ORIGINAL ARTICLE

Immunotherapy With Radiotherapy for Brain Metastases in Patients With NSCLC: NEJ060

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ABSTRACT

Introduction: Immune checkpoint inhibitor (ICI)–based treatment has become standard treatment for patients with advanced NSCLC. We aimed to determine the survival benefit of upfront radiotherapy for brain metastases (BMs) in patients with NSCLC who received ICI alone (ICI-alone) or with chemotherapy (ICI-chemo).

Methods: This study included consecutive patients with NSCLC having BMs who received ICI alone or ICI-chemo at 50 institutes between February 2017 and September 2021. The presence of BMs was confirmed by imaging before treatment. Treatment outcomes were compared between patients who did and did not receive upfront radiotherapy for BMs. Potential confounding factors were adjusted between the groups through inverse probability treatment weighting (IPTW) analysis and overlap weighting (OW) analysis with propensity scores.

Results: Patients were grouped as ICI-alone cohort, 224 patients (upfront-radiotherapy group, 135 patients; no-radiotherapy group, 89 patients) and ICI-chemo cohort, 367 patients (upfront-radiotherapy group, 212 patients; no-radiotherapy group, 155 patients). In the ICI-alone cohort,

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the overall survival of the upfront-radiotherapy group was significantly longer than that of the no-radiotherapy group (IPTW-adjusted hazards ratio [HR] = 0.45 [95% confidence interval [CI]: 0.29–0.72], OW-adjusted HR = 0.52 [95% CI: 0.35–0.77]). In contrast, in the ICI-chemo cohort, the OS of the upfront-radiotherapy group was not significantly different from that of the no-radiotherapy group (IPTW-adjusted HR = 1.02 [95% CI: 0.70–1.48], OW-adjusted HR = 0.93 [95% CI: 0.65–1.33]).

Conclusions: Upfront radiotherapy for BMs was associated with longer overall survival in patients with NSCLC who received ICI alone; however, it did not exhibit survival benefits in the patients who received ICI-chemo.

Keywords: Immunotherapy; Brain metastases; Non–small cell lung cancer; Radiotherapy

Introduction

Immune checkpoint inhibitor (ICI)–based treatment has become a standard treatment option for patients with advanced NSCLC without oncogenic drivers, such as EGFR and ALK. A study suggested that pembrolizumab prolongs progression-free survival (PFS) and overall survival (OS) in patients with NSCLC compared with chemotherapy, with a programmed cell death ligand 1 (PD-L1) tumor proportion score (TPS) greater than 50%.[1] Whereas anti–programmed cell death protein-1(PD-1) or PD-L1 antibodies plus chemotherapy improved PFS and OS in patients with NSCLC with any PD-L1 expression compared with chemotherapy.[2–4] Moreover, combination therapy with CTLA-4 and anti–PD-1 antibodies has been approved as a first-line treatment option.[5,6]

Brain metastases (BMs) are more common in patients with lung cancer than in patients with other cancer types.[7] Almost 20% of patients with lung cancer have BMs at diagnosis.[7] Patients with BMs have poor prognosis and reduced quality of life.[8,9] The efficacy of anticancer agents for BMs is restricted because the blood-brain barrier (BBB) limits drug penetration. Furthermore, the brain is protected by immune cells.[10]

Pivotal clinical trials of ICI-based regimens for the first-line treatment of NSCLC have only included a small number of patients with BMs.[1–6] The KEYNOTE-024 trial included approximately 10% of patients with BMs and excluded patients with untreated BMs.[1] Whereas the KEYNOTE-189 trial included patients with untreated BMs; however, less than 10% of patients had untreated BMs.[2] Therefore, the efficacy of ICI in patients with BMs has not been fully investigated.

Radiotherapy (RT), such as stereotactic radiosurgery, stereotactic RT, and whole brain RT, is an effective treatment option for BMs.[11] The American Society of Clinical Oncology– Society for Neuro-Oncology–American Society for Radiation Oncology guidelines state that local therapy should not be deferred, even for patients with asymptomatic BMs, except in special circumstances.[11] However, immunotherapy may be a risk for symptomatic radiation necrosis.[12] RT-related adverse events (AEs) are important issues in patients who achieved long-term survival with ICIs. Therefore, whether RT for BMs should precede systemic treatment in patients with NSCLC who received ICI-based treatment remains unclear. To address this uncertainty, the present study aimed to determine the survival benefit of upfront RT for BMs in patients with NSCLC treated with ICIs alone and ICI plus platinum-based chemotherapy (ICI-chemo).

Materials and Methods

Patient Selection and Study Design

The medical records of consecutive patients with NSCLC with BMs who received ICI alone or ICI-chemo as a first-line treatment between February 2017 and September 2021 at 50 institutes of the Northeast Japan Study Group in Japan were retrospectively reviewed. The inclusion criteria were as follows: cytologically or histologically confirmed NSCLC clinical stage IVA, IVB, postoperative-recurrence, or post-RT or chemo-RT-recurrence and patients with BMs confirmed by head computed tomography or magnetic resonance imaging before the treatment. The exclusion criteria were patients with EGFR mutations or ALK rearrangement, treated with SCLC treatment regimens, with meningitis, who had previously received anti–PD-1/PD-L1 antibodies, or who underwent surgery for BMs. Patients in the two cohorts, treated with ICI only (ICI-alone cohort) and treated with ICI-chemo (ICI-chemo cohort), were analyzed. In each cohort, patients were classified into two groups: the upfront-RT group (patients who received RT for BMs followed by systemic therapy) and the no-RT group (patients treated with systemic therapy without RT for BMs). The efficacy and safety of treatment in the upfront-RT group were compared with those in the no-RT group in each cohort.

The present study was conducted according to the Helsinki Declaration of the World Medical Association. The study protocol was approved by the Ethics Committee of Nippon Medical School (approval number M-2022-042). Informed consent from individuals was

obtained through an opt-out methodology on the website according to the instructions of the ethics committee.

Data Collection and Outcome Assessment

The following clinical data were collected: age, sex, Eastern Cooperative Oncology Group performance status (PS), smoking history, histologic diagnosis, clinical stage, presence of extracranial lesions, PD-L1 TPS, number of BMs, size of the largest BM, BM symptoms, use of steroids for BM symptoms (prednisolone equivalent $\geq$10 mg), chemotherapy regimen, and RT for BMs.

Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors version 1.1. PFS was defined as the time between the initiation of systemic therapy to disease progression or death. Disease progression in the central nervous system (CNS) was evaluated according to The Response Assessment in Neuro-Oncology BM criteria.[13] CNS-PFS was defined as the time from systemic therapy initiation until the date of disease progression in the CNS according to Response Assessment in Neuro-Oncology–BM or death.[14] OS was defined as the time between systemic therapy and death. CNS AEs were assessed according to the Common Terminology Criteria for Adverse Events version 5.0.

Statistical Analysis

The median follow-up period was estimated using the Kaplan-Meier method. Patient characteristics were compared using standardized differences. Propensity score weighted analysis was performed to minimize bias. The propensity scores of each patient were calculated as a probability from a logistic regression model that included influencing covariates. The factors used to calculate the propensity score were as follows: age (continuous variables), sex (male/female), PS (0–1/2–4), smoking history (never/current/former), histologic diagnosis (adenocarcinoma/squamous cell carcinoma/others), stage (IVA/IVB/recurrence), PD-L1 TPS ($\geq$50%/1–49%/$<$1%/unknown), number of BMs (1/2–4/$\geq$5), size of the largest BM ($<$10 mm/10–29 mm/$\geq$30 mm), BM symptoms (yes/no), steroid treatment for BMs, prednisolone equivalent $\geq$10 mg (yes/no), presence of extracranial disease lesions (yes/no), treatment with anti–CTLA-4 antibody (yes/no), and antivascular epithelial growth factor antibody (yes/no).

Two types of weighted analysis were performed using propensity scores: inverse probability of treatment weighted (IPTW) and OW analyses. The IPTW analysis assigned a weight of 1/(propensity scores) for the upfront-RT group and 1/(1 – propensity scores) for the no-RT group.[15–18] The OW analysis assigned a weight of 1 – propensity scores for the upfront-RT group and propensity scores alone for the no-RT group.[19,20]

IPTW- and OW-adjusted Kaplan-Meier methods were used to estimate OS, PFS, and CNS-PFS in the two groups. OS, PFS, and CNS-PFS were compared using IPTW- and OW-adjusted log-rank tests. Hazard ratios (HRs) for OS, PFS, and CNS-PFS were calculated by the IPTW-weighted and OW-adjusted cox proportional hazards model. A two-sided p value less than 0.05 was considered statistically significant. All statistical analyses were performed using the EZR version 1.61.[21]

Results

Patient Characteristics

Figure 1 illustrates the patient selection flowchart. The clinical data of 673 patients were collected. Three patients who had undergone previous SCLC treatment regimens and 79 who underwent surgery for BMs were excluded. The present study finally analyzed 591 patients. Of these, 224 and 367 patients were treated with ICI alone and ICI-chemo, respectively.

Patient characteristics are presented in Table 1. PS and symptoms of BMs were collected at the time of initiating systemic treatments. In the ICI-alone cohort, there was a trend toward more men (80.0% versus 69.7%) in the upfront-RT group compared with the no-RT group. Furthermore, more patients in the upfront-RT group had BMs greater than or equal to 10 mm (74.8% versus 36.0%), symptomatic BMs (46.7% versus 10.1%), and used steroids for BM symptoms (40.0% versus 9.0%) than those in the no-RT group. In the ICI-chemo cohort, more patients in the upfront-RT group had BMs $\geq$10 mm (74.5% versus 38.7%), symptomatic BMs (45.8% versus 5.8%), and used steroids for BM symptoms (43.9% versus 3.2%) than those in the no-RT group. The number of patients in the upfront-RT group that received each form of RT is shown in Supplementary Table 1. Among the 89 patients in the No-RT group of the ICI cohort, 23 patients (25.8%) received salvage RT. Among the 155 patients in the No-RT group of the ICI-chemo cohort, 50 patients (32.3%) received salvage RT. The number of patients in the No-RT group that received each form of salvage RT is presented in Supplementary Table 2. Moreover, the details of the treatment regimens are provided in Supplementary Table 3.

Efficacy

The median follow-up period of all patients was 24.8 months (95% confidence interval [CI]: 22.8–26.2). Standardized differences in the background factors using propensity scores are shown in Supplementary Figures 1 and 2.

In the ICI cohort, the IPTW-adjusted OS of patients in the upfront-RT group was significantly longer than that

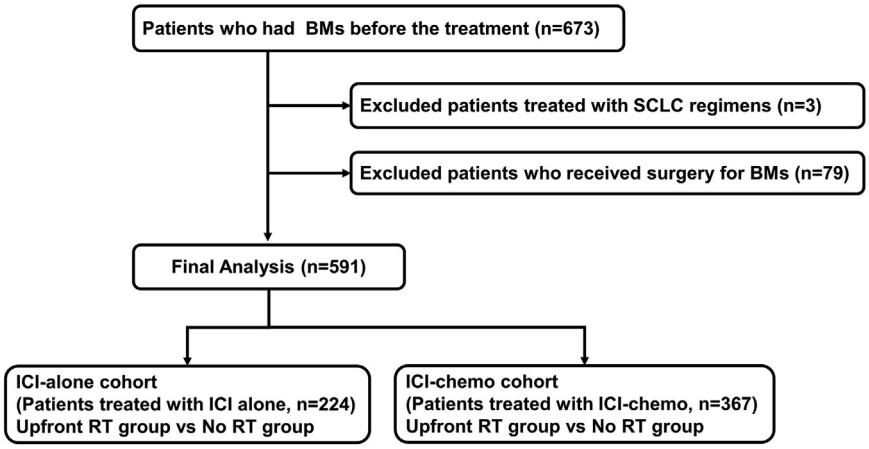

Figure 1. Patient selection flowchart. BM, brain metastasis; ICI, immune checkpoint inhibitor; RT, radiotherapy.

of patients in the no-RT group (median, 24.7 [95% CI: 21.2–32.0] mo versus 7.9 [95% CI: 4.9–10.5] mo HR = 0.45 [95% CI: 0.29–0.72] $p = 0.011$) (Fig. 2*A*). In contrast, in the ICI-chemo cohort, the IPTW-adjusted OS of patients in the upfront-RT group was not significantly different from that of patients in the no-RT group (median, 18.8 [95% CI: 16.4–20.4] mo versus 19.1 [95% CI: 16.0–21.3] mo HR = 1.02 [95% CI: 0.70–1.48] $p = 0.934$) (Fig. 2*B*). Within the ICI cohort, the OW-adjusted OS of patients in the upfront-RT group was significantly longer than that of patients in the no-RT group (median, 26.0 [95% CI: 8.2–NR] mo versus 12.6 [95% CI: 3.4–38.0] mo HR = 0.52 [95% CI: 0.35–0.77] $p = 0.002$) (Fig. 2*C*). In contrast, in the ICI-chemo cohort, the OW-adjusted OS of patients in the upfront-RT group was not significantly different from that of patients in the no-RT group (median, 18.8 [95% CI: 10.4–NR] mo versus 16.2 [95% CI: 9.2–NR] mo HR = 0.93 [95% CI: 0.65–1.33] $p = 0.677$) (Fig. 2*D*).

In the ICI cohort, the IPTW-adjusted PFS of patients in the upfront-RT group was significantly longer than that of patients in the no-RT group (median, 10.2 [95% CI: 8.6–12.9] mo versus 1.9 [95% CI: 1.6–3.0] mo HR = 0.56 [95% CI: 0.36–0.89] $p = 0.041$) (Fig. 3*A*). In contrast, in the ICI-chemo cohort, the IPTW-adjusted PFS of patients in the upfront-RT group was not significantly different from that of patients in the no-RT group (median, 6.6 [95% CI, 6.0–7.2] mo versus 5.3 [95% CI, 4.6–5.6] mo HR = 0.85 [95% CI, 0.55–1.31] $p = 0.492$) (Fig. 3*B*). In the ICI cohort, the OW-adjusted PFS of patients in the upfront-RT group was significantly longer than that of patients in the no-RT group (median, 12.3 [95% CI: 3.5–32.0] mo versus 4.0 [95% CI: 1.5–16.1] mo HR = 0.64 [95% CI: 0.44–0.94] $p = 0.025$) (Fig. 3*C*). In contrast, in the ICI-chemo cohort, the OW-adjusted PFS of patients in the upfront-RT group was not significantly different from that of patients in the no-RT group (median, 6.6 [95% CI: 3.6–12.9] mo versus 6.0 [95% CI: 3.7–10.6] mo HR = 0.98 [95% CI: 0.72–1.33] $p = 0.900$) (Fig. 3*D*).

In the ICI cohort, the IPTW-adjusted CNS-PFS of patients in the upfront-RT group was significantly longer than that of patients in the no-RT group (median, 39.8 [95% CI: 17.5–NR] mo versus 4.0 [95% CI: 2.1–4.0] mo HR = 0.40 [95% CI: 0.22–0.73] $p = 0.040$) (Fig. 4*A*). In contrast, in the ICI-chemo cohort, the IPTW-adjusted CNS-PFS of patients in the upfront-RT group was not significantly different from that of patients in the no-RT group (median, NR [95% CI: 12.8–NR] mo versus 6.2 [95% CI: 6.0–6.8] mo HR = 0.62 [95% CI: 0.31–1.23] $p = 0.277$) (Fig. 4*B*). In the ICI cohort, the OW-adjusted CNS-PFS of patients in the upfront-RT group was significantly longer than that of patients in the no-RT group (median, 39.8 [95% CI: 5.6–NR] mo versus 15.0 [95% CI: 1.6–NR] mo HR = 0.53 [95% CI: 0.31–0.89] $p = 0.025$) (Fig. 4*C*). In contrast, in the ICI-chemo cohort, the OW-adjusted CNS-PFS of patients in the upfront-RT group was not significantly different from that of patients in the no-RT group (median, NR [95% CI: 5.8–NR] mo versus 31.2 [95% CI: 5.6–NR] mo HR = 0.86 [95% CI: 0.54–1.36] $p = 0.507$) (Fig. 4*D*).

CNS AEs

In the ICI-alone cohort, 11 (8.1%) and 2 (2.2%) patients in the upfront-RT and no-RT groups, respectively experienced CNS AEs (Supplementary Table 4). In both the upfront-RT and no-RT groups, patients with symptomatic BMs before the treatment tended to have a higher frequency of CNS AEs than those with asymptomatic BMs. In the ICI-chemo cohort, 22 (10.4%) and three (1.9%) patients in the upfront-RT and no-RT groups, respectively, experienced CNS AEs (Supplementary Table 5). Likewise, in both groups,

Table 1. Patient Characteristics

Characteristics	ICI-alone cohort			ICI-chemo cohort		
	No RT	Upfront RT		No RT	Upfront RT	
N	89	135	SMD	155	212	SMD
Age, median (range)	71 (40-91)	69 (40-89)	0.072	67 (37-80)	64 (36-81)	0.143
Sex, n (%)						
Male	62 (69.7)	108 (80.0)	0.240	119 (76.8)	172 (81.1)	0.280
Female	27 (30.3)	27 (20.0)		36 (23.2)	40 (18.9)	
PS, n (%)						
0-1	71 (79.8)	97 (71.9)	0.186	137 (88.4)	191 (90.1)	0.135
2-4	18 (20.2)	38 (28.1)		18 (11.6)	21 (9.9)	
Smoking, n (%)						
Current/Former	75 (84.3)	125 (92.6)	0.262	130 (83.9)	195 (92.0)	0.251
Never	14 (15.7)	10 (7.4)		25 (16.1)	17 (8.0)	
Histologic diagnosis, n (%)						
Adeno	68 (76.4)	95 (70.4)	0.201	122 (78.7)	151 (71.2)	0.181
Sq	14 (15.7)	21 (15.6)		19 (12.3)	38 (17.9)	
Others	7 (7.9)	19 (14.1)		14 (9.0)	23 (10.8)	
PD-L1, n (%)						
≥50%	76 (85.4)	113 (83.7)	0.348	50 (32.3)	65 (30.7)	0.135
1%-49%	11 (12.4)	10 (7.4)		38 (24.5)	64 (30.2)	
<1%	2 (2.2)	8 (5.9)		49 (31.6)	63 (29.7)	
Unknown	0 (0.0)	4 (3.0)		18 (11.6)	20 (9.4)	
Stage, n (%)						
IVA	11 (12.4)	10 (7.4)	0.293	14 (9.0)	27 (12.7)	0.260
IVB	69 (77.5)	99 (73.3)		131 (84.5)	158 (74.5)	
Recurrence	9 (10.1)	26 (19.3)		10 (6.5)	27 (12.7)	
Extracranial disease lesions, n (%)						
Yes	83 (93.3)	128 (94.8)	0.066	155 (100)	203 (95.8)	0.298
No	6 (6.7)	7 (5.2)		0 (0.0)	9 (4.2)	
Number of BMs, n (%)						
1	41 (46.1)	56 (41.5)	0.099	57 (36.8)	57 (26.9)	0.221
2-4	26 (29.2)	41 (30.4)		53 (34.2)	89 (42.0)	
≥5	22 (24.7)	38 (28.1)		45 (29.0)	66 (31.1)	
Size of largest BMs, n (%)						
<10 mm	57 (64.0)	34 (25.2)	0.927	95 (61.3)	54 (25.5)	0.818
≥10, <30 mm	32 (36.0)	87 (64.4)		56 (36.1)	129 (60.8)	
≥30 mm	0 (0.0)	14 (10.4)		4 (2.6)	29 (13.7)	
Symptoms of BMs, n (%)						
Yes	9 (10.1)	63 (46.7)	0.887	9 (5.8)	97 (45.8)	1.027
No	80 (89.9)	72 (53.3)		146 (94.2)	115 (54.2)	
Use of steroid for BMs, n (%)						
Yes	8 (9.0)	54 (40.0)	0.773	5 (3.2)	93 (43.9)	1.091
No	81 (91.0)	81 (60.0)		150 (96.8)	119 (56.1)	
Addition of anti-CTLA-4 antibody, n (%)						
Yes	7 (7.9)	11 (8.1)	0.01	13 (8.4)	19 (9.0)	0.02
No	82 (92.1)	124 (91.9)		142 (91.6)	193 (91.0)	
Addition of anti-VEGF antibody, n (%)						
Yes	0 (0.0)	0 (0.0)	NA	14 (9.0)	29 (13.7)	0.147
No	89 (100)	135 (100)		141 (91.0)	183 (86.3)	
PEM-based chemotherapy, n (%)						
Yes	NA	NA	NA	111 (71.6)	131 (61.8)	0.210
No	NA	NA		44 (28.4)	81 (38.2)	

Adeno, adenocarcinoma; BMs, brain metastases; ICI, immune checkpoint inhibitors; ICI-chemo; ICI plus chemotherapy; NA, not applicable; PD-L1, programmed cell death ligand 1; PEM, pemetrexed; PS, performance status; RT, radiotherapy; SMD, standardized mean difference; Sq, squamous cell carcinoma; VEGF, vascular epithelial growth factor.

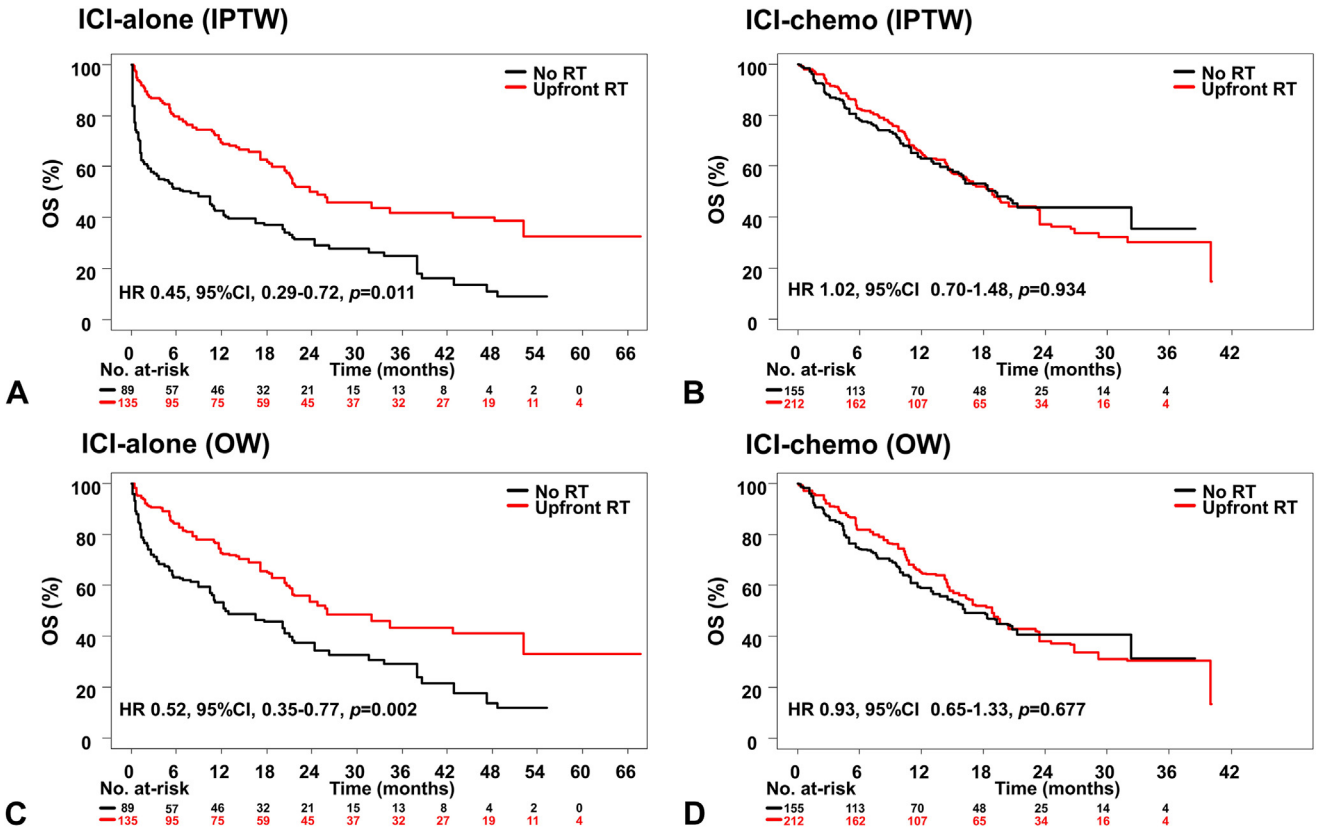

Figure 2. OS curves to compare the upfront-RT and no-RT groups,. IPTW-adjusted Kaplan-Meier curves: (*A*) ICI-alone cohort, (B) ICI-chemo cohort. OW-adjusted Kaplan-Meier curves: (*C*) ICI-alone cohort and (*D*) ICI-chemo cohort. ICI, immune checkpoint inhibitor; ICI-chemo, ICI plus chemotherapy; IPTW, inverse probability treatment weighting; OS, overall survival; OW, overlap weighting; RT, radiotherapy.

patients with symptomatic BMs before the treatment tended to have a higher frequency of CNS AEs than those with asymptomatic BMs. In both the ICI-alone and ICI-chemo cohorts, radiation necrosis and leukoencephalopathy occurred at approximately 1.5%, and less than 1.0%, respectively.

Discussion

Propensity score weighted analysis revealed that the OS, PFS, and CNS-PFS of patients who received upfront RT for BMs were significantly longer than those of patients without RT in the ICI-alone cohort. On the other hand, the OS, PFS, and CNS-PFS of patients who received upfront RT for BMs were not significantly different from those of patients without RT in the ICI-chemo cohort.

In the present study, patients treated with ICI alone without RT for BMs had poor prognoses, suggesting that BM was difficult to control with ICI alone. Furthermore, ICI alone was less effective in patients with active BM, including untreated BM.[22] The response rate to BMs in PD-L1–positive patients was 29.7% (11/37) in a phase 2 trial of pembrolizumab in patients with NSCLC and BMs.[23] However, half of the patients received previous local CNS therapy in the phase 2 trial. The intact BBB restricts molecules with a molecular weight less than 200 Da from entering the CNS.[24] Although certain antibody drugs, such as the antibody-drug conjugate, trastuzumab deruxtecan, exhibit reasonable CNS activity,[25] antibody drugs generally limit BBB penetration owing to their large molecular weight, resulting in less CNS penetration. The concentration of trastuzumab (148 kDa) was 300-fold lower in the cerebrospinal fluid (CSF) than in the serum.[24,26] Similar to trastuzumab, the molecular weights of nivolumab and pembrolizumab are 144 and 146 kDa, respectively[27]; hence, their penetration into the CNS is likely to be restricted by the BBB. The CSF/serum concentration ratio of nivolumab ranged from 0.88 to 1.9%.[27] Activated T cells, whose priming is enhanced by ICIs, can cross the BBB and act on the BMs, which is one of the mechanisms through which ICIs exert their effectiveness against BMs.[28] However, the limited ability of ICIs to penetrate the BBB may partly explain the modest efficacy observed with ICI monotherapy in patients with BMs. RT can disrupt the BBB and increase its permeability.[29] Patients treated with upfront RT for

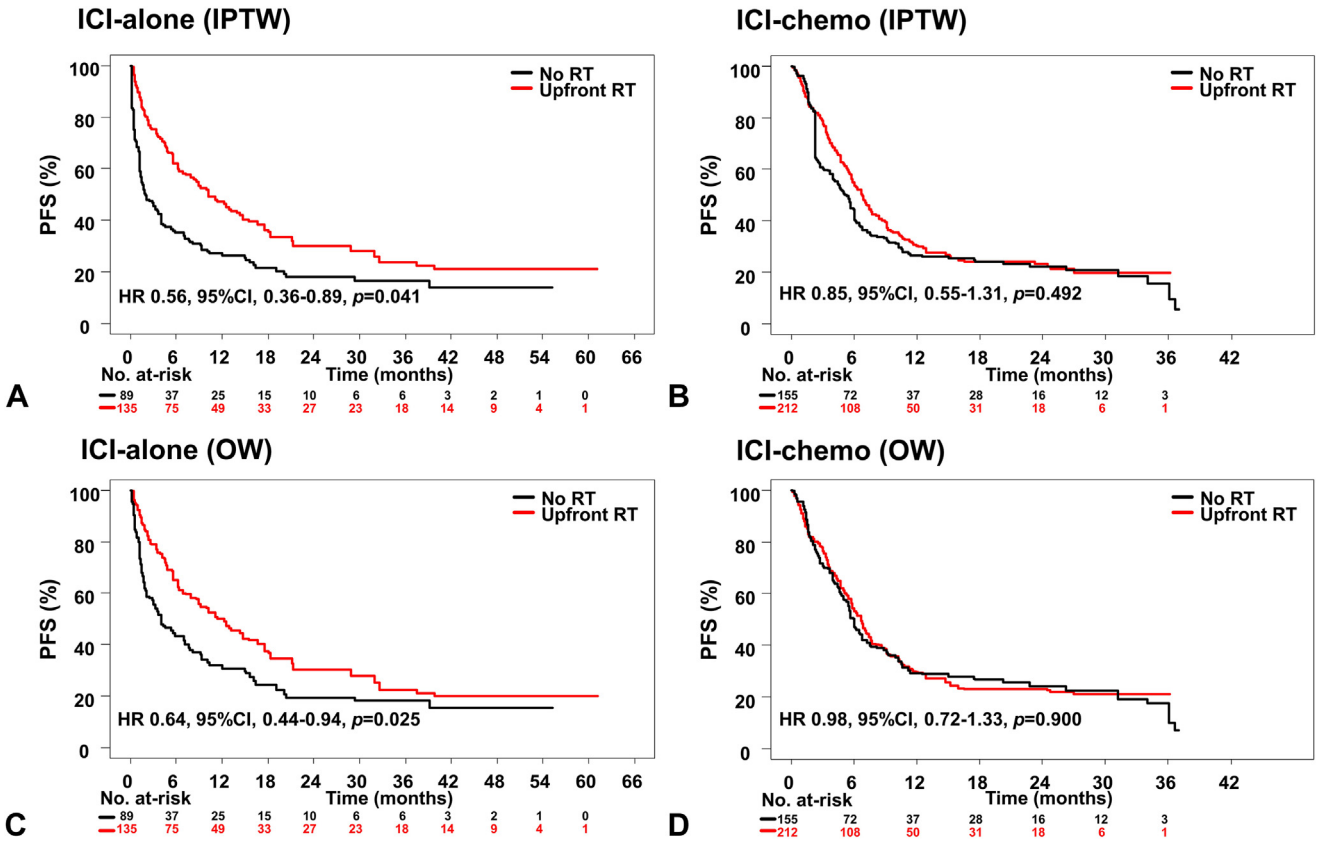

Figure 3. PFS curves to compare the upfront-RT and no-RT groups. IPTW-adjusted Kaplan-Meier curves: (*A*) ICI-alone cohort, (*B*) ICI-chemo cohort. OW-adjusted Kaplan-Meier curves: (*C*) ICI-alone cohort. (*D*) ICI-chemo cohort. ICI, immune checkpoint inhibitor; ICI-chemo, ICI plus chemotherapy; IPTW, inverse probability treatment weighting; OW, overlap weighting; PFS, progression-free survival; RT, radiotherapy.

BMs followed by ICI alone had better prognosis in the present study. Nivolumab plus ipilimumab with local therapy for BMs prolonged OS in melanoma patients.[30] In 255 Patients with NSCLC with BMs who received ICIs alone, cranial RT did not prolong OS.[31] However, unlike the present study, the previous study included patients who received ICI as both the first and late line treatments, after the third line. Furthermore, background factors may be different between patients with and without cranial RT. In the present study, propensity scores were used to adjust for background factors influencing treatment outcomes in the upfront-RT and no-RT groups.

The immunosuppressive environment of the tumor microenvironment of BMs may also be a reason for the poor efficacy of treatment with ICIs alone. Leukocyte invasion into the CNS is highly regulated to prevent brain damage from inflammatory responses.[32] PD-1–positive tumor-infiltrating lymphocytes were significantly decreased in BMs than primary lesions in patients with lung cancer.[33,34] Furthermore, PD-L1 expression by tumor or immune cells was greater in primary lung cancers than in paired BMs.[35] Although more than 80% of patients treated with ICIs alone exhibited high PD-L1 expression in the present study, PD-L1 expression of BMs may be lower than that of extracranial lesions. RT for BMs promotes drug penetration into the CNS and antitumor immunity by destroying the BBB.[36] PD-L1 expression was up-regulated in the tumor microenvironment after RT in a mice model.[37] Synergistic effects of RT and anti-PD-L1 antibody inhibited the local accumulation of tumor-infiltrating bone marrow-derived myeloid-derived suppressor cells.[36] RT can induce immunogenic cell death, releasing danger-associated molecular patterns, which activate antigen-presenting and tumor-specific cytotoxic T cells.[37] In the KEYNOTE-001 trial, the PFS and OS of patients who received previous RT tended to be longer than those of patients who did not receive RT.[38] Therefore, improved antitumor immunity with RT may also explain why patients in the upfront-RT group had longer PFS and OS than those in the no-RT group in the ICI-alone cohort.

In the ICI-chemo cohort, no differences were observed in the PFS, OS, and CNS-PFS between the upfront-RT and no-RT groups. Several pivotal clinical trials on ICI-chemo have reported that it is more

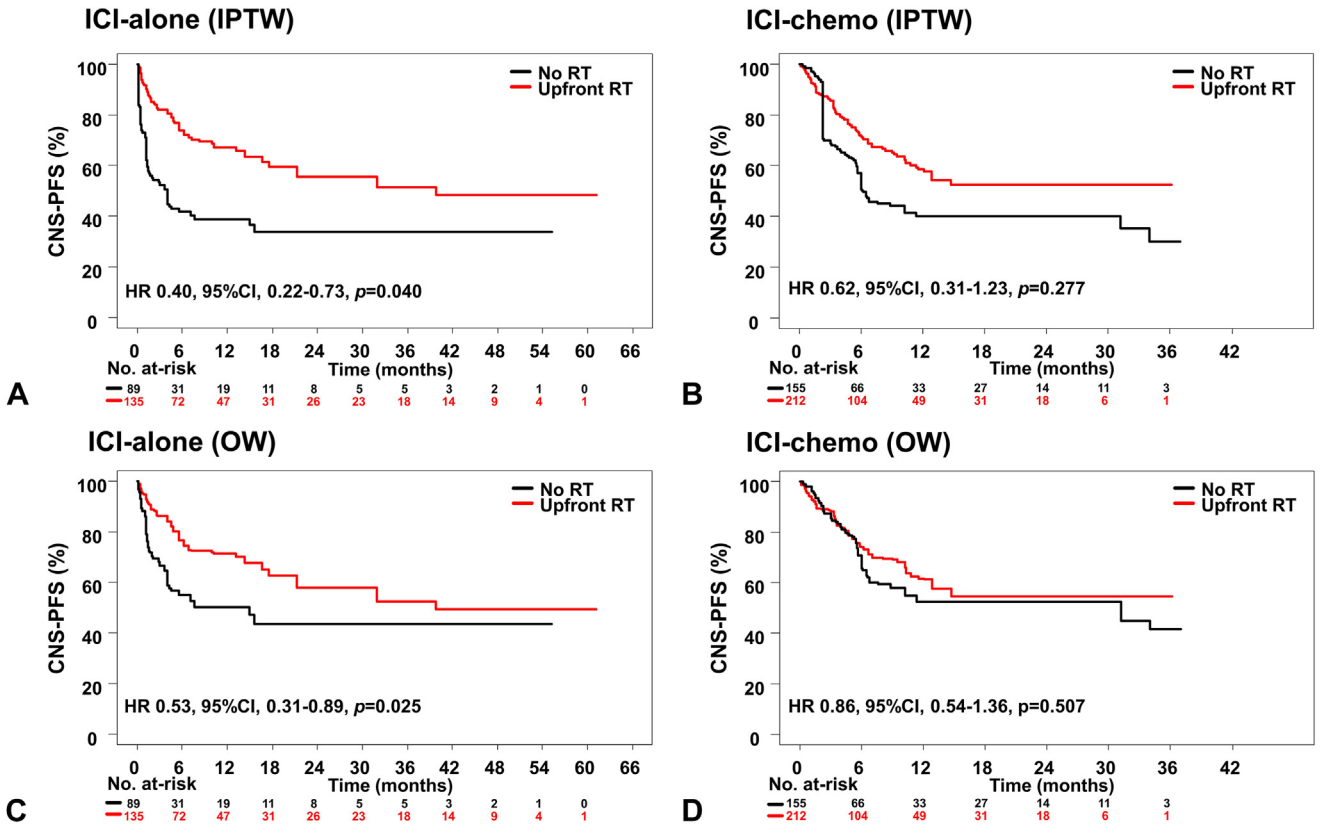

Figure 4. CNS-PFS curves to compare the upfront-RT and no-RT groups. IPTW-adjusted Kaplan-Meier curves: (*A*) ICI-alone cohort, (*B*) ICI-chemo cohort. OW-adjusted Kaplan-Meier curves: (*C*) ICI-alone cohort. (*D*) ICI-chemo cohort. CNS-PFS, central nervous system progression-free survival; ICI, immune checkpoint inhibitor; ICI-chemo, ICI plus chemotherapy; IPTW, inverse probability treatment weighting; OW, overlap weighting; RT, radiotherapy.

effective than platinum-based chemotherapy, regardless of PD-L1 expression.[2–4,6] Therefore, even patients with low PD-L1 expression of BMs may receive survival benefits from ICI-chemo without RT. Moreover, the combination of ICI with cytotoxic anticancer agents could enhance antitumor immunity by improving the tumor immune microenvironment.[39] Cytotoxic anticancer agents reduce immunosuppressor cells (myeloid-derived suppressor cells and regulatory T cells).[39] Chemotherapy also induces the immunogenic death of the tumor and release of danger-associated molecular patterns.[40,41] RT can also cause immunogenic cell death; however, if the tumor immune response has already been activated by chemotherapy, additional stimulation of the immune response by RT may be limited. Patients treated with ICI-chemo may have an improved immune microenvironment with the use of cytotoxic anticancer agents without RT. Patients treated with ICI-chemo may have an improved immune microenvironment with the use of cytotoxic anticancer agents without RT. Thus, in the ICI-chemo cohort of the present study, no difference in survival was observed between the upfront-RT and no-RT groups.

In the ICI and ICI-chemo cohorts, patients in the upfront-RT group tended to experience more CNS AEs than those in the no-RT group. This is partly because the upfront-RT group included more patients with symptomatic BMs before treatment initiation compared with the no-RT group. Radiation necrosis occurred at approximately 1.5%, and leukoencephalopathy occurred at less than 1.0%. The present study suggested that RT for BMs was well tolerated even in patients treated with ICI alone or ICI-chemo. However, a previous study reported that patients with BMs from NSCLC, malignant melanoma, or renal cancer who received immunotherapy had a higher risk of radiation brain necrosis than those who did not receive immunotherapy (HR = 2.56 95% CI: 1.35–4.86).[12] Hence, further long-term follow-up is warranted to evaluate late AEs because of RT and ICI.

The present study has several limitations. This was a retrospective observational study, and the RT group in the present study included only patients who had received RT for BMs and were in a satisfactory general condition to receive systemic treatment. This may have resulted in patient selection bias. In addition, the decision to perform RT for BMs was made at the discretion

of attending physicians. Therefore, the background factors are different between the upfront-RT and no-RT groups. To reduce biases, we adjusted for background factors between the two groups by performing two types of propensity score weighted analyses. Similar results were obtained in those propensity score weighted analyses. The timing of the imaging evaluation of the tumor was determined by the attending physician, and no central review of the images was performed. Therefore, prospective clinical studies are desirable in the future. Since late AEs of RT could not be evaluated in the present study, future studies with long-term follow-up are needed.

In conclusion, propensity score weighted analysis revealed that upfront RT for BMs was associated with longer OS, PFS, and CNS-PFS in patients with NSCLC who received ICIs alone. However, upfront RT for BMs did not exhibit survival benefits in patients with NSCLC who received ICI-chemo. These findings provide evidence that personalized treatment plans for patients with NSCLC with BMs are important.

CRediT Authorship Contribution Statement

Takehiro Tozuka: Study concept and design, Acquisition, analysis, or interpretation of data, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content, Statistical analysis.

Yuji Minegishi: Study concept and design, Acquisition, analysis, or interpretation of data, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content.

Ou Yamaguchi: Acquisition, analysis, or interpretation of data, Critical revision of the manuscript for important intellectual content.

Kana Watanabe: Acquisition, analysis, or interpretation of data, Critical revision of the manuscript for important intellectual content.

Yukihiro Toi: Acquisition, analysis, or interpretation of data, Critical revision of the manuscript for important intellectual content.

Ryota Saito: Acquisition, analysis, or interpretation of data, Critical revision of the manuscript for important intellectual content.

Yoshiaki Nagai: Acquisition, analysis, or interpretation of data, Critical revision of the manuscript for important intellectual content.

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Sayo Soda: Acquisition, analysis, or interpretation of data, Critical revision of the manuscript for important intellectual content.

Satoshi Watanabe: Acquisition, analysis, or interpretation of data, Critical revision of the manuscript for important intellectual content.

Satoshi Morita: Acquisition, analysis, or interpretation of data, Critical revision of the manuscript for important intellectual content, Statistical analysis.

Kunihiko Kobayashi: Acquisition, analysis, or interpretation of data, Critical revision of the manuscript for important intellectual content, Study supervision.

Masahiro Seike: Study concept and design, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content, Study supervision.

Disclosure

Dr. Tozuka has received honoraria from Chugai Pharmaceutical and AstraZeneca. Dr. Minegishi has received honoraria from AstraZeneca, Boehringer Ingelheim Japan, Eli Lilly Japan, Taiho Pharmaceutical, Chugai Pharmaceutical, Ono Pharmaceutical, Eisai, Bristol-Myers Squibb, Daiichi-Sankyo, Nippon Kayaku, Takeda Pharmaceutical, and GlaxoSmithKline. Dr. Yamaguchi has received honoraria from Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb Co. Ltd., and Chugai Pharmaceutical Co. Ltd. Dr. Toi has received honoraria from Bristol-Myers Squibb Company, Ono Pharmaceutical Co., Ltd., Merck Sharp & Dohme K.K., AstraZeneca Plc., Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Pfizer Inc., and Kyowa Kirin Co., Ltd. Dr. Tamura has received honoraria from Merck Sharp & Dohme (Merck & Co., Inc.), Chugai Pharmaceutical Co., Ltd., AstraZeneca K.K., and Ono Pharmaceutical Co., Ltd. Dr. Sakai has received grants from Eli Lilly Japan K.K.; and has received honoraria from AstraZeneca K.K., Nippon Boehringer Ingelheim Co., Ltd., Chugai Pharmaceutical Co., Ltd., Pfizer Japan Inc., and ThermoFisher Scientific

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Data Availability Statement

The data sets analyzed in the present study are not publicly available because of confidential clinical data for individual patients. However, the data sets are available from the corresponding author on reasonable request.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100655.

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