the safety of cranial RT in patients with NSCLC who are receiving ICIs, we retrospectively evaluated RT-related toxicity and radiographic intracranial inflammation in patients with NSCLC with and without a history of treatment with PD-1 or PD-L1 inhibitors. Particular focus was given to the potential effect of sequencing and timing of cranial RT and ICIs on treatment-related toxicities.

Materials and Methods

Patient Population

We identified patients with NSCLC and brain metastases treated with single-agent PD-1 or PD-L1 inhibitor therapy (the ICI+ cohort) at the Massachusetts General Hospital between August 2013 and September 2016. Patients were required to have a history of one or more courses of cranial RT, no history of nonlung malignancy metastatic to the brain, and at least 1 month of clinical follow-up after cranial RT and start of ICI therapy. For an ICI-naive (ICI–) comparator cohort, we identified patients with NSCLC meeting the aforementioned eligibility criteria and treated with cranial RT in the period immediately before regulatory approval/initiation of clinical trials of ICIs at our institution (January 2013–August 2013). Medical records were reviewed to extract data on clinicopathologic features, treatment histories, and patient outcomes. This study was approved by the institutional review board at our institution.

RT

All types of cranial RT (whole brain radiotherapy [WBRT], partial brain irradiation [PBI], and stereotactic radiosurgery [SRS]) were included to investigate a range of doses, volumes, and fractionation schedules. For SRS, photon or proton therapy was selected on the basis of clinical availability or patient preference. Photon SRS, as well as PBI and WBRT, were delivered with a linear accelerator. SRS was typically delivered in one fraction but was also delivered in a range of up to 5 fractions to increase safety. PBI and WBRT were generally delivered in 10 to 15 fractions; one patient discontinued PBI after receiving 5 Gy on account of unrelated clinical issues. Patients' most recent magnetic resonance imaging (MRI) scans were fused with planning computed tomography scans to assist in the delineation of target structures.

AE Assessment

Toxicity was graded retrospectively by investigators in accordance with the Common Terminology Criteria for Adverse Events), version 4.0. Motor deficits attributable to motor cortex–directed RT were graded as *nervous system disorders–other, specify*. To investigate whether the sequence or timing of ICI therapy relative to RT affected the frequency or severity of cranial RT–related adverse events (AEs), we performed a subgroup analysis according to RT and ICI timing. Patients were assigned to one of three RT and ICI timing groups: RT more than 4 weeks before ICI therapy, RT no more than 4 weeks before or after ICI (concurrent), and RT more than 4 weeks after ICI therapy.[19] Patients who received multiple courses of RT with different temporal relationships to ICI therapy were included in multiple groups as applicable; each AE was assigned to one group only.

Imaging Assessments

Brain imaging was retrospectively reviewed with input from the radiation oncology and neuroradiology

departments. Because of the retrospective nature of the study, the time interval between RT and posttreatment MRIs was not standardized. In general however, patients underwent repeat MRIs within 6 to 12 weeks of completion of RT. Post-RT MRIs were evaluated for treatment-related imaging change (TRIC). TRIC was defined as post-RT MRI findings consistent with inflammation, with subsequent histopathologic confirmation of non-malignancy or with resolution on serial imaging without intervention (e.g., surgical removal, systemic therapy, or corticosteroid initiation/dose increase).[19–22] To avoid the subjectivity of distinguishing between expected and excessive post-RT imaging change and to maximize clinical relevance, we included only TRIC with associated symptoms (sxTRIC) in our analysis.[17,19]

Statistical Analyses

Fisher's exact test was used to compare categorical characteristics between groups. Age and lines of therapy were compared using Wilcoxon rank sum test. All p values are based on a two-sided hypothesis with exact calculations performed using SAS 9.4 statistical software (SAS Institute, Inc., Cary, NC).

Results

Patient and Treatment Characteristics

We identified 163 patients with NSCLC treated with cranial RT, of whom 50 received an ICI (included in the ICI+ cohort) and 113 did not (included in the ICI– cohort). Baseline clinical and pathologic features are summarized in Table 1. In the overall study population, the median age at NSCLC diagnosis was 61 years (range 31–97 years), and most patients had a history of smoking (77%) and the adenocarcinoma histologic type (84%). Forty-five percent of the patients had brain metastases at initial NSCLC diagnosis. We found the burden of central nervous system (CNS) disease to be comparable between study cohorts as assessed by percentage of patients symptomatic at the time of diagnosis of brain metastases (56% in the ICI– cohort versus 48% in the ICI+ cohort [$p = 0.40$]) and size of largest lesion at the time of diagnosis of CNS involvement (median greatest diameter 16 mm in the ICI– cohort versus 13 mm in the ICI+ cohort [$p = 0.21$]). Although significantly more patients in the ICI– cohort presented with a single brain metastasis at diagnosis of CNS involvement (49% in the ICI– cohort versus 30% in the ICI+ cohort [$p = 0.04$]), rates of presentation with more than three brain metastases at diagnosis of CNS involvement did not differ significantly (27% in the ICI– cohort versus 20% in the ICI+ cohort [$p = 0.34$]). Otherwise, the ICI+ and ICI– cohorts had comparable baseline disease characteristics. Regarding history of systemic therapy, patients in the ICI+ cohort received more lines of therapy during their disease course than did patients in the ICI– cohort (median 3 versus 1 lines, respectively [$p < 0.0001$]), and were more likely to have received cytotoxic chemotherapy (98% versus 87%, respectively [$p = 0.02$]), including platinum-doublet chemotherapy (94% versus 81%, respectively [$p = 0.03$]). The ICIs administered to patients in the ICI+ cohort included nivolumab (n = 39), pembrolizumab (n = 8), and atezolizumab (n = 4) (Supplementary Table 1). The median number of ICI cycles received was 9 (range 1–95).

Overall, the 163 patients included in this study received 373 RT treatments, with 81 patients (50%) receiving more than one RT course. Significantly more patients in the ICI+ cohort received multiple RT courses (>1 RT course: 43% in the ICI– cohort versus 64% in the ICI+ cohort [$p = 0.02$]). Patients in the ICI+ cohort each received a median of two radiation treatments (range 1–10), whereas those in the ICI– group received a median of one (range 1–11). Overall, 94 patients underwent SRS (35 in the ICI+ cohort [70%] versus 59 in the ICI– cohort [52%]), 28 received PBI (8 in the ICI+ cohort [16%] and 20 in the ICI– cohort [18%]), and 101 received WBRT (29 in the ICI+ cohort [58%] and 72 in the ICI– cohort [64%]). The number of SRS treatments per patient was greater in the ICI+ cohort than in the ICI– cohort (a median of 2 SRS courses versus 1, respectively [$p = 0.0034$]) (Table 2). Additionally, a significantly greater percentage of patients in the ICI+ cohort received SRS at any point (70% versus 52%, respectively [$p = 0.0398$]). For patients with available RT plans (n = 78), total dose, dose per fraction, and target size were comparable between the ICI+ and ICI– cohorts, with the exception of smaller targets for SRS in the ICI+ cohort (Supplementary Table 2). Most PBI treatments (66%) were postoperative. Twenty-six percent of all RT was classified as reirradiation, which was defined as RT directed at previously irradiated brain parenchyma (27% of RT treatments in the ICI– cohort versus 25% of RT treatments in the ICI+ cohort [$p = 0.72$]).

Frequency of systemic corticosteroid use within 4 weeks of RT, including preventive and symptom-driven corticosteroid prescription, was not significantly different between groups (65% in the ICI– cohort versus 62% in the ICI+ cohort [$p = 0.72$]). Although the duration of steroid courses did not differ significantly between groups (median 50 versus 58 days of total steroid use in patients in the ICI– and ICI+ cohorts, respectively [$p = 0.61$]), the starting steroid dose was significantly higher in the ICI– group (a median of 14 mg versus 8 mg dexamethasone daily in patients in the ICI– and ICI+ cohorts, respectively [$p = 0.003$]).

Table 1. Baseline Patient Characteristics

Characteristic	Overall (N = 163)	ICI- (n = 113)	ICI+ (n = 50)	*p* Value
Median age at NSCLC diagnosis (range), y	61 (31-97)	62 (31-97)	61 (35-82)	0.74
Sex				0.60
Male, %	36	37	32	
Female, %	64	63	68	
History of smoking, %	77	75	80	0.55
Histologic type, %				0.14
Adenocarcinoma	84	88	76	
Squamous cell carcinoma	12	10	16	
Other	4	3	8	
Median ECOG performance status at diagnosis of brain metastasis (range)[a]	1 (0-4)	1 (0-4)	1 (0-3)	0.75
Brain metastases at NSCLC diagnosis, %	45	44	46	0.84
Symptomatic at diagnosis of brain metastasis, %	53	56	48	0.40
Median No. of brain lesions at diagnosis of brain metastasis (range)	2 (1-21)	2 (1-21)	2 (1-20)	0.40
Single brain lesion, %	43	49	30	0.04
>3 brain lesions, %	25	27	20	0.34
Median diameter of largest lesion at brain metastasis diagnosis (range), mm	16 (1-63)	16 (1-63)	13 (1-39)	0.21
Leptomeningeal disease at any time during disease course, %	22	22	22	1.0
Median total lines of systemic therapy during disease course (range)	2 (0-10)	1 (0-9)	3 (1-10)	<0.0001
Chemotherapy of any kind, %	90	87	98	0.02
Platinum-doublet chemotherapy, %	85	81	94	0.03
Targeted therapy (EGFR-, ALK-, or ROS1-directed), %	22	23	20	0.67
Brain surgery at any point during disease course, %	36	37	32	0.60

[a]Reported for patients with ECOG performance status documented within 1 month of brain metastasis diagnosis only (n = 110 ICI-, 45 ICI+).
ICI-, immune checkpoint inhibitor-naive; ICI+, immune checkpoint inhibitor-treated; ECOG, Eastern Cooperative Oncology Group; ALK, anaplastic lymphoma kinase.

AEs

The median duration of follow-up from first RT treatment was 16 months (range 1–140 months). Overall, cranial RT was well tolerated, with predominantly grade 1 or 2 AEs. No significant difference was observed in the rate of all-grade RT-related AEs between patients in the ICI+ cohort and those in the ICI– cohort for any particular cranial RT type (Fig. 1 and Supplementary Table 3). The incidence of grade 3 or higher AEs was 8% to 13% across treatment groups and

Table 2. Cranial Radiation Therapy

Type of Cranial Radiation Therapy	Overall (N = 163)	ICI- (n = 113)	ICI+ (n = 50)	*p* Value
Cranial radiation therapy, all modalities				
Median cranial radiation treatments per patient (range)	1 (1-11)	1 (1-11)	2 (1-10)	0.0045
Patients receiving >1 radiation therapy course, %	50	43	64	0.02
SRS				
Patients receiving SRS, %	58	52	70	0.0398
Median SRS treatments per patient (range)	1 (0-11)	1 (0-11)	2 (0-10)	0.0034
PBI				
Patients receiving PBI, %	17	18	16	1.00
Median PBI treatments per patient (range)	0 (0-3)	0 (0-2)	0 (0-3)	0.88
WBRT				
Patients receiving WBRT, %	62	64	58	0.49
Median WBRT treatments per patient (range)	1 (0-2)	1 (0-2)	1 (0-2)	0.54

ICI-, immune checkpoint inhibitor-naive; ICI+, immune checkpoint inhibitor-treated; SRS, stereotactic radiosurgery; PBI, partial brain irradiation; WBRT, whole brain radiotherapy.

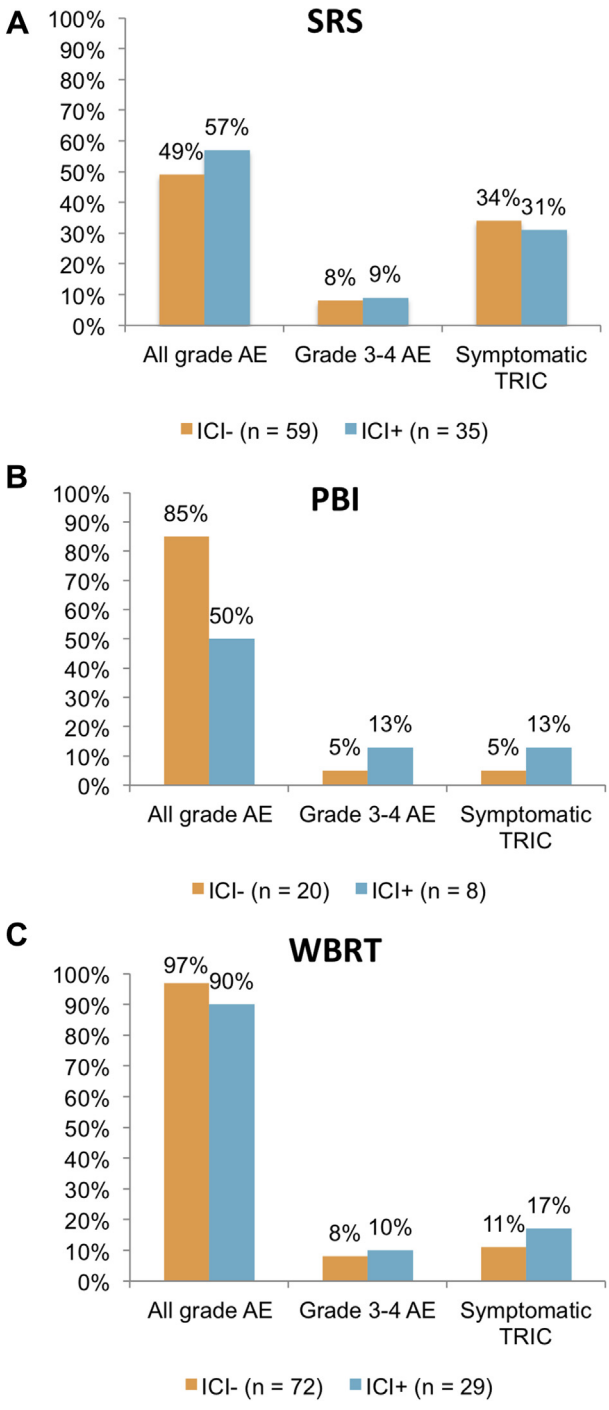

Figure 1. Cranial radiation therapy-related adverse events (AEs) according to the receipt of immune checkpoint inhibitors (ICIs), in patients who received stereotactic radiosurgery (SRS) (*A*), partial brain irradiation (PBI) (*B*), or whole brain radiotherapy (WBRT) (*C*) as cranial radiation therapy. TRIC, treatment-related imaging change.

did not differ significantly between the ICI+ and ICI– cohorts.

Among patients in the ICI+ cohort, the most commonly observed AEs included fatigue (76%), radiation dermatitis (48%), and cognitive disturbance (41%) after WBRT and headache (26%) after SRS (Supplementary Table 4). The most frequently observed grade 3 or higher AEs in patients the ICI+ cohort were headache (n = 2), anorexia (n = 2), and cognitive disturbance (n = 2) (Supplementary Table 5). The distribution of AEs was similar in the ICI– cohort, with fatigue as the most frequently observed AE after WBRT or PBI and headache observed most frequently after SRS. Frequently observed grade 3 or higher AEs in the ICI– cohort were fatigue (n = 4), motor deficit (n = 4), seizure (n =3), and radiation necrosis (n = 2, pathologically confirmed). One grade 4 AE was observed in a patient in the ICI– cohort; this patient experienced CNS necrosis resulting in midline shift and requiring emergent craniotomy.

TRIC was observed on the brain MRI scans of 41 patients (25%) across both cohorts. In six patients, brain biopsy or resection specimens were available for histopathologic review, which demonstrated inflammatory findings consistent with TRIC (see Fig. 2 for representative images). Rates of sxTRIC were comparable between patients in the ICI+ cohort and those in the ICI– cohort across cranial RT treatment types (sxTRIC: 34% in the ICI– cohort versus 31% in the ICI+ cohort for SRS [$p = 1.00$], 5% in the ICI– cohort versus 13% in the ICI+ cohort for PBI [$p = 0.50$], and 11% in the ICI– cohort versus 17% in the ICI+ cohort for WBRT [$p = 0.51$]). The median time from RT start to the first MRI documentation of sxTRIC was 5 months in both cohorts.

Timing of RT and ICI Therapy

Within the ICI+ cohort, RT was most frequently administered before (n = 31) or concurrently with (n = 20) ICI therapy. Ten patients underwent cranial RT after ICI therapy. The median time between RT and ICI therapy was 13 months for RT before ICI therapy, 9 days for concurrent RT and ICI therapy, and 4 months for RT after ICI. RT parameters, including rates of reirradiation and brain surgery before RT, were consistent across timing groups. There were no significant differences in rates of AEs of any grade and grade 3 or higher AEs on the basis of sequencing of RT and ICI (Table 3). Rates of sxTRIC were also similar irrespective of RT and ICI timing.

Discussion

PD-1 pathway blockade now represents a standard therapy for patients with advanced NSCLC. Importantly, initial clinical trials evaluating these agents routinely excluded patients with active brain metastases. With the recent regulatory approvals of three PD-1/PD-L1 inhibitors in NSCLC, clinicians are now faced with real-world clinical questions, such as whether cranial RT

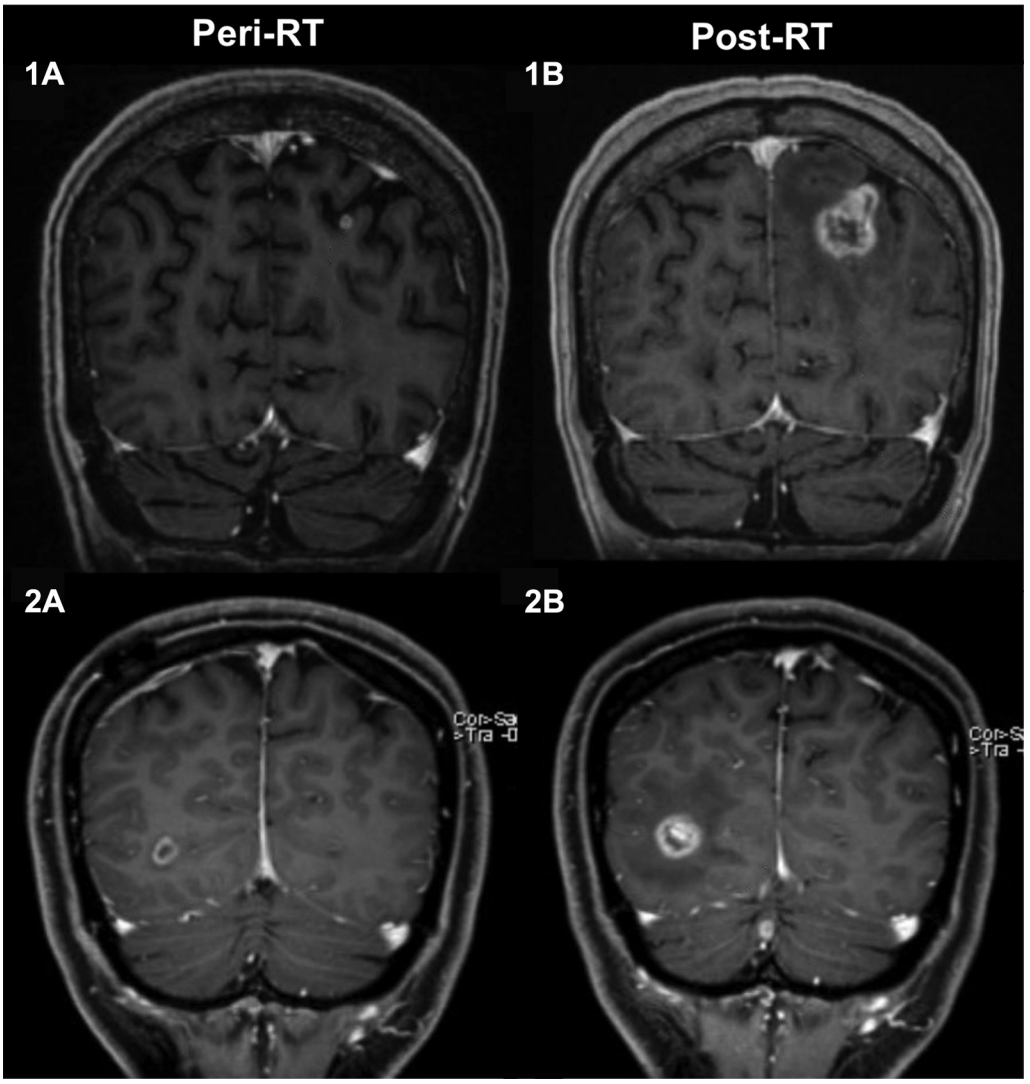

Figure 2. Representative axial postcontrast magnetic resonance images of pathologically confirmed radiation necrosis in an immunotherapy-naive patient (1A/B) and an immunotherapy-treated patient (2A/B), respectively (magnetic resonance imaging sequence: 1A/B, brain volume imaging; 2A, magnetization-prepared, rapid-acquired gradient echo; 2B, stealth three-dimensional fast spoiled gradient recalled acquisition in the steady state.

can be delivered against a background of PD-1 pathway blockade. To date, there have been limited data available to inform these therapeutic questions. Small retrospective studies in melanoma have reported mixed results, with some describing potential toxicities of combined cranial RT and ICI, including neurocognitive decline, radiation necrosis, and intratumoral hemorrhage, although most of these studies have focused on cytotoxic T-lymphocyte–associated protein 4 (CTLA4) rather than on PD-1 inhibition.[23–27] Given the distinct histopathologic features of melanoma brain metastases and the unique toxicity of CTLA4 inhibition, such findings may not translate to other malignancies, including NSCLC.

Here, we have presented the largest series to date evaluating the safety of combined cranial RT and PD-1 pathway inhibition in patients with NSCLC with brain metastases. Overall, the combination of ICI therapy and RT was well tolerated, and the rate of grade 3 or higher AEs reported here (9%-13% among patients in the ICI+ cohort) is consistent with the 0% to 20% incidence of grade 3 or higher AEs reported previously in melanoma.[19,23,24,27] Of note, this is the first study to include a comparator cohort of ICI–naive patients who received cranial RT. Using this comparative approach, we observed similar rates of RT-related toxicity between the ICI+ and ICI– cohorts, suggesting that PD-1 pathway blockade may not substantially elevate the risks associated with radiation compared with those associated with cranial RT alone. These results are consistent with those of recent studies evaluating the toxicity of thoracic RT, in which the addition of ICI therapy was not observed to significantly increase treatment-related AEs.[28,29]

Table 3. Cranial RT-Related AEs by Immune Checkpoint Inhibitor Timing

AE Incidence by Cranial RT Type	RT → ICI	ICI/RT	ICI → RT	*p* Value
Stereotactic radiosurgery	n = 21	n = 14	n = 5	
All-grade AE, %	57	64	20	0.27
Grade 3–4 AE, %	10	7	0	1.00
Symptomatic TRIC, %	29	36	20	0.90
Partial brain irradiation	n = 5	n = 3	n = 1	
All grade AE, %	60	33	100	1.00
Grade 3–4 AE, %	20	0	0	1.00
Symptomatic TRIC, %	20	0	100	0.31
Whole brain radiotherapy	n = 18	n = 6	n = 5	
All grade AE, %	89	100	80	0.53
Grade 3–4 AE, %	6	33	0	0.17
Symptomatic TRIC, %	17	33	0	0.51

RT, radiation therapy; AE, adverse event; ICI, immune checkpoint inhibitor; RT → ICI, patients irradiated more than 1 month before receipt of an ICI; ICI/RT, patients irradiated within 1 month of ICI receipt; ICI → RT, patients irradiated more than 1 month after receipt of an ICI; TRIC, treatment-related imaging change.

A recent subanalysis of KEYNOTE-001 noted improved efficacy of pembrolizumab among patients receiving radiation before immunotherapy, supporting the notion that clinically relevant immune synergy between RT and ICI therapy may occur.[28] To investigate whether the frequency and/or spectrum of RT-related toxicities may differ depending on the relative timing and sequencing of RT with ICI therapy, we conducted additional subgroup analyses. Again, no difference was observed in rates of cranial RT–related AEs between groups; however, the total number of patients in each group was relatively small. Nonetheless, these findings provide preliminary support for the safety and tolerability of pursuing cranial RT in patients being treated with ICIs.

The comparable rates of AEs that we observed between treatment timing groups are largely consistent with the limited prior literature examining AEs by sequence of RT and ICI therapy, although it notably does not recapitulate the trend toward increased inflammation and toxicity with concurrent RT and ICI therapy observed by several groups.[18,19,30] In a recent study of mixed tumor types, including NSCLC treated with CTLA4 and PD-1 inhibitors and all-site RT, Bang et al. noted a trend toward increased immune-related AEs with RT administration within 14 days of ICI therapy; however, this finding did not reach statistical significance. Furthermore, neurologic toxicity was not specifically assessed.[30] Similarly, in a study examining AEs by sequence of RT and ICI therapy among patients with melanoma, a slightly higher incidence of central nervous system toxicity was observed in patients receiving cranial RT within 1 month of ICI therapy; however, there were too few events to allow statistical analysis.[19]

In this study, lesions that were radiographically consistent with radiation necrosis or pseudoprogression were assessed collectively as TRIC. We did not observe any differences in symptomatic TRIC based on exposure to immunotherapy or on timing of cranial RT with respect to ICI therapy. However, it is worth noting that we did not evaluate for asymptomatic transient increases in lesion size—a post-RT phenomenon that has been associated with immunotherapy in other studies.[19,31] Thus, our findings do not contradict the notion of timing-dependent immune synergy but rather suggest that this synergy may not have a significant clinical impact, at least with respect to toxicity.

This study has several important limitations. First, it was a single-institution, retrospective study evaluating heterogeneous RT modalities. To overcome this limitation, we used a near-contemporaneous control cohort and stratified toxicity outcomes according to RT modality. Secondly, the total sample size in this study was small, reflecting the recent clinical approval of PD-1 and PD-L1 inhibitors in NSCLC. Third, although the control cohort was treated within 8 months of the earliest-treated patient in the immunotherapy cohort, temporal separation does introduce practice pattern changes between cohorts (e.g., increasing use of SRS for management of brain metastases, as reflected in the greater number of SRS treatments per patient in the more recently treated ICI+ cohort). Improvements in practice patterns over time could also potentially obscure an increase in toxicity emerging with the addition of an ICI.

Notably, though we found the two cohorts to be generally comparable with respect to baseline characteristics, the ICI+ group received more lines of systemic chemotherapy. To investigate this further, we evaluated Eastern Cooperative Oncology Group performance status and burden of disease at diagnosis of brain metastases between the two cohorts, finding that both were comparable, with the exception of there being significantly more patients with limited CNS burden (i.e., a solitary brain metastasis) in the ICI– cohort, a difference that

would likely accentuate rather than obscure any possible increase in treatment-related toxicity in the ICI+ cohort.

Nonetheless, given the nonrandomized sampling, unanticipated differences between the patient cohorts could have introduced confounders. Finally, in this study we were unable to assess several important potential modifiers of immune synergy. Because of incomplete access to RT plans, we were unable to comprehensively assess the effects of RT dose and volume on adverse outcomes. Additionally, the status of predictive markers such as PD-L1, tumor-infiltrating lymphocytes, and mutational load was unavailable for most of the patients included in this study.

In summary, we found that cranial RT and PD-1 pathway inhibition in combination were overall well tolerated in the study population. No significant differences in rates of RT-related AEs were observed between PD-1 pathway inhibitor-naive and PD-1 inhibitor-treated patients. Furthermore, the sequence and timing of PD-1 pathway inhibitor administration with respect to RT did not appear to affect RT-related toxicity. Further prospective investigation is needed to establish the optimal timing of this increasingly utilized combination approach and to further validate and evaluate its safety and tolerability, including its impact on quality of life and long-term cognitive outcomes.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2018.01.012.

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