Radiation-induced enterocolitis after combination therapy with palliative radiotherapy and immune checkpoint inhibitors in patients with metastatic lung cancer

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Abstract. The impact of immune checkpoint inhibitors (ICIs) on radiation-induced enterocolitis (RIE) after palliative radiotherapy (PRT) to the bowel has remained to be fully investigated. The aim of the present study was to investigate whether ICIs affect RIE after PRT. For this purpose, 32 lesions (vertebral bone, 13; pelvic bone, 12; adrenal gland, 3; lymph node, 3; liver, 1) in 28 patients with metastatic lung cancer who were treated with both PRT involving the bowel (8-48 Gy; typically 30 Gy in 10 fractions or 20 Gy in 5 fractions) and ICIs between December 2015 and June 2021 were retrospectively reviewed. A total of 12 lesions were treated with ICIs only prior to PRT, 16 received ICIs only after PRT and the remaining 4 received ICIs both prior to and after PRT. The 1-year overall survival rate was 53%. The median PRT dose was 30 Gy (range, 8-48 Gy) in 10 fractions (range, 1-24 fractions). The median interval between PRT and the closest administration of ICIs was 20.5 days (range, 1-212 days). Combination therapy with PRT and ICIs was well tolerated by the majority of patients. However, grade 2 or higher RIE occurred in 6.3% of the patients. In these patients, ICIs were administered within 7 days after completing PRT with 3.6 Gy or a higher-fraction dose (evaluated at the isocenter). There were significant differences in the incidence of RIE between administration of ICIs <7 days after PRT completion and ≥7 days (P=0.05), between <3.6 Gy per fraction and ≥3.6 Gy (P=0.04), and between maximum dose to 2 cc (D2cc) of large bowel <3.3 Gy and D2cc of large bowel ≥3.3 Gy (P=0.02). There was no clear association between the incidence of RIE and any other factors. These results suggest that the administration of ICIs soon after PRT completion and a comparatively high fraction dose may potentially increase the risk of grade 2 or higher RIE.

Introduction

In recent years, significant progress has been made regarding systemic therapies for lung cancer. For patients with advanced, epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) in particular, EGFR tyrosine kinase inhibitors are widely used as the first-line therapy and provide significantly improved overall survival (OS) (1,2). However, NSCLC frequently gains resistance to these drug therapies during the course of treatment. In such cases, immune checkpoint inhibitors (ICIs) with or without chemotherapy are alternatives for treating NSCLC that is resistant to cytotoxic chemotherapies/molecular targeted therapies or does not have any EGFR mutations.

ICIs, including inhibitors of programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), are widely used in patients with advanced NSCLC. However, a variety of immune-related adverse events (irAEs) after the administration of ICIs have been reported. IrAEs occur in ~45% of patients with NSCLC. Endocrine, gastrointestinal and dermatologic toxicities are common events associated with irAE (3,4). The incidence of fatal irAEs is ~1% (5).

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Abbreviations: ICI, immune-checkpoint inhibitors; RIE, radiation-induced enterocolitis; PRT, palliative radiotherapy; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; a CTLA-4, cytotoxic T-lymphocyte-associated protein 4; NSCLC, non-small cell lung cancer; irAEs, immune-related adverse events; CT, computed tomography; EQD2, equivalent doses in 2 Gy fractions; D2cc, maximum dose to 2 cc; OS, overall survival; PS, performance status; ECOG, Eastern Cooperative Oncology Group

Key words: immune checkpoint inhibitors, palliative radiotherapy, radiation-induced enterocolitis, metastatic lung cancer

In palliative radiotherapy (PRT), the delivered doses are lower than the maximum tolerated doses of gastrointestinal tissues [mean PRT equivalent dose in 2 Gy fractions (EQD2), 36 Gy; maximum tolerance dose of small bowel, 50 Gy; maximum tolerance dose of large bowel, 55 Gy) (6). In PRT, the delivered doses (mean PRT EQD2, 36 Gy) are lower than the maximum tolerated dose of gastrointestinal tissue. However, there is a possibility that RT toxicity in the bowel is enhanced when RT and ICIs are combined. Regarding combination therapy of PRT and ICIs, certain studies suggested that it is well-tolerated (7-9). They reported that the incidence of colitis in patients treated with PRT involving the bowel was 5% or less and gastrointestinal toxicities did not increase. However, these studies were limited by the heterogeneity of patients and treatments. Therefore, further studies on the safety of PRT and ICI combination therapy are required.

In a study of adjuvant ICIs with durvalumab after definitive chemoradiotherapy for NSCLC (PACIFIC study), adjuvant ICI therapy appeared to slightly increase the incidence of pneumonitis (statistically not significant) (10). Patel *et al* (11) suggested that T- and natural killer (NK) cell infiltration are enhanced in lesions treated with low-dose radiotherapy. These results suggest that activated T- and NK cells accumulate in normal tissue damaged by RT and these accumulated T- and NK cells damage the tissue further. Based on these studies, the administration of ICIs may have the potential to enhance radiation toxicity. Despite the comparatively lower dose and small irradiation field size, administration of ICIs may also increase the toxicity of PRT. To the best of our knowledge, only a small number of studies have investigated whether gastrointestinal toxicities are associated with combination therapy of PRT and ICIs (7). Therefore, the present retrospective study aimed to investigate the occurrence of radiation-induced enterocolitis (RIE) after the administration of a combination therapy of PRT and ICIs in patients with metastatic lung cancer.

Patients and methods

A total of 45 abdominal-pelvic metastatic lesions in 38 patients with lung cancer who were treated with PRT involving the bowel and ICIs (a PD-1/L1 inhibitor and/or a CTLA-4 inhibitor) between December 2015 and June 2021 were reviewed. Of these, patients who did not undergo follow-up computed tomography (CT) after treatment (n=12) and those in whom the interval between PRT and closest administration of ICIs was more than one year (n=4) were excluded from this study. Finally, the remaining 32 lesions in 28 patients were retrospectively evaluated. This retrospective study was approved by the institutional review board (Shikoku Cancer Center, Ehime, Japan). An opt-out form of consent was used to obtain consent for this study.

PRT doses were determined at the discretion of each physician and 30 Gy in 10 fractions was the most frequently used regimen. To compare the different dose-fraction schedules, total doses of PRT were calculated with EQD2 values using an α/β ratio of 3 for the bowel. PRT was performed using 6-10 MV linear accelerators (Varian Medical Systems, Inc.) and the doses of the target volumes were ≥90% of the PRT dose in principle. The treatment of all lesions was planned using three-dimensional conformal RT.

RIE after combination therapy of PRT and ICIs was graded using the Common Terminology Criteria for Adverse Events version 5.0 (12). The definition of RIE was 'segmental and circumferential bowel wall thickening and inflammatory stranding in the area of an irradiated field occurring within 6 months after PRT on CT images'. The diagnosis of RIE was based on the patient's symptoms, physical examination and CT imaging and/or colonoscopy. The dose-volume parameters of the large and small bowel were assessed using CT simulation images. The dose-volume parameters of the large and small bowel were analyzed to determine the absolute volume cubic centimeters (cc) receiving doses from 10 to 20 Gy (V10 and V20), as well as the maximum dose to 2 cc volume (D2cc) and D2cc per fraction (D2cc/fr).

Statistical analysis. Kaplan-Meier survival analysis was used to calculate the OS rate and the duration of follow-up was calculated from the initiation of PRT. The statistical significance of differences in OS was evaluated using the generalized Wilcoxon test. The interval between PRT and the closest administration of ICIs was calculated from the date of initiation of PRT if ICIs were administered prior to PRT and the date of completion of PRT if ICIs were administered after PRT. Fisher's exact test was used to examine the relationship between the incidence of RIE and the risk factors. P-values were calculated by rounding to the nearest three decimal places and a two-sided $P \leq 0.05$ was considered to indicate statistical significance.

In addition, receiver operating characteristic (ROC) analysis was performed to examine optimal cut-off values of the interval between PRT and the closest administration of ICIs, fraction dose evaluated at the isocenter, total EQD2, V10 Gy, V20 Gy, D2cc and D2cc/fr for the incidence of RIE. Statistical analyses were performed using JMP software (version 14.3.0; SAS Institute, Inc.).

Results

Patients. Data from 32 lesions in 28 patients (one with SCLC and 27 with NSCLC; male/female, 23/5; age 42-75 years, median age, 64 years) were included in the analysis dataset (Table I). Of these, two patients had recurrent distant metastases that were not present at the initial diagnosis, while the remaining 26 had distant metastases at the initial diagnosis. The median follow-up time from the initiation of PRT was nine months (range, 1-41 months).

ROC analysis. The areas under the ROC curves for the incidence of RIE were 0.56 (sensitivity, 100%; specificity, 47%) for the interval between PRT and the closest administration of ICIs, 0.88 (sensitivity, 100%; specificity, 84%) for the fraction dose and 0.54 (sensitivity, 50%; specificity, 87%) for total EQD2. Regarding the dose-volume parameters of the large bowel, the areas under the ROC curve were 0.60 (sensitivity, 100%; specificity, 43%) for V10 Gy, 0.43 (sensitivity, 100%; specificity, 43%) for V20 Gy, 0.37 (sensitivity, 100%; specificity, 27%) for D2cc and 0.92 (sensitivity, 100%; specificity, 90%) for D2cc/fr. For the dose-volume parameters of the small bowel, the areas under the ROC curve were 0.65 (sensitivity, 100%; specificity, 53%) for V10 Gy, 0.58 (sensitivity, 100%; specificity, 50%) for V20 Gy, 0.63 (sensitivity, 100%; specificity,

Table I. Characteristics of the lesions.

Characteristic	Value (%)
Age, years [range]	64.0 [42-75]
<65	17 (53.1)
≥65	15 (46.9)
Sex	
Male	27 (84.4)
Female	5 (15.6)
PS (ECOG)	
0	2 (6.3)
1	18 (56.2)
2	9 (28.1)
3	1 (3.1)
4	2 (6.3)
Primary cancer histology	
Non-small cell lung cancer	30 (93.8)
Small cell lung cancer	2 (6.3)
PRT sites	
Vertebral bone	13 (40.6)
Pelvic bone	12 (37.5)
Adrenal gland	3 (9.4)
Lymph node	3 (9.4)
Liver	1 (3.1)
PRT dose, Gy (total dose/number of fractions)	30 [8-48]
8.0/1	1 (3.1)
20/5	4 (12.5)
28.8/8	2 (6.3)
30/10	20 (62.5)
37.5/15	1 (3.1)
40/16	1 (3.1)
45/18	1 (3.1)
45/15	1 (3.1)
48/24	1 (3.1)
Chemotherapy	
Yes	30 (93.8)
Administration before PRT	19 (59.4)
Administration after PRT	28 (87.5)
No	2 (6.3)
Biotherapy	
Yes	9 (28.1)
Administration before PRT	4 (12.5)
Administration after PRT	6 (18.8)
No	23 (71.9)
ICIs therapy	
Anti-PD-1 monotherapy	22 (68.8)
Anti-PD-L1 monotherapy	5 (15.6)
Anti-PD-1/PD-L1 + anti-CTLA-4 combination therapy	5 (15.6)
No. of ICI cycles [range]	
Anti-PD1/PD-L1 monotherapy	4 [1-30]
Anti-PD-1/PD-L1 + anti-CTLA-4 combination therapy	4.0 [1.0-8]
Interval between PRT and the closest administration of ICIs, days	
Administration of ICIs before PRT	11 (34.4)
≤7	1 (3.1)
8-14	1 (3.1)
15-30	4 (12.5)
31-90	4 (12.5)
>90	1 (3.1)
Administration of ICIs after PRT	17 (53.1)
≤7	4 (12.5)
8-14	2 (6.3)
15-30	4 (12.5)
31-90	4 (12.5)
>90	3 (9.4)
Administration of ICIs before and after PRT	4 (12.5)
≤7	3 (9.4)
8-14	1 (3.1)

Values are expressed as the median (range) or n (%). PS (ECOG), Performance Status (Eastern Cooperative Oncology Group); PRT, palliative radiotherapy; ICIs, immune checkpoint inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4.

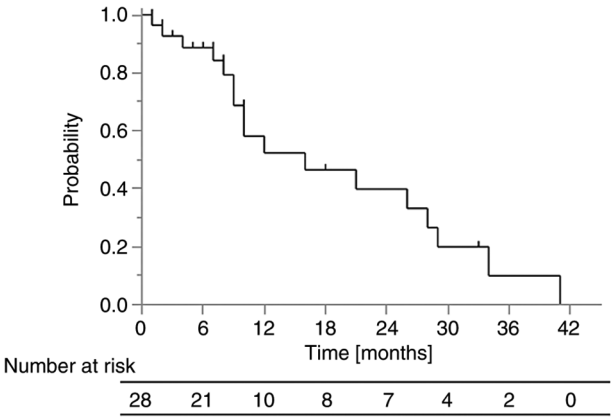

Figure 1. Overall survival rates.

60%) for D2cc and 0.63 (sensitivity, 50%; specificity, 43%) for D2cc/fr. For the incidence of RIE, the interval between PRT and closest administration of ICIs of 6-10 days, 3.6 Gy per fraction, total EQD2 of 28 Gy, V10 (large bowel) of 67.2 cc, V20 (large bowel) of 49.6 cc, D2cc (large bowel) of 21.2 Gy, D2cc/fr (large bowel) of 3.4 Gy, V10 (small bowel) of 43 cc, V20 (small bowel) of 7.8 cc, D2cc (small bowel) of 19.7 Gy and D2cc/fr (small bowel) of 3.9 Gy corresponded to the maximum sum of sensitivity and specificity.

Treatment. A total of 19 patients with 22 lesions received anti-PD-1 (pembrolizumab or nivolumab) monotherapy,

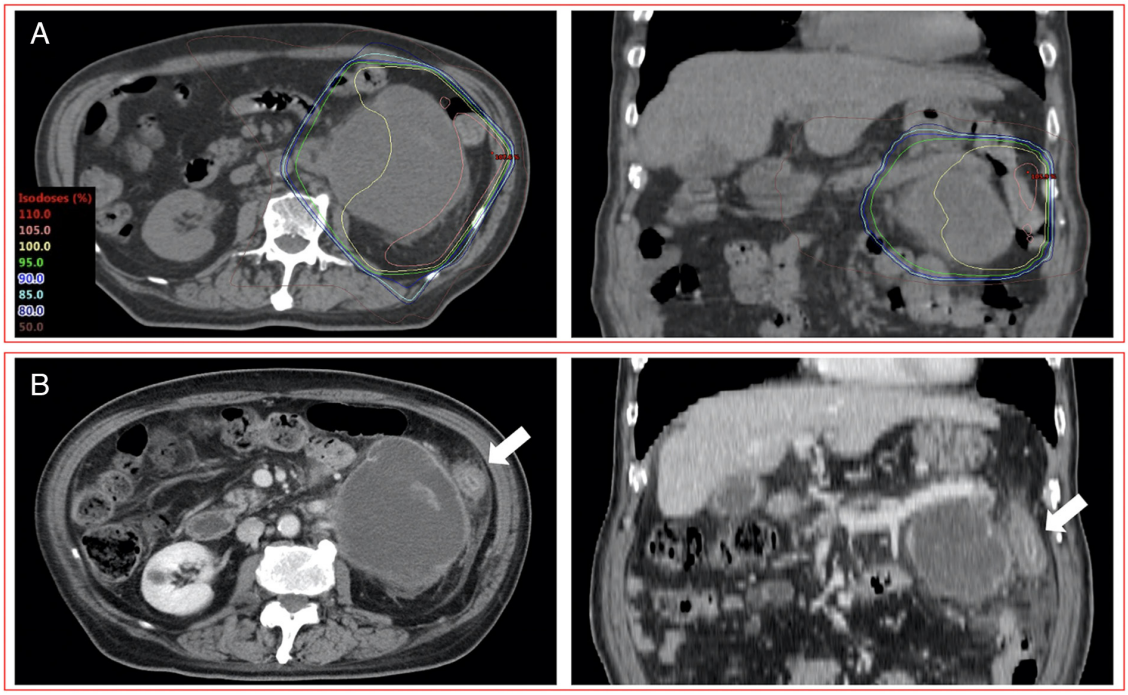

Figure 2. A patient (75 years, male) with grade 4 RIE after PRT involving the large bowel and administration of ICIs. (A) CT images displaying dose distribution of PRT to an adrenal metastasis (20 Gy in 5 fractions); (B) Contrast-enhanced CT images acquired 28 days after completion of PRT. This patient with grade 4 RIE exhibited segmental and circumferential bowel wall thickening, pericolic fat stranding and mucosal hyperenhancement in the area of the irradiated field (white arrow) as seen on CT imaging after receiving combination therapy of PRT and ICIs. Left panel showed transverse images and the right panel showed coronal images. RIE, radiation-induced enterocolitis; PRT, palliative radiotherapy; ICIs, immune checkpoint inhibitors; CT, computed tomography.

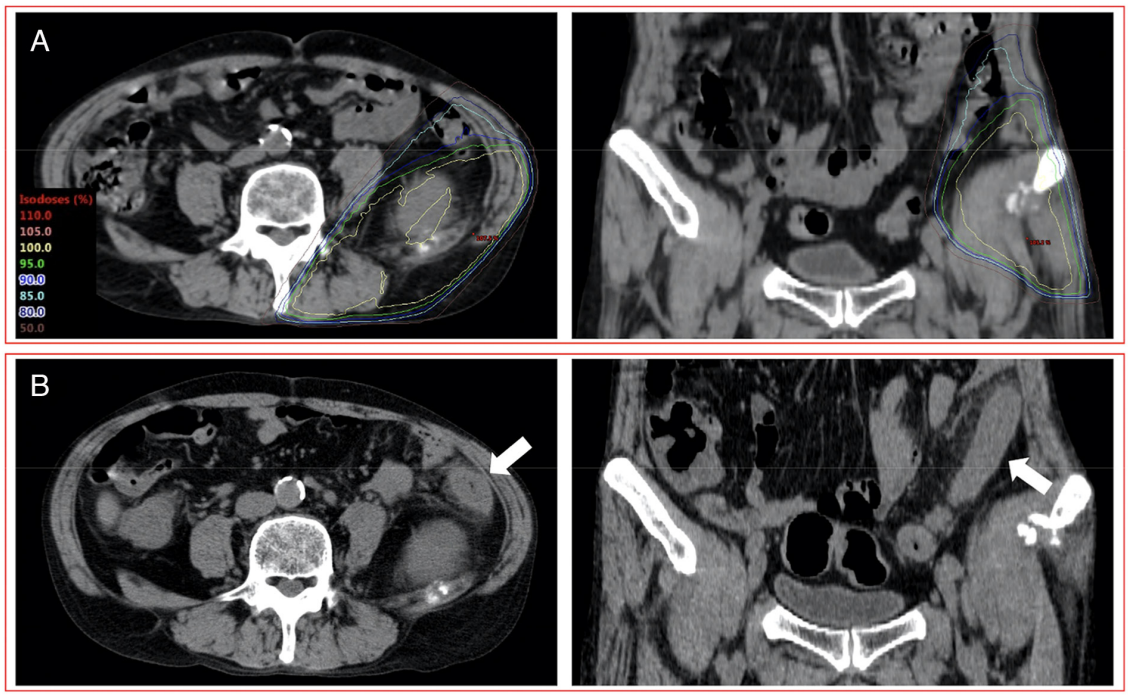

Figure 3. A patient (58 years, male) with grade 2 RIE after PRT involving the large bowel and administration of ICIs. (A) CT images indicating the dose distribution of PRT to an iliac bone metastasis (28.8 Gy in 8 fractions). (B) CT images acquired 17 days after the completion of PRT. This patient developed grade 2 RIE with segmental and circumferential bowel wall thickening and pericolic fat stranding in the area of the irradiated field (white arrow) as observed in CT images after combination therapy with PRT and ICIs. Left panel showed transverse images and the right panel showed coronal images. RIE, radiation-induced enterocolitis; PRT, palliative radiotherapy; ICIs, immune checkpoint inhibitors; CT, computed tomography.

5 patients with 5 lesions received anti-PD-L1 (durvalumab or atezolizumab) monotherapy and 4 patients with 5 lesions received anti-PD-1/PD-L1 (nivolumab, pembrolizumab or durvalumab) and anti-CTLA-4 (ipilimumab) therapy.

Table II. Incidence of grade 2 or higher radiation-induced enterocolitis.

	Administration of ICIs before and/or after PRT		Administration of ICIs after PRT	
Characteristic	No. of lesions	P-value	No. of lesions	P-value
Age, years		1.00		1.00
<65	1/17		1/10	
≥65	1/15		1/9	
Sex		1.00		1.00
Male	2/27		2/16	
Female	0/5		0/3	
PS (ECOG)		0.13		0.12
0-1	0/20		0/12	
2-4	2/12		2/7	
PRT sites		0.40		0.30
Bone	1/25		1/16	
Others	1/6		1/3	
Total EQD2, Gy		1.00		-
<28	0/1		0/0	
≥28	2/31		2/19	
Fraction dose, Gy		0.04		0.04
<3.6	0/25		0/15	
≥3.6	2/7		2/4	
Chemotherapy before PRT		1.00		1.00
Yes	1/19		1/9	
No	1/13		1/10	
Chemotherapy after PRT		1.00		-
Yes	2/28		2/19	
No	0/4		0/0	
Biotherapy before PRT		1.00		1.00
Yes	0/4		0/1	
No	2/28		2/18	
Biotherapy after PRT		1.00		1.00
Yes	0/6		0/4	
No	2/26		2/15	
Administration of ICIs before PRT		0.49		1.00
Yes	0/15		0/2	
No	2/17		2/17	
Administration of ICIs after PRT		0.53		0.30
Yes	2/21		1/16	
No	0/11		1/3	
ICIs monotherapy		0.29		0.30
Yes	1/27		1/16	
No	1/5		1/3	
Interval between the closest administration of ICIs and PRT, days		0.07		0.05
<7	2/9		2/5	
≥7	0/23		0/14	
V10 of the small bowel		1.00		1.00
<43	1/12		1/6	
≥43	1/20		1/13	
V20 of the small bowel		1.00		1.00
<7.8	1/16		0/4	
≥7.8	1/16		2/15	

Table II. Continued.

Characteristic	Administration of ICIs before and/or after PRT		Administration of ICIs after PRT	
	No. of lesions	P-value	No. of lesions	P-value
D2cc of the small bowel		1.00		1.00
<19.7	1/12		1/6	
≥19.7	1/20		1/13	
D2cc/fr of the small bowel		0.12		0.20
<3.9	1/30		1/17	
≥3.9	1/2		1/2	
V10 of the large bowel		0.50		0.51
<67.2	0/13		0/7	
≥67.2	2/19		2/12	
V20 of the large bowel		1.00		1.00
<49.6	1/18		1/9	
≥49.6	1/14		1/10	
D2cc of the large bowel		1.00		1.00
<21.2	0/9		1/11	
≥21.2	2/23		1/8	
D2cc/fr of the large bowel		0.02		0.02
<3.4	0/27		0/16	
≥3.4	2/5		2/3	

In all cases (the administration of ICIs before and/or after PRT), fraction dose and D2cc/fr of the large bowel were statistically significant factors for the grade 2 or higher RIE. In cases where ICIs were administered after PRT, fraction dose, D2cc/fr of the large bowel, and the interval between the closest administration of ICIs and PRT were significant factors for the incidence of grade 2 or higher RIE. PS (ECOG), Performance Status (Eastern Cooperative Oncology Group); PRT, palliative radiotherapy; ICIs, immune-checkpoint inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; D2cc, the minimal radiation doses for the most irradiated volumes of 2 cc; V10, percentage of the large or small bowel volume that received at least 10 Gy; V20, percentage of the large or small bowel volume that received at least 20 Gy; D2cc/fr, D2cc per fraction; EQD2, equivalent doses at 2 Gy.

Furthermore, 19 lesions were treated with ICIs prior to the initiation of PRT, 19 lesions were treated with ICIs after the initiation of PRT and the remaining 4 lesions were treated with ICIs both prior to and after PRT. The median interval between PRT and the closest administration of ICIs was 20.5 days (range, 1-212 days).

In addition, 17 patients with 19 lesions received chemotherapy prior to PRT and 24 patients with 28 lesions received chemotherapy after PRT. Furthermore, two patients with four lesions (one, bevacizumab; one, erlotinib) and six patients with six lesions (four, ramucirumab; two, bevacizumab) received biotherapy prior to and after PRT, respectively.

The median PRT dose was 30 Gy (range, 8-48 Gy) and the median total EQD2 was 36.0 Gy (range, 17.6-49.5 Gy). In addition, the frequently used dose-fractionation schedules, in sequential order, were as follows for the PRT dose (EQD2): 1x8 Gy (17.6 Gy), 5x4 Gy (28.0 Gy), 8x3.6 Gy (38.0 Gy), 10x3 Gy (36.0 Gy), 15-18x2.5 Gy (41.3-49.5 Gy), 24x2 Gy (48.0 Gy) and 10x2 Gy + 5x3 Gy (38.0 Gy). The irradiated sites were the vertebral bones (n=13), pelvic bones (n=12), adrenal glands (n=3), lymph nodes (n=3) and liver (n=1). The details of patients and lesions characteristics are shown in Table I.

OS. The 1-year OS rate was 53% (Fig. 1). The median survival time in all patients was 10 months (range, 1-41 months) and the median follow-up time in surviving patients was 7 months (range, 1-33 months). The 1-year OS rate in the group in which ICIs were administered after PRT was 70%, while that in the group in which ICIs were not administered after PRT was 38% (P=0.0091).

Factors affecting grade 2 or higher RIE. Grade 2 or higher RIE was observed in 2 patients (2/28 patients, 7.1%; 2/32 lesions, 6.3%; Figs. 2 and 3). Regarding the fraction dose of PRT evaluated at the isocenter, there was a significant difference in the incidence of RIE between <3.6 and ≥3.6 Gy per fraction (P=0.04, Table II). In addition, there tended to be differences in the incidence of RIE between administration of ICIs <7 and ≥7 days after PRT completion (P=0.07). In 19 lesions that were treated with ICIs after PRT, these two factors (<3.6 vs. ≥3.6 Gy per fraction and the administration of ICIs <7 vs. ≥7 days after PRT completion) were associated with significantly different incidences of RIE (P=0.04 and 0.05, respectively; Fig. 4, Table II). In addition, D2cc/fr of the large bowel (<3.4 vs. ≥3.4 Gy) had a significant influence on the incidence of RIE (P=0.02, Table II). However, the other

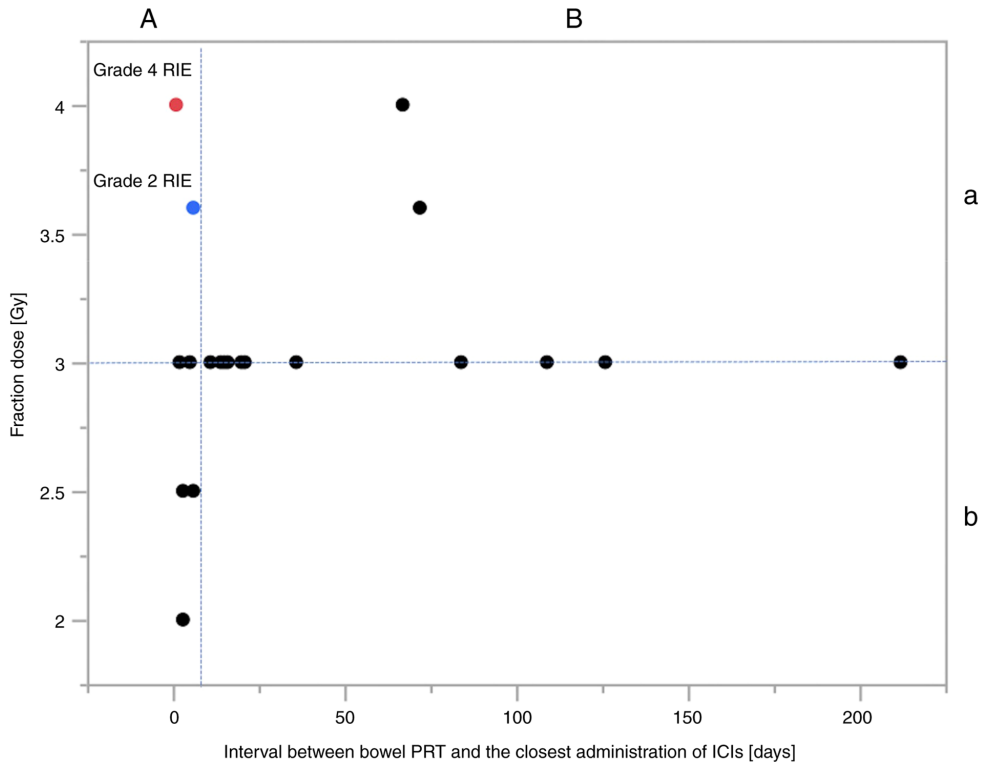

Figure 4. Relationship between the fraction dose and the interval between bowel PRT and the closest administration of ICIs. The blue dotted vertical line in the figure denotes seven days after the completion of PRT (A, <7 days; B, ≥7 days), and the blue dotted horizontal line marks 3 Gy per fraction (a, >3 Gy; b, ≤3 Gy). PRT, palliative radiotherapy; ICIs, immune checkpoint inhibitors.

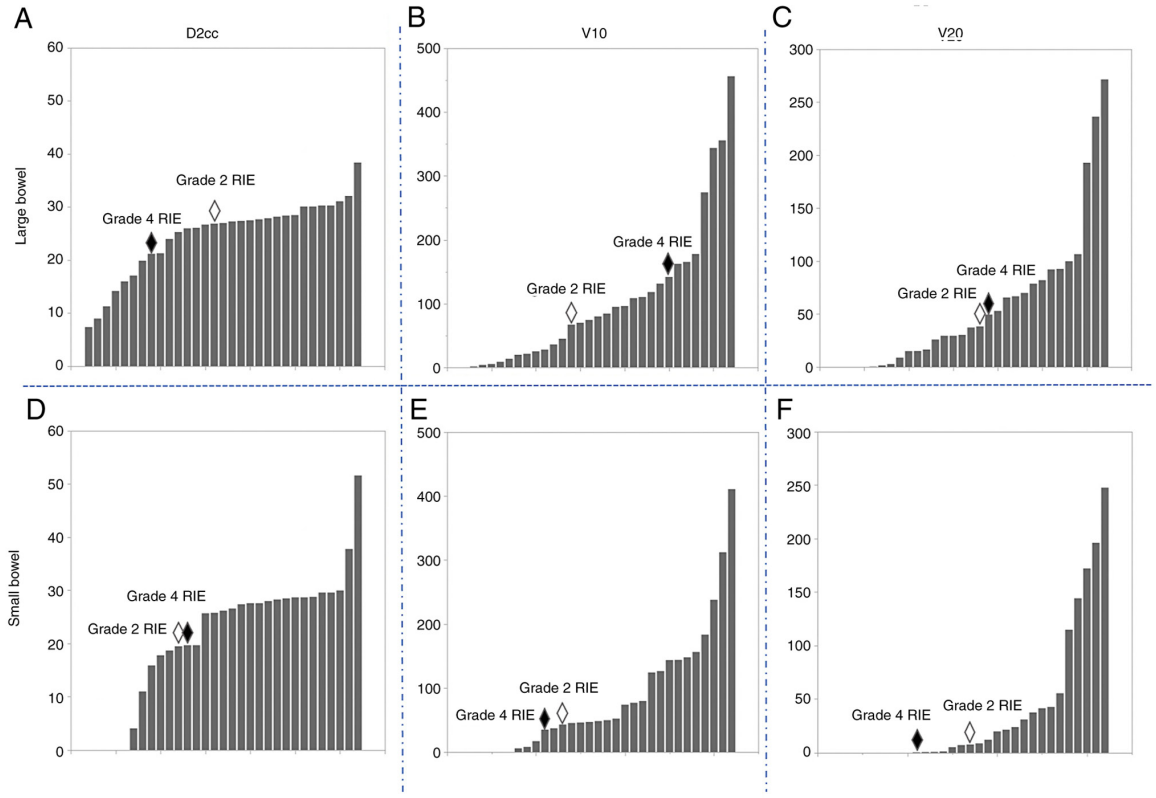

Figure 5. Dose-volume parameters of the bowel. (A) D2cc of the large bowel. (B) V10 of the large bowel. (C) V20 of the large bowel. (D) D2cc of the small bowel. (E) V10 of the small bowel. (F) V20 of the small bowel. The black diamond on the bar chart denotes the case with grade 4 RIE and the white diamond on the bar chart denotes the case with grade 2 RIE. The D2cc, V10 and V20 in the large and small bowels of all cases were listed in decreasing orders. There was no clear association of these dose-volume parameters between the two cases of grade 2 or higher RIE and the other cases. D2cc, the minimal radiation doses for the most irradiated volumes of 2 cc; V10, percentage of the large or small bowel volume receiving at least 10 Gy; V20, percentage of the large or small bowel volume receiving at least 20 Gy; RIE, radiation-induced enterocolitis.

Table III. Dose-volume parameters for the patients/lesions.

Subgroup	EQD2	Fraction doses	Grade of enterocolitis	Large bowel				Small bowel		
				D2cc/fr	D2cc	V20	V10	D2cc/fr	D2cc	V20	V10
All	36.0	3.0	-	2.8	27.0	33.9	77.35	2.8	26.0	7.6	47.7
	(17.6-49.5)	(2-8)		(0-7.4)	(0-38.4)	(0-271.5)	(0-456.2)	(0-4.1)	(0-51.6)	(0-247.7)	(0-410.9)
ICIs after PRT	36.0	3	-	2.8	26.9	37.3	74.6	2.8	25.7	7.3	48.4
	(28.0-49.5)	(2-4)		(1.6-4.2)	(9-31.1)	(0-236.4)	(1.7-456.2)	(0-3.9)	(0-29.6)	(0-247.7)	(0-410.9)
No ICIs after PRT	36.0	3	-	2.8	27.3	29.5	84.6	2.9	28.3	19.9	47.0
	(17.6-41.3)	(2.5-8)		(0-7.4)	(0-38.4)	(0-271.5)	(0-355.7)	(0-4.1)	(0-51.6)	(0-144.3)	(0-183.3)
Patient 1	28.0	4	4	4.2	21.2	49.6	141.8	3.9	19.7	0.5	35.1
Patient 2	38.0	3.6	2	3.4	26.9	38.4	67.2	2.4	19.5	7.8	43

Values are expressed as the median (range). In patients with grade 2 or higher RIE, the total dose (EQD2) and dose-volume parameters of the bowel were not substantially different from those of other patients. D2cc, minimal radiation doses for the most irradiated volumes of 2 cc; V10, percentage of the large or small bowel volume that received at least 10 Gy; V20, percentage of the large or small bowel volume that received at least 20 Gy; D2cc/fr, D2cc per fraction; EQD2, equivalent doses at 2 Gy; RIE, radiation-induced enterocolitis.

dose-volume parameters of the bowel (V10, V20 and D2cc of small and large bowel) were not associated with the incidence of RIE (Fig. 5, Tables II and III). In addition, age, sex, performance status, PRT sites, total dose (EQD2), chemotherapy and biotherapy were not associated with the incidence of RIE. The clinical and treatment details of subgroups of patients that received >3 Gy per fraction and/or were administered ICIs within seven days after completing PRT are provided in Table IV.

Cases with grade 2 or higher RIE. Grade 4 RIE was reported in one patient (75 years, male) who received anti-PD-L1 (atezolizumab) monotherapy with chemotherapy (carboplatin and paclitaxel) one day after completing PRT (5x4 Gy) (Fig. 2). After completing PRT, this patient had diarrhea and abdominal pain after 8 days and hematochezia after 18 days. CT images acquired 28 days after the completion of PRT indicated enterocolitis limited to the irradiated field. These symptoms were improved 49 days after the completion of PRT. However, after the third administration of anti-PD-L1 (atezolizumab) monotherapy, enterocolitis deteriorated 98 days after the completion of PRT (11 days after the third ICI administration). Eventually, as colonoscopy performed 128 days after the completion of PRT revealed erosion and angiectasis of the descending colon limited to the irradiated field without neutrophilic infiltration of the intra-epithelial compartment or formation of neutrophilic crypt abscess, this patient was diagnosed with RIE and colostomy was performed. The dose-volume parameters of D2cc, V10 and V20 of the large bowel were 21.2 Gy, 141.8 cc and 49.6 cc, respectively.

Another patient (58 years, male) who had grade 2 RIE was administered anti-PD-1 (nivolumab) plus anti-CTLA-4 (ipilimumab) combination therapy with chemotherapy (carboplatin and pemetrexed) 6 days after the completion of PRT (8x3.6 Gy) (Fig. 3). This patient had diarrhea and abdominal pain 7 days after the completion of PRT. CT images acquired 17 days after the completion of PRT revealed findings of enterocolitis limited to the irradiated field. Biopsy was not performed. The dose-volume parameters of D2cc, V10 and V20 of the large bowel were 26.9 Gy, 67.2 cc and 38.4 cc, respectively.

Discussion

The present study indicated that the combination of PRT involving the bowel and ICIs were well tolerated by a majority of patients. However, RIE of grade 2 or higher was observed in 6.3% (2/32) of patients. In all of these cases, the interval between the administration of ICIs and the completion of PRT was within 7 days and fraction doses were >3.6 Gy (evaluated at the isocenter), and D2cc/fr ≥3.4 Gy. A clear relationship between grade 2 or higher RIE and other dose-volume parameters of the bowel was not observed in patients who received PRT in combination with ICIs. However, it was indicated that a larger fraction dose of PRT and a shorter interval between the administration of ICIs and PRT may affect the incidence of grade 2 or higher RIE.

RIE is typically associated with progressive occlusive vasculitis. Although the role of ICIs in RIE remains elusive, PRT alone, as it involves a comparatively low dose, is unlikely

Table IV. Characteristics of patients/lesions given >3 Gy per fraction or ICIs within 7 days after PRT.

A, Series with grade 2 or higher RIE

Patient	Age	Sex	PS (ECOG)	Grade of enterocolitis	PRT sites	Total dose in Gy/fractions	ICIs therapy	Interval between PRT and closest administration of ICIs	Timing of onset of RIE symptoms	CT image	Max fraction dose of descending colon, Gy (%)
1	75	Male	2	4	Adrenal gland	20.0/5.0	Anti-PD-L1 monotherapy	1 day after completion of PRT	8 days after completion of PRT	Descending colitis	4.28 (107)
2	58	Male	2	2	Pelvic bone	28.8/8.0	Anti-PD-1 + anti-CTLA-4 combination therapy	6 days completion after end of PRT	7 days after completion of PRT	Descending colitis	3.63 (104)

B, series received >3 Gy per fraction

Patient	Age	Sex	PS (ECOG)	Grade of enterocolitis	PRT sites	Total dose in Gy/fractions	ICIs therapy	Interval between PRT and closest administration of ICIs	Timing of onset of RIE symptoms	CT image	Max fraction dose of descending colon, Gy (%)
3	63	Male	2	0	Pelvic bone	20/5	Anti-PD-1 monotherapy	75 days before initiation of PRT	-	No enterocolitis	4.12 (103)
5	65	Male	1	0	Pelvic bone	20/5	Anti-PD-1 monotherapy	67 days after completion of PRT	-	No enterocolitis	4.24 (106)
4	63	Male	2	0	Vertebral bone	20/5	Anti-PD-1 monotherapy	82 days before initiation of PRT	-	No enterocolitis	3.44 (86)
6	73	Male	1	0	Vertebral bone	28.8/8.0	Anti-PD-1 monotherapy	72 days after completion of PRT	-	No enterocolitis	3.31 (92)
7	48	Male	1	0	Vertebral bone	8/1.0	Anti-PD-L1 monotherapy	183 days before initiation of PRT	-	No enterocolitis	7.52 (94)

C, Series received the administration of ICIs within seven days after completion of PRT

Patient	Age	Sex	PS (ECOG)	Grade of enterocolitis	PRT sites	Total dose in Gy/fractions	ICIs therapy	Interval between PRT and closest administration of ICIs	Timing of onset of RIE symptoms	CT image	Max fraction dose of descending colon, Gy (%)
8	73	Male	3	0	Pelvic bone	30/10	Anti-PD-1 monotherapy	2 days after completion of PRT	-	No enterocolitis	2.58 (86)

Table IV. Continued.

C, Series received the administration of ICIs within seven days after completion of PRT

Patient	Age	Sex	PS (ECOG)	Grade of enterocolitis	PRT sites	Total dose in Gy/fractions	ICIs therapy	Interval between PRT and closest administration of ICIs	Timing of onset of RIE symptoms	CT image	Max fraction dose of descending colon, Gy (%)
9	67	Male	0	0	Lymph node	48/24	Anti-PD-L1 monotherapy	3 days after completion of PRT and 26 days before initiation of PRT	-	No enterocolitis	1.21 (60)
10	64	Female	1	0	Pelvic bone	40/16	Anti-PD-1 monotherapy	3 days after completion of PRT and 20 days before initiation of PRT	-	No enterocolitis	2.29 (92)
11	70	Male	1	0	Pelvic bone	30/10	Anti-PD-1 monotherapy	5 days after completion of PRT	-	No enterocolitis	3.08 (103)
12	57	Male	0	0	Adrenal gland	45/18	Anti-PD-1 monotherapy	6 days after completion of PRT and 5 days before initiation of PRT	-	No enterocolitis	1.76 (70)

PS (ECOG), Performance Status (Eastern Cooperative Oncology Group); PRT, palliative radiotherapy; RIE, radiation-induced enterocolitis; ICIs, immune checkpoint inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4.

to cause severe RIE (6,13). Bang *et al* (7) reported that mild colitis was observed in 4% of the patients who received ICIs and PRT to the bowel. The present results also suggested that the incidence of enterocolitis was not high after combination therapy with PRT and ICIs. By contrast, Bang *et al* (7) indicated that irAEs occurred more frequently when ICIs were administered within 14 days prior to and after PRT compared to when ICIs were administered 14 days or more after PRT (statistically not significant). In the present study, patients who experienced grade 2 or higher RIE received ICIs within 7 days after the completion of PRT. Although the optimal intervals between RT and ICIs to achieve a systemic effect of RT and ICIs remained to be determined (14), the administration of ICIs immediately after PRT may also be a potential risk factor for severe RIE.

In addition, several studies suggested that moderate hypofractionated regimens (6-8 Gy per fraction) may increase the synergistic effect of ICIs (15,16). In the present study, the fraction doses (3.6 and 4 Gy per fraction) in the two patients with RIE were lower than this fraction dose. A fraction dose of >3 Gy (D2cc/fr of large bowel ≥3.4 Gy) may be associated with the risk of severe RIE with PRT and ICI combination therapy. Thus, for combination therapy with PRT and ICIs, two factors, namely the fraction dose and interval between PRT and ICIs, may be important. Furthermore, the interaction between a higher fraction dose of PRT and the interval between PRT and administration of ICIs may be significant in the development of grade 2 or higher RIE.

In addition, elevated levels and imbalance of several cytokines generally result in various symptoms in advanced cancers (17). The RT-induced inflammatory response in the bowel involves the recruitment of activated inflammatory cells (18). These immune cells synthesize and release several different cytokines, inflammatory mediators and reactive oxygen metabolites (19). In addition to the RT-induced inflammatory response, ICIs also promote the activity of immune cells and facilitate autoimmune responses against any organ (20). The combination of these two factors may lead to RIE even when PRT is administered.

In the present study, one patient (3.1%) experienced grade 4 RIE after combination therapy with PRT and ICIs. In this patient, the interaction between PRT and ICIs may have induced severe RIE. Although RIE was initially alleviated in this patient, it worsened again and grade 4 RIE was developed after the subsequent administration of ICIs. Radiation recall phenomenon is an inflammatory reaction that manifests within a previously irradiated field after the administration of a variety of pharmacological agents (21). This grade 4 RIE may have been caused by a radiation recall phenomenon associated with the subsequent administration of ICIs.

There were certain limitations to the present study owing to its retrospective nature and small sample size. Selection bias and confounding factors must also be considered. In addition, based on symptoms alone, accurate differentiation between RIE and irAE is difficult in numerous cases, as RIE and irAE enterocolitis exhibit similar symptoms. Therefore, the present study focused on the importance of CT images in addition to the symptoms of enterocolitis. Although the incidence of mild irAEs in the bowel, such as diarrhea, abdominal pain and nausea, is 12.1-13.7% for anti-PD-1 and 30.2-35.4% for anti-CTLA-4, the incidence of severe irAEs of the bowel (enterocolitis) is 0.7-1.6% for anti-PD-1, 5.7-9.1% for anti-CTLA-4 and 13.6% for the combination of both therapies (22,23). In the present study, the incidence of RIE was similar to the incidence of irAEs of the bowel. However, as the CT images of RIE (grade 2 and 4) were consistent with the irradiated fields and the histology of grade 4 RIE was not typical for an irAE of the bowel, these two cases were diagnosed as RIE. Although irAE enterocolitis and RIE may not be completely separated, the results of the present study suggested that RIE may appear even after administering PRT in combination with ICIs.

Severe RIE may at times be induced by PRT involving the bowel and ICI administration. Although further studies are required, administration of ICIs immediately after PRT with a higher fraction dose (at the isocenter) was indicated to be a risk factor for severe RIE. However, a relationship between dose-volume parameters other than D2cc/fr and RIE was not observed in the present study.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

KM, YH, HK, and KN were involved in the conception and design of the study. KM, YH, HK and KN collected patient data and drafted the manuscript. KM, YH, HK, KN, YS, TN, DH and TK interpreted the data. KM and YH prepared the manuscript and HK, KN, YS and TK edited the manuscript. All authors confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This retrospective study was approved by the institutional review board (Shikoku Cancer Center, Ehime, Japan).

Patient consent for publication

Patients consented in writing to the possibility of the use of their anonymous data for research at the time of tissue collection. In addition, the Opt-out method was used to obtain consent for this study.

Competing interests

DH received honoraria from MSD, Ono, Kyowa Hakko Kirin, AstraZeneca, Boehringer Ingelheim, TOWA, Chugai, TAIHO, and Eli Lilly, and received research funding MSD, Chugai, AstraZeneca, Eli Lilly, Pfizer, BMS, Novartis, Kissei and Takeda. TK received honoraria from MSD, Ono, Kyowa Hakko Kirin, AstraZeneca, Boehringer Ingelheim, Chugai, TAIHO, Eli Lilly, Bristol Myers Squibb, Pfizer, Merck Biopharma, Nippon Kayaku, Novartis, Daiichi-Sankyo, AbbVie and Bayer, and received research funding MSD, Kyowa Hakko Kirin, AstraZeneca, Eli Lilly, Pfizer, BMS, Novartis, Kissei, Takeda, Chugai, TAIHO, Bristol-Myers, Merck Biopharma, Daiichi-Sankyo, AbbVie and AMGEN. All other authors declare that they have no competing interests.

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