

## Carbon-ion Radiotherapy for Oligometastatic Colorectal Cancer in the Liver or Lung

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**Abstract.** *Background/Aim:* We aimed to evaluate the clinical outcomes of oligometastatic colorectal cancer in the liver and lung treated with carbon-ion radiotherapy (C-ion RT). *Patients and Methods:* Nineteen consecutive patients with oligometastatic colorectal cancer in the liver or lung who received C-ion RT were analyzed. The doses of C-ion RT were 60.0 Gy [relative biological effectiveness (RBE)] in 4 fractions, 60.0 Gy (RBE) in 12 fractions, or 64.8 Gy (BRE) in 12 fractions. *Results:* The median follow-up duration was 19 months. There were 23 tumors in 19 patients. The 2-year overall survival and local control rates for the whole patient cohort were 100% and 67%, respectively. None of the patients developed grade 2 or higher acute or late toxicities. *Conclusion:* C-ion RT for oligometastatic colorectal cancer in liver and lung provides favorable clinical outcomes. These outcomes suggest C-ion RT is a treatment option for oligometastatic colorectal cancer in liver and lung.

Oligometastatic disease is an intermediate state between localization and widespread dissemination (1). Therefore, controlling oligometastatic disease by local treatment may improve survival. Colorectal cancer is one of the cancer types that are characterized by oligometastases of the liver and lung. Local treatment of oligometastatic colorectal cancer, with or without chemotherapy, is performed to improve survival (2-7). In contrast, radiotherapy (RT) is performed as a local treatment approach for patients who are not indicated for surgery due to comorbidity or refusal of surgery (8-15).

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Carbon-ion (C-ion) RT is performed to treat various types of cancer, including hepatocellular carcinoma, lung cancer, and oligometastatic disease (16-21). C-ion RT has biological and physical advantages over photon therapy. Owing to its biological properties, C-ion RT has a higher relative biological effectiveness (RBE) due to the high linear energy transfer in the Bragg peak. Furthermore, its physical properties allow administration of high doses while sparing normal tissues because of its higher dose localization ability with distal tail-off enabled by the Bragg peak and sharp lateral penumbra (22). Previous studies have demonstrated a dose distribution advantage, showing that C-ion RT delivered a reduced dose to the normal liver and lung compared with stereotactic body RT (SBRT) and intensity-modulated RT (23-25). The biological and physical advantages may contribute to favorable clinical outcomes. However, research on the clinical outcomes of oligometastatic colorectal cancer treated with C-ion RT is limited. Hence, we aimed to evaluate the clinical outcomes of oligometastatic colorectal cancer in the liver and lung treated with C-ion RT.

### Patients and Methods

*Patients.* We reviewed the medical records of patients with oligometastatic colorectal cancer in the liver or lung treated with C-ion RT at Gunma University Heavy Ion Medical Center between October 2013 and March 2020. We enrolled 19 consecutive patients who met the following criteria: i) Liver or lung metastases from colorectal cancer as confirmed by histology or radiography; ii) curative resection for primary disease and regional lymph nodes, without gross or microscopic residual disease; iii) absence of local primary colorectal lesion and lymph node recurrence; iv) absence or control of extrahepatic or extra-thoracic disease; v)  $\leq 3$  synchronous liver or lung metastases at the time of treatment; vi) not indicated or refused surgery for metastatic disease of liver or lung; vii) radiographically measurable tumor; and viii) performance status  $\leq 3$  by the Eastern Cooperative Oncology Group classification. Cases were excluded if they had received prior RT to the target area, had intractable infections in the target area, or had received chemotherapy/molecular targeted therapy within 4 weeks before the

initiation of C-ion RT. The treatment protocol was reviewed and approved by the Gunma University Institutional Review Board (approval number: HS2019-130), and all patients signed an informed consent form before the initiation of therapy.

**Carbon-ion radiotherapy.** A heavy ion accelerator at Gunma University Heavy Ion Medical Center generated C-ion beams, and the beam energy was either 290 MeV/u, 380 MeV/u, or 400 MeV/u according to the tumor depth. The XiO-N system (version 4.47; collaborated product of Elekta AB, Stockholm, Sweden, and Mitsubishi Electric, Tokyo, Japan) was used for treatment planning. This system incorporates a dosing engine for ion beam RT (K2dose) (25). We calculated the clinical radiation dose based on the physical dose multiplied by the RBE of the C-ions. Before C-ion RT, patients were immobilized using tailor-made fixation cushions and thermoplastic shells to allow computed tomography (CT); respiratory-gated and 4-dimensional CT images were acquired. In actual treatment, the gating level for respiratory-gated irradiation was within 30% of the wave height around the peak exhalation. Patients received C-ion RT once daily, 4 days a week (Tuesday to Friday).

The gross tumor volume (GTV) was delineated by the treatment planning CT images, which were merged with the contrast-enhanced CT images, contrast-enhanced magnetic resonance imaging (MRI), with/without 2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose (FDG)-positron-emission tomography (PET)/CT images if necessary. The clinical target volume had 5-10 mm margin around the GTV to include microscopic disease. The internal margin was assessed using 4-dimensional CT images for tumor movement. The planning target volume was defined as the summation of the clinical target volume, internal margin, and setup margin. The prescribed doses were 60 Gy (RBE) in four fractions for cases with peripheral metastatic tumor, 60 Gy (RBE) in 12 fractions for cases with metastatic tumor close to the gastrointestinal tract, and 64.8 Gy (RBE) in 12 fractions for cases with large metastatic tumor (>5 cm). The treatment aim was to cover 95% of the PTV with at least 95% of the prescribed dose. The dose constraints were as follows: Dose to 1 cm<sup>3</sup> (D<sub>1cc</sub>) <40 Gy (RBE) administered to the gastrointestinal tract in standard cases; D<sub>1cc</sub> <45 Gy (RBE) administered to the gastrointestinal tract in the cases treated with 12 fractions; organ volume that received at least 10% of the administered dose (V<sub>10</sub>) <55% and V<sub>20</sub> <40% administered to the liver; V<sub>20</sub> <20% administered to the lung; maximum dose (D<sub>max</sub>) <30 Gy (RBE) administered to the spinal cord; D<sub>max</sub> <52.8 Gy (RBE) administered outside the PTV at the porta hepatis (including the first branch of the portal vein and hepatic duct); D<sub>max</sub> <45 Gy (RBE) administered to the skin in standard cases; and D<sub>max</sub> <50 Gy (RBE) administered to the skin in the cases treated with 12 fractions. Figures 1 and 2 show radiographical images before C-ion RT and typical clinical dose distribution with C-ion RT of patients with oligometastatic colorectal cancer in the liver and lung.

**Evaluation during follow-up.** Patients were followed-up for 1 month after the completion of C-ion RT and every 3 months thereafter. Follow-up examinations comprised routine testing of blood cell counts and chemistry and diagnostic imaging using CT, MRI, or FDG-PET. Acute and late toxicities were graded according to the Common Terminology Criteria for Adverse Events (version 4.0) of the National Cancer Institute (27). Acute and late toxicities were evaluated as the highest grade of toxicity that occurred within 3 months and after 3 months of initiating C-ion RT, respectively.

**Dose-volume histogram analysis.** Dose-volume histogram (DVH) analysis was used to evaluate the dose of C-ion RT to normal liver and normal lung (*i.e.* total liver or lung volume minus GTV). We assessed the mean liver or lung dose, and the percentage of the normal liver or lung that received at least 5, 10, 15, 20, 25, 30, 40, and 50 Gy (RBE) (V<sub>5</sub>, V<sub>10</sub>, V<sub>15</sub>, V<sub>20</sub>, V<sub>25</sub>, V<sub>30</sub>, V<sub>40</sub>, and V<sub>50</sub>) based on the DVH.

**Statistical analysis.** All statistical analyses were performed using the Statistical Package for the Social Sciences software (version 25.0; IBM Inc., Armonk, NY, USA). Survival was measured from the date of C-ion RT initiation to death or the most recent follow-up. Local control (LC) was defined as no evidence of local recurrence without an increase in tumor size on CT or MRI and no increase in FDG uptake on PET. Progression-free survival (PFS) was defined as the absence of progression of both local and distant metastases. PFS was measured from the date of initiation of C-ion RT to the date of tumor progression or death from any cause. The probabilities of overall survival (OS), LC, and PFS rates were calculated using the Kaplan-Meier method. Next, we evaluated the potential prognostic effect of sex (male or female), age (<65 or ≥65 years), performance score (0 or 1), primary tumor site (rectum or colon), tumor location (liver or lung), tumor size (<3 or ≥3 cm), GTV volume (<10 cm<sup>3</sup> or ≥10 cm<sup>3</sup>), clinical target volume (<40 or ≥40 cm<sup>3</sup>), serum carcinoembryonic antigen level (<5.0 or ≥5.0 ng/ml), duration between surgery and C-ion RT (<27 or ≥27 months), and surgical indication (not indicated or refused) in OS and LC using the log-rank test.

## Results

**Patient characteristics.** The clinical characteristics of the 19 patients are summarized in Table I. The median follow-up duration after the initiation of C-ion RT was 19 months (range=4-55 months). The median age at the time of registration for C-ion RT was 65 years (range=47-86 years). Four patients had two metastatic tumors that received C-ion RT. The number of oligometastatic tumors in the liver and lung was 14 in 11 patients and nine in eight patients, respectively. The median tumor size of 23 lesions was 2.6 cm (range=1.1-6.5 cm) in maximum diameter, in two cases larger than 5 cm. At the time of C-ion RT, six patients had chemoresistant disease or were unable to continue chemotherapy due to toxicities; 11 patients were unsuitable due to comorbidity and age, or refused chemotherapy. In patients who received chemotherapy before C-ion RT, the median duration from the initiation of chemotherapy for oligometastatic disease to the initiation of C-ion RT was 10 months (range=5-28 months). All patients with liver metastases had Child-Pugh class A and had no liver cirrhosis, and no patients with lung metastases had chronic lung disease or interstitial pneumonia. The dose-fractionation schedules for liver metastases were as follows: Nine lesions received 60 Gy (RBE) in four fractions, one lesion received 60 Gy (RBE) in 12 fractions, and four lesions received 64.8 Gy (RBE) in 12 fractions. For lung metastases, there were nine lesions, which

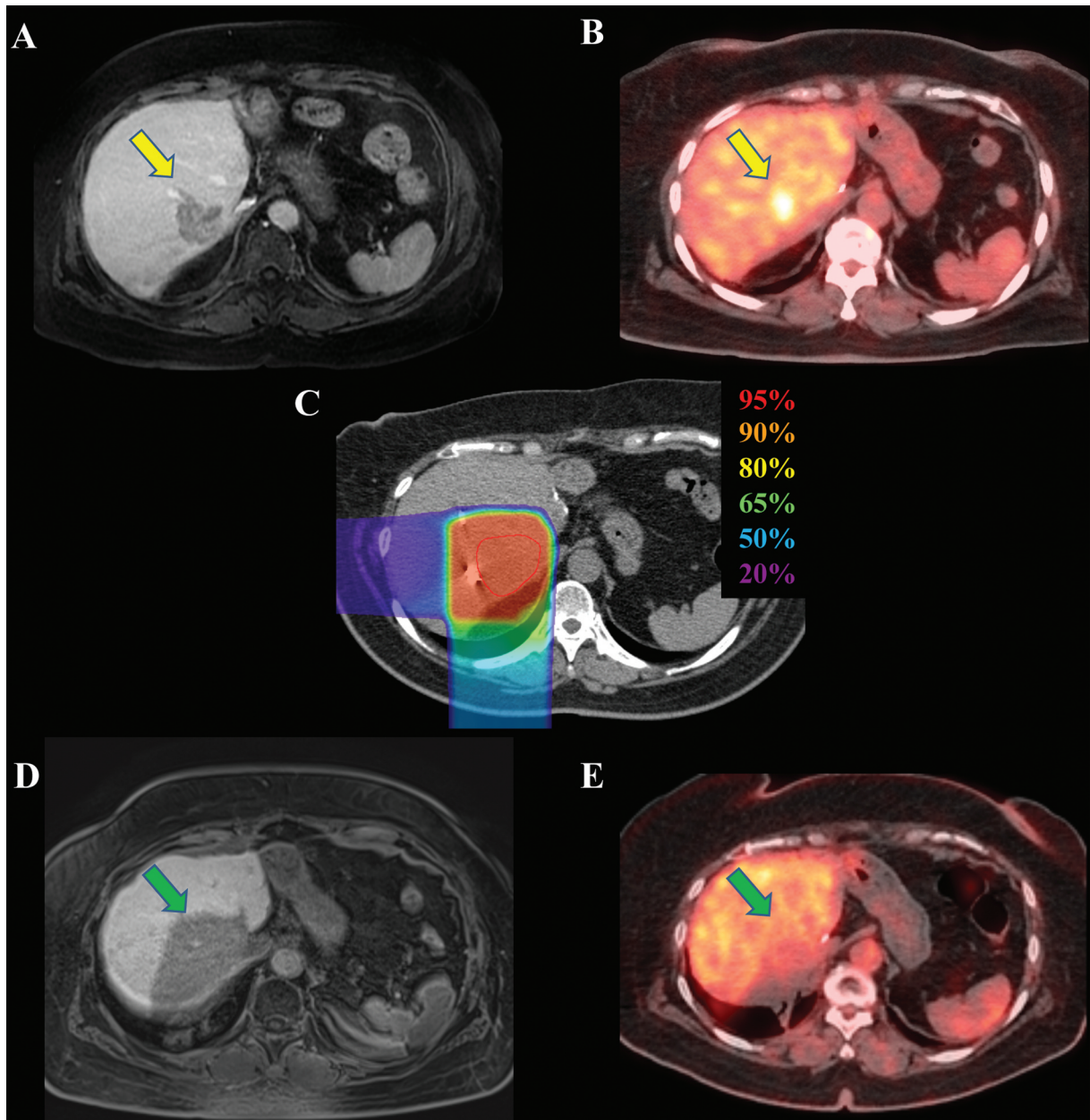


Figure 1. A 65-year-old female with oligometastatic sigmoid colon cancer in the liver treated with carbon-ion radiotherapy. A: Contrast-enhanced magnetic resonance imaging in hepatocyte phase before treatment. Yellow arrow shows the tumor with tumor washout. B: 2-Deoxy-2-[ $^{18}\text{F}$ ]fluoro-D-glucose (FDG) positron-emission tomography before treatment. Yellow arrow shows the tumor with abnormal FDG uptake. C: Dose distribution on axial computed tomographic images. The area within the red outline is the gross tumor volume. The 95% (red), 90% (orange), 80% (yellow), 65% (green), 50% (blue), and 20% (purple) isodose curves are highlighted (100% was 60 Gy relative biological effectiveness). D: Contrast-enhanced magnetic resonance imaging in hepatocyte phase 3 months after treatment. Contrast-enhanced deterioration is observed at the site of the carbon-ion beam path and no recurrence or residual tumor evident (green arrow). E: FDG positron-emission tomography 12 months after treatment. FDG uptake was reduced compared to that before treatment (green arrow).

received 60 Gy (RBE) in four fractions. Three patients did not achieve dose coverage of the 95% PTV with at least 95% of the prescribed dose as priority was given to the dose constraint of normal organs such as the gastrointestinal tract or skin.

**Clinical outcomes.** Figures 1D and 1E, and 2D and 2E show typical radiographic images after C-ion RT. The estimated 2-year OS, LC, and PFS rates for the cohort overall were 100%, 67%, and 35%, respectively; for those with liver



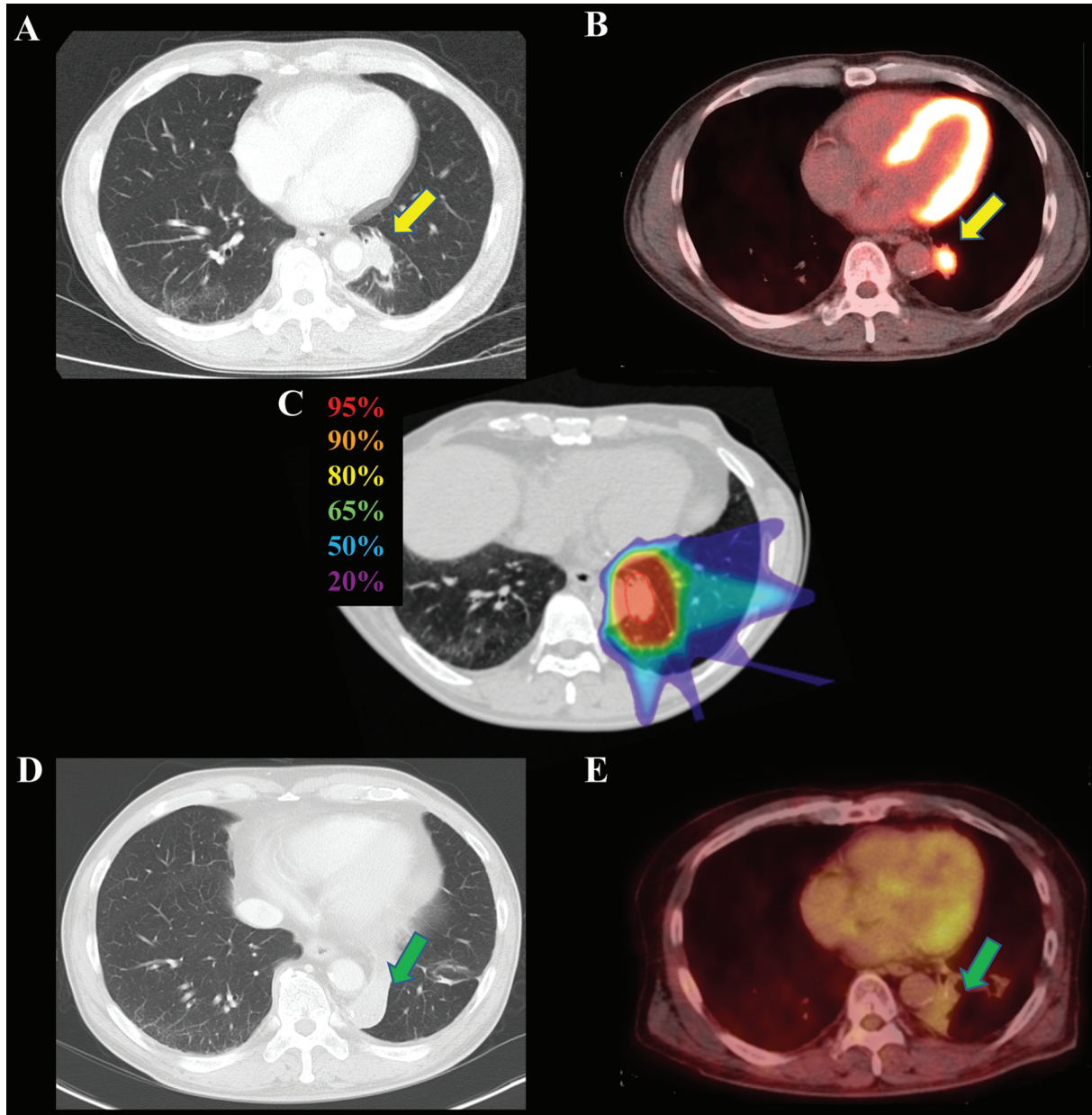


Figure 2. A 58-year-old male with oligometastatic colorectal cancer in lung treated with carbon-ion radiotherapy. A: Plain computed tomography (CT) before treatment. Yellow arrow shows the tumor with contrast enhancement. B: 2-Deoxy-2- $[^{18}\text{F}]$ fluoro-D-glucose (FDG) positron-emission tomography before treatment. Yellow arrow shows the tumor with abnormal FDG uptake. C: Dose distribution on axial CT images. The area within the red outline is the gross tumor volume. The 95% (red), 90% (orange), 80% (yellow), 65% (green), 50% (blue), and 20% (purple) isodose curves are highlighted [100% was 60 Gy (relative biological effectiveness)]. D: Plain CT 12 months after treatment. No recurrence or residual tumor evident (green arrow). E: FDG positron-emission tomography 12 months after treatment. FDG uptake was reduced compared to that before treatment (green arrow).

metastases, the corresponding rates were 100%, 61%, and 27%; and for those with lung metastases, the rates were 100%, 83%, and 48%, respectively (Figure 3).

Four out of 14 lesions (29%) in the liver and one out of nine lesions (11%) in the lung developed local recurrence

after C-ion RT. Two locally recurrent lesions in the liver received 64.8 Gy (RBE) in 12 fractions, and the other two received 60.0 Gy (RBE) in four fractions. A local recurrence in the lung received 60.0 Gy (RBE) in four fractions. All local recurrences were central tumor recurrences. All patients

Table I. Patient characteristics.

Characteristic		All	Liver metastases	Lung metastases
Total	Number	19	11	8
Age, years	Median (range)	65 (47-86)	65 (47-76)	73 (58-86)
Gender, n	Male	14	8	6
	Female	5	3	2
Performance status, n	0	9	5	4
	1	10	6	4
Primary tumor site, n	Colon	11	5	6
	Rectum	8	6	2
Tumor number, n	1	15	8	7
	2	4	3	1
Surgery for primary disease to C-ion RT, months	Median (range)	27 (4-159)	24 (6-38)	36 (4-159)
Chemotherapy before C-ion RT	Presence	8	8	0
	Absence	11	3	8
Adjuvant treatment of C-ion RT	Presence	2	1	1
	Absence	17	10	7
Surgical indication	Not indicated	9	5	4
	Refused	10	6	4
Serum CEA level before C-ion RT, ng/ml	Median (range)	4.1 (1.6-3,677.0)	8.4 (1.6-3,677.0)	3.2 (1.4-10.9)
Tumor size, cm	Median (range)	2.6 (1.1-6.5)	3.1 (1.5-6.5)	2.1 (1.1-3.2)
GTV volume, cm <sup>3</sup>	Median (range)	8.4 (0.6-113.7)	24.7 (2.9-113.7)	2.8 (0.6-23.2)
CTV volume, cm <sup>3</sup>	Median (range)	42.0 (5.8-248.2)	112.8 (29.0-248.2)	13.5 (5.8-53.1)

CEA: Carcinoembryonic antigen; C-ion RT: carbon ion radiotherapy; CTV volume: clinical target volume; GTV: gross tumor volume; RBE: relative biological effectiveness.

with local recurrence also developed distant or lymph node metastases. Twelve patients developed distant or lymph node metastases. Three patients died of colorectal cancer.

The observed cases of acute and late toxicities are shown in Table II. None of the patients developed grade 2 or higher acute and late toxicities. No patients developed radiation-induced liver disease (RILD) or Child–Pugh class decline. Table III lists DVH parameters. Analysis did not reveal any significant prognostic factors for OS and LC (Table IV).

## Discussion

Surgery for oligometastatic colorectal cancer in the liver and lung is well established, and previous studies have reported 5-year survival of 30-61% (2-7). These results suggest that local treatment for oligometastatic colorectal cancer improves survival. Another local treatment approach is SBRT, which is indicated for patients who are unsuitable for surgery or refuse surgery. Previous reports of SBRT for oligometastatic colorectal cancer showed that the 2-year OS and LC were 57-75% and 36-91%, respectively, for patients with liver metastases and 68-89% and 58-80%, respectively, for those with lung metastases, with grade 3-4 toxicities developing in 0-9% of patients (8-15). These results suggest that SBRT is an effective local treatment approach and might improve OS in oligometastatic colorectal cancer. In our

study, C-ion RT was performed in patients with oligometastatic colorectal cancer who were unsuitable for surgery or refused surgery. The OS and LC rates were 100% and 61%, respectively, for those with liver metastases, and 100% and 83%, respectively, for those with lung metastases, with no grade 2 or higher toxicities. These outcomes are comparable to those in previous reports of SBRT. Additionally, we included patients with inoperable disease and those difficult to treat with chemotherapy; hence, local treatment with C-ion RT might improve OS, underscoring the value of C-ion RT.

We performed DVH analysis for the normal liver. A previous report investigating the relationship between normal liver DVH parameters and liver function after photon therapy found that a mean liver dose >23 Gy, V<sub>5</sub> >86%, V<sub>10</sub> >68%, V<sub>15</sub> >59%, V<sub>20</sub> >49%, V<sub>25</sub> >35%, V<sub>30</sub> >28%, and V<sub>40</sub> >20% were risk factors of RILD (28). Another study on SBRT showed that V<sub>25</sub> >32% was a risk factor for Child–Pugh class decline in patients with hepatocellular carcinoma (29). In the present study, V<sub>25</sub>-V<sub>40</sub> DVH parameters of liver were exceeded in a few patients with multiple or tumors of 3 cm or larger. However, none of the patients developed RILD and Child–Pugh class decline. In previous studies, a risk factor of RILD and Child–Pugh class decline was liver cirrhosis in patients with hepatocellular carcinoma. However, we did not include patients with liver cirrhosis in our cohort,

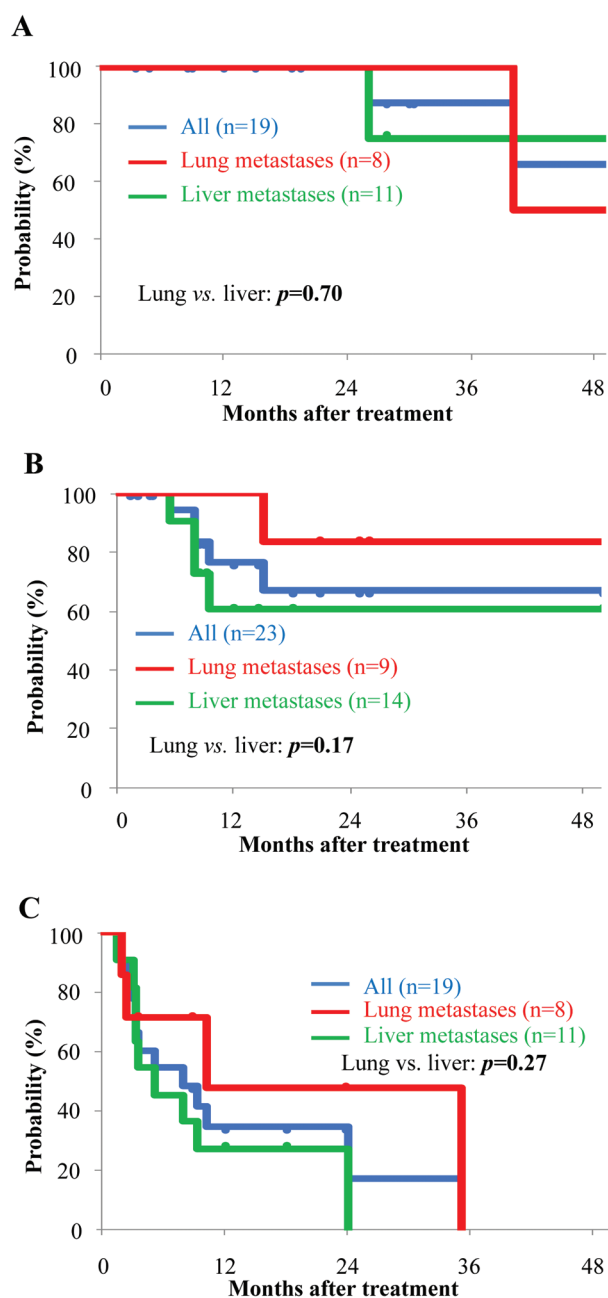


Figure 3. Kaplan-Meier curves of overall survival (OS) (A), local control (LC) (B) and progression-free survival (C) for the whole patient cohort, patients with liver metastases, and those with lung metastases.

which explains the absence of RILD and Child-Pugh class decline in our study. The DVH analysis for normal lung in previous studies showed that risk factors for grade 2 or higher radiation-induced pneumonitis were a mean lung dose of  $>5$  Gy and  $V_{20} >7\%$  in those treated with SBRT and  $V_{30} >15\%$  in C-ion those treated with RT (30, 31). In the present

Table II. Acute and late toxicities according to Common Terminology Criteria for Adverse Events, version 4.0 (27) (N=19).

		Grade, n				
		0	1	2	3	4
Acute	Dermatitis	13	6	0	0	0
	GI tract	19	0	0	0	0
	Pneumonitis	18	1	0	0	0
	Pleural effusion/ascites	19	0	0	0	0
	Hepatobiliary	19	0	0	0	0
Late	Dermatitis	17	2	0	0	0
	GI tract	19	0	0	0	0
	Pneumonitis	13	6	0	0	0
	Pleural effusion/ascites	19	0	0	0	0
	Hepatobiliary	19	0	0	0	0
	Bone fracture	19	0	0	0	0

GI: Gastrointestinal.

study,  $V_{30}$  did not exceed 15% in any of the patients, and in only a few patients with multiple or large tumors ( $\geq 3$  cm) did the mean lung dose exceed  $>5$  Gy and  $V_{20}$  exceed 7%. However, none of the patients developed grade 2 or higher radiation-induced pneumonitis. These clinical results and DVH parameters suggest that the use of C-ion RT for oligometastatic colorectal cancer in patients with single 3-cm or smaller tumors in liver and lung is a safe treatment approach, and in those with multiple tumors or 3 cm or larger tumor might be safe considering the liver or lung background.

The improvement of LC might trigger more interest in C-ion RT for oligometastatic colorectal cancer. In a previous report of C-ion RT for oligometastatic colorectal cancer in the liver, 3-year LC rates were 82% in those receiving single-fraction doses of 53 Gy (RBE) or higher and 28% in those receiving 48 Gy (RBE) or lower ( $p=0.01$ ) (21). Additionally, 3-year LC was 86-93% after the administration of 70 Gy (RBE) in 16 fractions or higher in patients with pelvic recurrence of colorectal cancer (32, 33). In the present study, all cases with local recurrence had central recurrence after administration of 60 Gy (RBE) in four fractions or 64.8 Gy (RBE) in 12 fractions. These results suggest a dose deficiency with the prescribed dose in our study. Higher dose irradiation such as 53 Gy (RBE) in a single fraction or 70 Gy (RBE) in 16 fractions without exceeding the tolerable dose with DVH in normal liver or lung might improve LC. In the present study, we considered that increasing the prescribed dose might be safe for small and single tumors.

Research on particle therapy, including proton beam therapy and C-ion RT, for oligometastatic colorectal cancer in the liver or lung is limited (21, 34, 35). All reports showed favorable and similar results to those using SBRT. Our

Table III. Dose–volume histogram parameters.

Organ	Parameter	Median (range)		
		All (N=11)	Single and small tumor (<3 cm) (N=6)	Multiple or large tumor (≥3 cm) (N=5)
Liver	Mean dose, Gy	13.9 (5.2-26.3)	7.0 (5.2-17.2)	21.2 (13.9-26.4)
	V <sub>5</sub>	35% (12-69%)	21% (12-37%)	61% (35-69%)
	V <sub>10</sub>	32% (10-51%)	18% (10-33%)	47% (32-51%)
	V <sub>15</sub>	30% (9-47%)	17% (9-32%)	41% (30-47%)
	V <sub>20</sub>	28% (8-45%)	11% (8-31%)	39% (28-45%)
	V <sub>25</sub>	25% (6-41%)	10% (6-29%)	37% (25-41%)
	V <sub>30</sub>	21% (5-40%)	9% (5-27%)	34% (21-40%)
	V <sub>40</sub>	16% (5-36%)	8% (5-23%)	27% (16-36%)
	V <sub>50</sub>	13% (4-33%)	7% (4-21%)	23% (13-33%)
Lung	Mean dose, Gy	3.1 (1.7-7.3)	1.9 (1.7-2.8)	5.3 (3.4-7.3)
	V <sub>5</sub>	12% (6-23%)	7% (6-10%)	18% (14-23%)
	V <sub>10</sub>	10% (4-19%)	5% (4-8%)	16% (12-19%)
	V <sub>15</sub>	8% (4-17%)	4% (4-7%)	13% (9-17%)
	V <sub>20</sub>	6% (3-14%)	3% (3-5%)	11% (6-14%)
	V <sub>25</sub>	5% (3-13%)	3% (3-5%)	8% (5-13%)
	V <sub>30</sub>	4% (2-11%)	2% (2-4%)	7% (4-11%)
	V <sub>40</sub>	2% (1-8%)	2% (1-2%)	4% (2-8%)
	V <sub>50</sub>	2% (1-6%)	1% (1-2%)	3% (2-6%)

V<sub>5</sub>-V<sub>50</sub>: The percentage of the liver or lung volume that received at least 5-50 Gy (relative biological effectiveness).

Table IV. Univariate analysis of overall survival (OS) and local control (LC).

Factor		OS		LC	
		2-Year OS	<i>p</i> -Value	2-Year LC	<i>p</i> -Value
Gender	Male vs. female	100% vs. 100%	0.34	51% vs. 100%	0.10
Age	<65 vs. ≥65 years	100% vs. 100%	0.96	57% vs. 73%	0.36
PS	0 vs. 1	100% vs. 100%	0.43	60% vs. 80%	0.63
Primary tumor site	Rectum vs. colon	100% vs. 100%	0.52	64% vs. 75%	0.62
Tumor location	Liver vs. lung	100% vs. 100%	0.70	61% vs. 83%	0.17
Tumor number	1 vs. 2	100% vs. 100%	0.25	67% vs. 67%	0.57
Surgery for primary disease to C-ion RT	<27 vs. ≥27 months	100% vs. 100%	0.52	56% vs. 75%	0.33
Surgical indication	Not indicated vs. refused	100% vs. 100%	0.80	67% vs. 66%	0.51
CEA	<5.0 vs. ≥5.0 ng/ml	100% vs. 100%	0.07	88% vs. 43%	0.05
Tumor size	<3 vs. ≥3 cm	100% vs. 100%	0.23	69% vs. 63%	0.39
GTV	<10 vs. ≥10 cm <sup>3</sup>	100% vs. 100%	0.18	70% vs. 57%	0.26
CTV	<40 vs. ≥40 cm <sup>3</sup>	100% vs. 100%	0.35	80% vs. 56%	0.13

CEA: Carcinoembryonic antigen; C-ion RT: carbon-ion radiotherapy; CTV: clinical target volume; GTV: gross tumor volume; PS: performance status.

findings are also favorable and comparable to the SBRT results and previous particle therapy.

Our study had several limitations. Firstly, this was a single-institutional retrospective analysis with a small number of patients and a short follow-up duration. Secondly, the patient backgrounds were heterogeneous. Thirdly, analyses of DVH and toxicities for C-ion RT were few, and

the threshold risk value in the incidence of toxicities is unknown. Despite these limitations, this study confirmed the safety of C-ion RT. Our study offers useful information on the treatment of oligometastatic colorectal cancer, especially in patients who are unsuitable for surgery.

In conclusion, C-ion RT is a favorable treatment approach for oligometastatic colorectal cancer in the liver and lungs



and has comparable clinical outcomes to SBRT. Additionally, C-ion RT might be a safe treatment option, as exemplified by the absence of RILD and radiation-induced pneumonitis. Therefore, C-ion RT can be used in patients with oligometastatic colorectal cancer in the liver and lungs who are unsuitable for surgery.

## Conflicts of Interest

The Authors declare no conflicts of interest in regard to this study.

## Authors' Contributions

Conceptualization, S.S., T.O.; methodology, S.S., K.S., O.M., H.K., T.O.; validation, S.S.; formal analysis, S.S.; investigation, S.S., K.S., M.O., H.K.; resources, S.S., K.S., M.O., H.K.; data curation, S.S.; writing—original draft preparation, S.S.; writing—review and editing, K.S., M.O., N.O., N.K., T.K., H.S., S.O., Y.M., H.K., T.O.; visualization, S.S.; supervision, T.O.; project administration, T.O.; funding acquisition, T.O. All Authors read and approved the final article.

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## References

- Hellman S and Weichselbaum RR: Oligometastases. *J Clin Oncol* 13(1): 8-10, 1995. PMID: 7799047. DOI: 10.1200/JCO.1995.13.1.8
- Rees M, Tekkis PP, Welsh FK, O'Rourke T and John TG: Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: A multifactorial model of 929 patients. *Ann Surg* 247(1): 125-135, 2008. PMID: 18156932. DOI: 10.1097/SLA.0b013e31815aa2c2
- Elias D, Liberale G, Vernerey D, Pocard M, Ducreux M, Boige V, Malka D, Pignon JP and Lasser P: Hepatic and extrahepatic colorectal metastases: When resectable, their localization does not matter, but their total number has a prognostic effect. *Ann Surg Oncol* 12(11): 900-909, 2005. PMID: 16184442. DOI: 10.1245/ASO.2005.01.010
- Inoue M, Ohta M, Iuchi K, Matsumura A, Ideguchi K, Yasumitsu T, Nakagawa K, Fukuhara K, Maeda H, Takeda S, Minami M, Ohno Y, Matsuda H and Thoracic Surgery Study Group of Osaka University.: Benefits of surgery for patients with pulmonary metastases from colorectal carcinoma. *Ann Thorac Surg* 78(1): 238-244, 2004. PMID: 15223436. DOI: 10.1016/j.athoracsur.2004.02.017
- Pfannschmidt J, Dienemann H and Hoffmann H: Surgical resection of pulmonary metastases from colorectal cancer: A systematic review of published series. *Ann Thorac Surg* 84(1): 324-338, 2007. PMID: 17588454. DOI: 10.1016/j.athoracsur.2007.02.093
- Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, Grothey A, Vauthey JN, Nagorney DM and McWilliams RR: Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol* 27(22): 3677-3683, 2009. PMID: 19470929. DOI: 10.1200/JCO.2008.20.5278
- Salah S, Watanabe K, Welter S, Park JS, Park JW, Zabaleta J, Ardisson F, Kim J, Riquet M, Nojiri K, Gisabella M, Kim SY, Tanaka K and Al-Haj Ali B: Colorectal cancer pulmonary oligometastases: Pooled analysis and construction of a clinical lung metastasectomy prognostic model. *Ann Oncol* 23(10): 2649-2655, 2012. PMID: 22547539. DOI: 10.1093/annonc/mds100
- Petrelli F, Comito T, Barni S, Pancera G, Scorsetti M, Ghidini A and SBRT for CRC liver metastases.: Stereotactic body radiotherapy for colorectal cancer liver metastases: A systematic review. *Radiother Oncol* 129(3): 427-434, 2018. PMID: 29997034. DOI: 10.1016/j.radonc.2018.06.035
- Comito T, Cozzi L, Clerici E, Campisi MC, Liardo RL, Navarria P, Ascolese A, Tozzi A, Iftode C, De Rose F, Villa E, Personeni N, Rimassa L, Santoro A, Fogliata A, Mancosu P, Tomatis S and Scorsetti M: Stereotactic Ablative Radiotherapy (SABR) in inoperable oligometastatic disease from colorectal cancer: A safe and effective approach. *BMC Cancer* 14: 619, 2014. PMID: 25163798. DOI: 10.1186/1471-2407-14-619
- Habermehl D, Herfarth KK, Bermejo JL, Hof H, Rieken S, Kuhn S, Welzel T, Debus J and Combs SE: Single-dose radiosurgical treatment for hepatic metastases—therapeutic outcome of 138 treated lesions from a single institution. *Radiat Oncol* 8: 175, 2013. PMID: 23837905. DOI: 10.1186/1748-717X-8-175
- Joo JH, Park JH, Kim JC, Yu CS, Lim SB, Park IJ, Kim TW, Hong YS, Kim KP, Yoon SM, Park J and Kim JH: Local control outcomes using stereotactic body radiation therapy for liver metastases from colorectal cancer. *Int J Radiat Oncol Biol Phys* 99(4): 876-883, 2017. PMID: 29063852. DOI: 10.1016/j.ijrobp.2017.07.030
- Jingu K, Matsushita H, Yamamoto T, Umezawa R, Ishikawa Y, Takahashi N, Katagiri Y, Takeda K and Kadota N: Stereotactic radiotherapy for pulmonary oligometastases from colorectal cancer: A systematic review and meta-analysis. *Technol Cancer Res Treat* 17: 1533033818794936, 2018. PMID: 30145943. DOI: 10.1177/1533033818794936
- Agolli L, Bracci S, Nicosia L, Valeriani M, De Sanctis V and Osti MF: Lung metastases treated with stereotactic ablative radiation therapy in oligometastatic colorectal cancer patients: Outcomes and prognostic factors after long-term follow-up. *Clin Colorectal Cancer* 16(1): 58-64, 2017. PMID: 27522627. DOI: 10.1016/j.clcc.2016.07.004
- Kinj R, Bondiau PY, François E, Gérard JP, Naghavi AO, Leysalle A, Chamorey E, Evesque L, Padovani B, Ianessi A, Benezery K and Doyen J: Radiosensitivity of colon and rectal lung oligometastasis treated with stereotactic ablative radiotherapy. *Clin Colorectal Cancer* 16(3): e211-e220, 2017. PMID: 27670890. DOI: 10.1016/j.clcc.2016.08.003
- Kobayashi N, Abe T, Noda SE, Kumazaki YU, Hirai R, Igari M, Aoshika T, Saito S, Ryuno Y and Kato S: Stereotactic body radiotherapy for pulmonary oligometastasis from colorectal cancer. *In Vivo* 34(5): 2991-2996, 2020. PMID: 32871842. DOI: 10.21873/invivo.12130
- Shibuya K, Ohno T, Terashima K, Toyama S, Yasuda S, Tsuji H, Okimoto T, Shioyama Y, Nemoto K, Kamada T, Nakano T and Japan Carbon Ion Radiotherapy Study Group.: Short-course carbon-ion radiotherapy for hepatocellular carcinoma: A multi-



- institutional retrospective study. *Liver Int* 38(12): 2239-2247, 2018. PMID: 30240527. DOI: 10.1111/liv.13969
- 17 Shiba S, Shibuya K, Okamoto M, Okazaki S, Komatsu S, Kubota Y, Nakano T and Ohno T: Clinical impact of hypofractionated carbon ion radiotherapy on locally advanced hepatocellular carcinoma. *Radiat Oncol* 15(1): 195, 2020. PMID: 32795340. DOI: 10.1186/s13014-020-01634-z
  - 18 Saitoh JI, Shirai K, Mizukami T, Abe T, Ebara T, Ohno T, Minato K, Saito R, Yamada M and Nakano T: Hypofractionated carbon-ion radiotherapy for stage I peripheral nonsmall cell lung cancer (GUNMA0701): Prospective phase II study. *Cancer Med* 8(15): 6644-6650, 2019. PMID: 31532584. DOI: 10.1002/cam4.2561
  - 19 Okonogi N, Kaminuma T, Okimoto T, Shinoto M, Yamamoto N, Yamada S, Murata K, Ohno T, Shioyama Y, Tsuji H, Nakano T and Kamada T: Carbon-ion radiotherapy for lymph node oligo-recurrence: a multi-institutional study by the Japan Carbon-Ion Radiation Oncology Study Group (J-CROS). *Int J Clin Oncol* 24(9): 1143-1150, 2019. PMID: 30968270. DOI: 10.1007/s10147-019-01440-y
  - 20 Shiba S, Okonogi N, Kato S, Wakatsuki M, Kobayashi D, Kiyohara H, Ohno T, Karasawa K, Nakano T and Kamada T: Clinical impact of re-irradiation with carbon-ion radiotherapy for lymph node recurrence of gynecological cancers. *Anticancer Res* 37(10): 5577-5583, 2017. PMID: 28982873. DOI: 10.21873/anticancer.11991
  - 21 Makishima H, Yasuda S, Isozaki Y, Kasuya G, Okada N, Miyazaki M, Mohamad O, Matsufuji N, Yamada S, Tsuji H, Kamada T and Liver Cancer Working Group.: Single fraction carbon ion radiotherapy for colorectal cancer liver metastasis: A dose escalation study. *Cancer Sci* 110(1): 303-309, 2019. PMID: 30417485. DOI: 10.1111/cas.13872
  - 22 Kanai T, Endo M, Minohara S, Miyahara N, Koyama-ito H, Tomura H, Matsufuji N, Futami Y, Fukumura A, Hiraoka T, Furusawa Y, Ando K, Suzuki M, Soga F and Kawachi K: Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. *Int J Radiat Oncol Biol Phys* 44(1): 201-210, 1999. PMID: 10219815. DOI: 10.1016/s0360-3016(98)00544-6
  - 23 Abe T, Saitoh J, Kobayashi D, Shibuya K, Koyama Y, Shimada H, Shirai K, Ohno T and Nakano T: Dosimetric comparison of carbon ion radiotherapy and stereotactic body radiotherapy with photon beams for the treatment of hepatocellular carcinoma. *Radiat Oncol* 10: 187, 2015. PMID: 26377092. DOI: 10.1186/s13014-015-0491-8
  - 24 Shiba S, Shibuya K, Kawashima M, Okano N, Kaminuma T, Okamoto M, Kubota Y, Nakano T and Ohno T: Comparison of dose distributions when using carbon ion radiotherapy versus intensity-modulated radiotherapy for hepatocellular carcinoma with macroscopic vascular invasion: A retrospective analysis. *Anticancer Res* 40(1): 459-464, 2020. PMID: 31892601. DOI: 10.21873/anticancer.13974
  - 25 Ebara T, Shimada H, Kawamura H, Shirai K, Saito J, Kawashima M, Tashiro M, Ohno T, Kanai T and Nakano T: Dosimetric analysis between carbon ion radiotherapy and stereotactic body radiotherapy in stage I lung cancer. *Anticancer Res* 34(9): 5099-5104, 2014. PMID: 25202098.
  - 26 Inaniwa T, Kanematsu N, Matsufuji N, Kanai T, Shirai T, Noda K, Tsuji H, Kamada T and Tsujii H: Reformulation of a clinical-dose system for carbon-ion radiotherapy treatment planning at the National Institute of Radiological Sciences, Japan. *Phys Med Biol* 60(8): 3271-3286, 2015. PMID: 25826534. DOI: 10.1088/0031-9155/60/8/3271
  - 27 NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. National Institutes of Health, National Cancer Institute, Bethesda, MA, USA, 2009. Available at: [https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03/Archive/CTC\\_AE\\_4.0\\_2009-05-29\\_QuickReference\\_8.5x11.pdf](https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTC_AE_4.0_2009-05-29_QuickReference_8.5x11.pdf) [Last accessed on February 24, 2021]
  - 28 Liang SX, Zhu XD, Xu ZY, Zhu J, Zhao JD, Lu HJ, Yang YL, Chen L, Wang AY, Fu XL and Jiang GL: Radiation-induced liver disease in three-dimensional conformal radiation therapy for primary liver carcinoma: the risk factors and hepatic radiation tolerance. *Int J Radiat Oncol Biol Phys* 65(2): 426-434, 2006. PMID: 16690430. DOI: 10.1016/j.ijrobp.2005.12.031
  - 29 Dyk P, Weiner A, Badiyan S, Myerson R, Parikh P and Olsen J: Effect of high-dose stereotactic body radiation therapy on liver function in the treatment of primary and metastatic liver malignancies using the Child-Pugh score classification system. *Pract Radiat Oncol* 5(3): 176-182, 2015. PMID: 25423889. DOI: 10.1016/j.prro.2014.09.007
  - 30 Barriger RB, Forquer JA, Brabham JG, Andolino DL, Shapiro RH, Henderson MA, Johnstone PA and Fakiris AJ: A dose-volume analysis of radiation pneumonitis in non-small cell lung cancer patients treated with stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 82(1): 457-462, 2012. PMID: 21035956. DOI: 10.1016/j.ijrobp.2010.08.056
  - 31 Hayashi K, Yamamoto N, Karube M, Nakajima M, Matsufuji N, Tsuji H, Ogawa K and Kamada T: Prognostic analysis of radiation pneumonitis: Carbon-ion radiotherapy in patients with locally advanced lung cancer. *Radiat Oncol* 12(1): 91, 2017. PMID: 28558766. DOI: 10.1186/s13014-017-0830-z
  - 32 Shiba S, Okamoto M, Kiyohara H, Ohno T, Kaminuma T, Asao T, Ojima H, Shirabe K, Kuwano H and Nakano T: Prospective observational study of high-dose carbon-ion radiotherapy for pelvic recurrence of rectal cancer (GUNMA 0801). *Front Oncol* 9: 702, 2019. PMID: 31417874. DOI: 10.3389/fonc.2019.00702
  - 33 Shinoto M, Yamada S, Okamoto M, Shioyama Y, Ohno T, Nakano T, Nemoto K, Isozaki Y, Kawashiro S, Tsuji H and Kamada T: Carbon-ion radiotherapy for locally recurrent rectal cancer: Japan Carbon-ion Radiation Oncology Study Group (J-CROS) Study 1404 Rectum. *Radiother Oncol* 132: 236-240, 2019. PMID: 30360998. DOI: 10.1016/j.radonc.2018.10.007
  - 34 Takahashi W, Nakajima M, Yamamoto N, Yamada S, Yamashita H, Nakagawa K, Tsuji H and Kamada T: Carbon ion radiotherapy for oligo-recurrent lung metastases from colorectal cancer: a feasibility study. *Radiat Oncol* 9: 68, 2014. PMID: 24581481. DOI: 10.1186/1748-717X-9-68
  - 35 Fukumitsu N, Okumura T, Takizawa D, Makishima H, Numajiri H, Murofushi K, Ohnishi K, Mizumoto M, Aihara T, Ishikawa H, Tsuboi K and Sakurai H: Proton beam therapy for metastatic liver tumors. *Radiother Oncol* 117(2): 322-327, 2015. PMID: 26385268. DOI: 10.1016/j.radonc.2015.09.011

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