



Carbon-ion radiotherapy for lymph node oligo-recurrence: a multi-institutional study by the Japan Carbon-Ion Radiation Oncology Study Group (J-CROS)

Noriyuki Okonogi¹ · Takuya Kaminuma² · Tomoaki Okimoto³ · Makoto Shinoto⁴ · Naoyoshi Yamamoto¹ · Shigeru Yamada¹ · Kazutoshi Murata² · Tatsuya Ohno² · Yoshiyuki Shioyama⁴ · Hiroshi Tsuji¹ · Takashi Nakano² · Tadashi Kamada¹

Received: 10 February 2019 / Accepted: 2 April 2019 / Published online: 9 April 2019
© The Author(s) 2019

Abstract

Background The efficacy of carbon-ion radiotherapy (C-ion RT) for lymph node (LN) oligo-recurrence has only been evaluated in limited single-center studies. We aimed to investigate the benefit of C-ion RT for LN oligo-recurrence in a large multi-center study.

Methods Patients who received C-ion RT between December 1996 and December 2015 at 4 participating facilities and who met the following eligibility criteria were included: (i) histological or clinical diagnosis of LN recurrence; (ii) controlled primary lesion; (iii) no recurrence other than LN; (iv) LN recurrence involved in a single lymphatic site; and (v) age ≥ 20 years.

Results A total of 323 patients were enrolled. Median follow-up period was 34 months for surviving patients. The most common dose fractionation of C-ion RT was 48.0 Gy (relative biological effectiveness) in 12 fractions. Forty-seven patients had a history of RT at the recurrent site. The 2-year local control (LC) and overall survival (OS) rates after C-ion RT were 85% and 63%, respectively. Only 1 patient developed grade-3 toxicity. Factors such as LN diameter, histology, and history of previous RT did not correlate with LC. Smaller diameters (< 30 mm) and numbers (≤ 3) of LN metastases as well as longer disease-free intervals post-primary therapy (≥ 16 months) were associated with significantly better OS.

Conclusions C-ion RT for LN oligo-recurrence appeared to be effective and safe. C-ion RT may provide a survival benefit to patients with LN oligo-recurrence, particularly to those with few LN metastases, smaller LN diameters, and longer disease-free intervals.

Keywords Carbon-ion radiotherapy · Radiotherapy · Lymph nodes metastasis · Oligo-recurrence

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s10147-019-01440-y>) contains supplementary material, which is available to authorized users.

✉ Tadashi Kamada
kamada.tadashi@qst.go.jp

¹ QST Hospital, National Institutes for Quantum and Radiological Science and Technology, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan

² Department of Radiation Oncology, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

³ Department of Radiology, Hyogo Ion Beam Medical Center, Tatsuno, Hyogo, Japan

⁴ Ion Beam Therapy Center, SAGA HIMAT Foundation, Saga, Japan

Introduction

Metastatic tumors have traditionally been managed with systemic treatment administered with palliative intent. The presence of metastases is considered a clinical manifestation of widespread microscopic disseminated disease. To that end, the concept of oligometastases was described in 1995 as a distinct clinical entity involving limited metastatic disease [1]; it was suggested that few metastases initially exist in patients with cancer of multiple types before malignant cells acquire widespread metastatic potential [1]. Regarding this point, Niibe et al. distinguished the states of oligometastases and oligo-recurrence [2]. Oligometastases is the state in which the patient shows distant relapse in only a limited number of regions. However, the concept of oligometastases includes the state of uncontrolled primary site with several

distant metastases. Meanwhile, oligo-recurrence means the state of recurrence or metastases with a controlled primary lesion, meaning that all metastatic sites could be cured using local therapy [2]. Consistent with this concept, many studies have demonstrated improved survival and long-term disease control after surgical resection of metastases in cancer patients with certain histological subtypes [3–7].

Surgical resection of metastatic lesions is the preferred curative treatment. However, such surgeries are sometimes restricted in patients with oligo-recurrence because of technical obstacles, patient refusal, advanced age, or associated clinical comorbidities. In recent years, state of the art radiotherapy (RT) techniques, such as stereotactic body RT (SBRT), have shown clinical benefits for patients with oligo-recurrence while avoiding the risks associated with surgery [8, 9]. Growing evidence suggests that lung and liver metastases can be treated locally using SBRT, with low toxicity and excellent outcomes [10, 11]. However, the number of studies on the use of SBRT for lymph node (LN) metastasis is still limited.

Ion beams, such as protons and carbon ions (C-ions), provide a dose distribution that is superior to that of photons during cancer treatment. Additionally, C-ion beams are heavier than protons and provide a higher relative biological effectiveness (RBE) and thus a higher probability of tumor control, while delivering a smaller dose to the surrounding normal tissues [12, 13]. Several studies have shown the effectiveness of C-ion RT in treating LN oligo-recurrences of radioresistant tumors or for managing recurrences after other RT methods [14–16]. These studies suggest that C-ion RT for patients with LN oligo-recurrence could be a useful treatment option. However, available data have been derived from single institutions, were limited in the type of cancers included, and were extracted from a small number of patients. Hence, we conducted a retrospective multicenter study to investigate the efficacy of C-ion RT in patients with LN oligo-recurrence.

Materials and methods

Eligibility

This retrospective multicenter study was conducted within the framework of the Japan Carbon-Ion Radiation Oncology Study Group (J-CROS) and is registered with the University Hospital Medical Information Network Clinical Trials Registry (<http://www.umin.ac.jp/ctr/index-j.htm>), identification number UMIN000027300. The study was approved by the institutional review board of each participating institution and conducted in compliance with the Declaration of Helsinki.

Among patients who received C-ion RT between December 1996 and December 2015 at the 4 participating facilities (the Hospital of the National Institute of Radiological Sciences, Hyogo Ion Beam Medical Center, Gunma University Heavy Ion Medical Center, and the SAGA-HIMAT Foundation), those who met the following eligibility criteria were enrolled: (i) histological or clinical diagnosis of LN recurrence; (ii) controlled primary tumor; (iii) no recurrence other than that of the solitary LN; (iv) LN recurrence involved at a single lymphatic site; and (v) 20 years of age or older. Based on these criteria, 323 patients with LN oligo-recurrences from the 4 institutions were included in this study. An LN with a short-axis diameter of > 10 mm was defined as a metastatic LN in the present study.

Treatment planning system and dose fractionation

Patients were positioned in customized cradles and immobilized with a low-temperature thermoplastic sheet. A set of 2.0–2.5-mm-thick computed tomography (CT) images were acquired for 3-dimensional treatment planning using the HiPLAN or Xio-N system. Patients received C-ion RT daily for 4 days/week (Tuesday through Friday). The radiation dose was calculated for the target volume and is expressed in Gy (RBE), which is defined as the physical dose multiplied by the RBE of the C-ions [17]. Treatment consisted of regional LN irradiation or prophylactic irradiation and local LN boost; the clinical target volume included all swollen LNs and potentially microscopic disease. The planning target volume included the clinical target volume plus a 2–10 mm safety margin to account for intra- and inter-movement. The planning target volume was covered by $\geq 90\%$ of the prescribed dose. A representative dose distribution of C-ion RT is shown in the supplementary figure. The dose fractionation schemes are listed in Table 1.

Follow-up and evaluation

Following treatment, patients had follow-up visits 1 month after treatment, then every 3–4 months for the first 2 years, and every 3–6 months thereafter. Regular follow-up studies included physical examination and diagnostic imaging (i.e., CT and/or magnetic resonance imaging). Local control (LC) was defined as no evidence of LN regrowth within the irradiated field. Progression-free survival (PFS) was defined as the absence of locoregional or distant failure or death from any cause. Overall survival (OS) and adverse events after C-ion treatment were also evaluated. Late toxicity was graded according to the Common Terminology Criteria for Adverse Events (version 4.0) [18]. The highest toxicities occurring 3 months after commencing C-ion RT were defined as late toxicities in the present study.

Table 1 Characteristics of carbon-ion radiotherapy

Dose fractionation schemes	Number of patients
36.0 Gy (RBE)/8 fr.	1
52.8 Gy (RBE)/8 fr.	1
60.0 Gy (RBE)/8 fr.	1
64.0 Gy (RBE)/8 fr.	4
66.0 Gy (RBE)/10 fr.	2
38.4 Gy (RBE)/12 fr.	1
40.0 Gy (RBE)/12 fr.	2
43.2 Gy (RBE)/12 fr.	2
44.0 Gy (RBE)/12 fr.	1
45.6 Gy (RBE)/12 fr.	8
48.0 Gy (RBE)/12 fr.	114
50.4 Gy (RBE)/12 fr.	7
51.6 Gy (RBE)/12 fr.	1
52.8 Gy (RBE)/12 fr.	101
55.2 Gy (RBE)/12 fr.	14
57.6 Gy (RBE)/12 fr.	14
64.8 Gy (RBE)/12 fr.	1
72.0 Gy (RBE)/12 fr.	1
52.0 Gy (RBE)/13 fr.	1
50.4 Gy (RBE)/14 fr.	1
52.8 Gy (RBE)/16 fr.	8
56.0 Gy (RBE)/16 fr.	1
57.6 Gy (RBE)/16 fr.	10
60.8 Gy (RBE)/16 fr.	1
64.0 Gy (RBE)/16 fr.	9
60.0 Gy (RBE)/20 fr.	1
65.0 Gy (RBE)/25 fr.	1
65.0 Gy (RBE)/26 fr.	6
70.2 Gy (RBE)/26 fr.	4
70.4 Gy (RBE)/32 fr.	2
74.0 Gy (RBE)/37 fr.	2

RBE relative biological effectiveness, fr. fractions

Statistical analysis

The incidences of LC, OS, and PFS were determined using the Kaplan–Meier method. These endpoints were calculated from the initiation of C-ion RT to the date of last follow-up or death from any cause. The log-rank test was used for univariate analyses. All factors with statistically significant associations in the univariate analysis were included in the multivariate analysis, and a Cox proportional hazards regression model was used. p values < 0.05 were considered significant; all statistical tests were two-sided. Statistical calculations were performed using the IBM SPSS Statistics 24 software (IBM, Armonk, NY, USA).

Table 2 Patient and tumor characteristics ($n = 323$)

Characteristic	n (%)
Age (years), median (range)	66 (29–90)
LN diameter in maximal length (mm), median (range)	22 (10–80)
Number of LNs	
1	215 (66.6)
2	65 (20.1)
3	15 (4.6)
≥ 4	28 (8.7)
History of radiotherapy to the lesion	
No (initial irradiation)	276 (85.4)
Yes (re-irradiation)	47 (14.6)
Disease-free interval (months), median (range)	16 (1–247)
Histology	
SCC	66 (20.4)
Non-SCC	257 (79.6)
Primary site of carcinomas	
Head and neck	17 (5.3)
Lung	99 (30.7)
Breast	4 (1.2)
Upper GI (esophagus, stomach, duodenum)	26 (8.0)
Lower GI (colon, rectum)	77 (23.8)
Pancreas	20 (6.2)
Liver, cholecyst, bile duct	11 (3.4)
Urinary system (kidney, renal pelvis, bladder)	8 (2.5)
Prostate	7 (2.2)
Uterine	38 (11.8)
Ovary	8 (2.5)
Primary unknown	1 (0.3)
Others (vagina, skin, chordoma, adrenal gland)	7 (2.2)

LN metastatic lymph node, SCC squamous cell carcinoma, GI gastro-intestinal tract

Results

Cohort characteristics

Patient and tumor characteristics are summarized in Table 2. The median patient age was 66 years (range, 29–90 years), and the median maximal LN diameter was 22 mm (range, 10–80 mm). The median disease-free interval (i.e., the time between primary treatment administration and the day of recurrence detection) was 16 months (range, 1–247 months). Sixty-six patients were diagnosed with squamous cell carcinoma (SCC), while the remaining 257 patients were diagnosed with non-SCC (including adenocarcinoma, adenosquamous carcinoma, and other carcinomas).

Treatment efficacy and prognostic factors

The median follow-up period was 34 months (range, 2–181 months) for surviving patients. The 2-year LC, OS, and PFS rates were 85.4% (95% confidence interval [CI] 81.0–89.9%), 62.9% (95% CI 57.4–68.4%), and 33.5% (95% CI 28.3–38.7%), respectively (Fig. 1). Site-specific clinical results (the 5 most common primary sites) are shown in Supplementary Table 1. Table 3 lists the results of the log-rank tests for prognostic factors. Regarding the setting of cutoff values in the univariate or multivariate analysis, median values were used as the cutoff for age (66 years) and disease-free interval (16 months). The cutoff value for LN diameter was set as 30 mm based on previous studies [19, 20]. In addition, the analyses for the number of LNs were conducted between 2 groups (1–3 versus ≥ 4) based on a previous study [21]. None of the analyzed factors, including LN diameter and histology, were significantly correlated with LC in the univariate analysis. However, the number of LN metastases was associated with PFS. Furthermore, the LN diameter (maximum length), number of LN metastases, and disease-free interval were associated with OS. The factors that were significant in the univariate analysis were then assessed to identify predictors of clinical outcomes using multivariate analyses based on the Cox proportional hazards model (Table 4). A smaller number (≤ 3) of LN metastases was associated with significantly better PFS ($p=0.047$). Moreover, a smaller LN diameter (< 30 mm) ($p=0.011$), smaller number (≤ 3) of LN metastases ($p=0.006$), and longer disease-free interval (≥ 16 months) following primary

therapy ($p=0.003$) were associated with significantly better OS.

Toxicities

All patients completed their planned C-ion RT except for 1 who developed grade 2 esophagitis; this patient received 50.4 Gy (RBE) in 14 fractions and ceased treatment. The esophagitis resolved after treatment, and no late toxicity was observed in this patient. As shown in Supplementary Table 2, 15 patients (4.6%) developed grade ≥ 2 late toxicities [Supplementary Table 2(A)]; of these, 1 developed severe (grade 3) late toxicity [Supplementary Table 2(B)]. The patient who developed grade 3 late toxicity had originally undergone surgery for tongue carcinoma; this patient received C-ion RT at a dose of 65.0 Gy (RBE) in 26 fractions for submandibular LN and subsequently developed grade 3 facial nerve disorder.

Discussion

Ours is the first multicenter study to investigate the efficacy of C-ion RT in patients with LN oligo-recurrence. Few published data exist regarding the use of conventional RT in the context of LN oligo-recurrence. However, reports of the clinical outcomes of patients with LN oligo-recurrence who underwent SBRT have been published in recent years; Table 5 lists the published studies of patients with LN oligo-recurrence in which the median follow-up times

Fig. 1 Kaplan–Meier curves of local control (green), overall survival (red), and progression-free survival (blue) for all 323 patients. The numbers at risk are shown below the figure. *CI* confidence interval, *LC* local control, *PFS* progression-free survival, *OS* overall survival

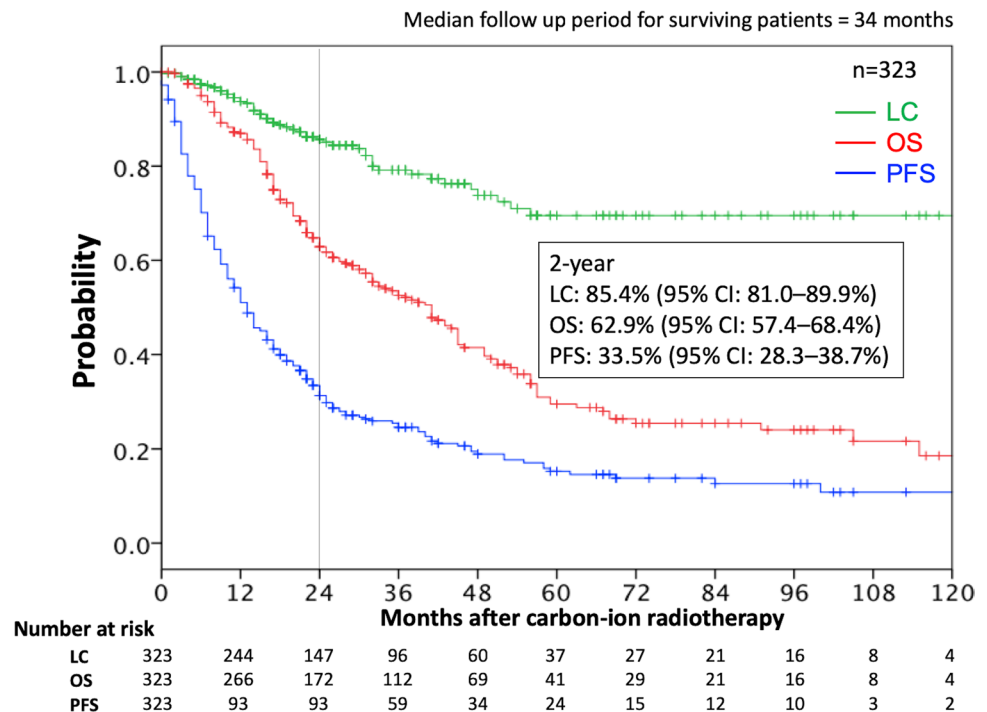


Table 3 Assessment of prognostic factors with univariate analysis

Factor	Number of patients	LC		PFS		OS	
		2-year (%)	<i>p</i> value	2-year (%)	<i>p</i> value	2-year (%)	<i>p</i> value
Age (years)			0.235		0.114		0.664
< 66	154	80.4		27.0		61.4	
≥ 66	169	89.6		35.3		64.2	
LN diameter in maximal length (mm)			0.485		0.056		0.010
< 30	229	85.4		34.2		68.8	
≥ 30	94	86.1		24.5		48.6	
Number of LNs			0.242		0.023		0.001
1–3	295	86.5		33.1		65.2	
≥ 4	28	67.3		12.5		38.9	
History of radiotherapy to the lesion			0.394		0.009		0.016
No (initial irradiation)	276	84.8		28.9		61.5	
Yes (re-irradiation)	47	88.9		45.7		70.7	
Histology			0.703		0.585		0.181
SCC	66	83.8		29.3		54.1	
Non-SCC	257	85.7		31.9		65.3	
Disease-free interval (months)			0.269		0.324		0.001
< 16	162	81.9		25.8		53.2	
≥ 16	161	88.6		37.0		72.6	

LN metastatic lymph node, SCC squamous cell carcinoma, EQD₂ equivalent dose in 2-Gy fraction, LC local control, PFS progression-free survival, OS overall survival

Table 4 Assessment of prognostic factors with multivariate analysis

Factor	PFS		OS	
	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)
LN size in maximal length < 30 mm			0.011	0.668 (0.490–0.912)
Number of LNs (1–3)	0.047	0.658 (0.435–0.995)	0.006	0.535 (0.341–0.837)
History of RT to the lesion (re-irradiation)	–		–	
Disease-free interval ≥ 16 months			0.003	0.629 (0.466–0.851)

LN metastatic lymph node, SCC squamous cell carcinoma, PFS progression-free survival, OS overall survival, CI confidence interval, HR hazard ratio

were ≥ 12 months [19, 22–29]. Although these studies are heterogeneous in terms of site, primary histology, and dose, the control rates for treated metastatic LNs were 64–78%, except for patients with prostate cancer. The present study showed a 2-year LC of 85.4% despite the larger number of patients, the majority of whom had non-SCCs (79.6%) and among whom prostate cancer was rare (2.2%). Thus, C-ion RT can be a powerful focal therapy for patients with LN oligo-recurrence.

Previous studies found that LN diameter and volume may be predictors of in-field control [19, 30]. The information in Table 5 implies that patients with LN oligo-recurrence of prostate cancer had better LC rates. Regarding the association between LC in patients with irradiated LNs and histological tumor type, Milano et al. reported a better LC rate in patients with breast cancer than in those with non-breast

cancers [31]. However, other factors, such as LN diameter or histology, did not significantly affect LC in the univariate analysis in the present study. Notably, a history of RT at the site of recurrence did not compromise LC, which is consistent with recent studies investigating C-ion RT for LN recurrence [15, 16]. Additionally, our study revealed that C-ion RT for LN oligo-recurrence caused relatively few late toxicities, with only 1 patient developing grade 3 late toxicity. Thus, C-ion RT appears to be beneficial for conventionally difficult-to-cure patients with LN oligo-recurrence.

Several researchers reported an association between dose fractionation and in-field control when using SBRT for LN oligo-recurrence. Bae et al. found that a dose of 48 Gy or greater in 3 fractions was associated with better in-field control in a series of 41 patients with colorectal cancer metastases [26]. Conde-Moreno et al. proposed using

Table 5 Clinical outcomes of SBRT and present study for lymph node oligo-recurrence

Author (references)	Year	Number of patients	Primary disease	Dose fractionation	Median follow-up time (months)	Local control	Grade ≥ 3 late toxicity
Kim et al. [22]	2008	23	Colorectal	30–51 Gy/3 fr.	31	74% at 4 years	4% (Grade 4 in 1 patient)
Choi et al. [19]	2009	30	Uterine	33–45 Gy/3 fr.	15	67% at 4 years	20%
Kim et al. [23]	2009	7	Gastric	48 Gy/3 fr. (median)	26	NR	0%
Bignardi et al. [24]	2011	19	Mixed	45 Gy/6 fr. (median)	12	78% at 2 years	5%
Casamassima et al. [25]	2011	25	Prostate	30 Gy/3 fr. (most common)	29	90% at 3 years	0%
Bea et al. [26]	2012	41	Colorectal	48 Gy/3 fr. (median)	28	64% at 3 years	7%
Wang et al. [27]	2016	85	Mixed	45 Gy/5 fr. (most common)	27	77% at 5 years	7% (Grade 5 in 3 patients)
Napieralska et al. [28]	2016	18	Prostate	30 Gy/3 fr. (median)	16	70% at 2 years	NR
Jerezek-Fossa et al. [29]	2017	94	Prostate	33 Gy/3 fr. (median)	19	84% at 2 years	0%
Present study	2019	323	Mixed	48 Gy (RBE)/12 fr. (most common)	25 (34) ^a	85% at 2 years	0% ^b (Grade 3 in 1 patient)

SBRT stereotactic body radiotherapy, *fr.* fractions, *RBE* relative biological effectiveness, *NR* not reported

^aMedian follow-up period for surviving patients

^b0.31% (one out of 323 patients) for the record

dose fractionation schemes of either 6 fractions of 7.5 Gy or 3 fractions of ≥ 10 Gy based on criteria that depended on the tolerance of the surrounding structures [20]. However, univariate analysis revealed no significant difference in LC according to the C-ion RT dose in our study; this could be owing to the variety of maximum LN diameters, which ranged from 10 to 80 mm. Prospective trials to determine the optimal C-ion RT dose fractionation scheme for LN oligo-recurrence are warranted.

In our study, having ≤ 3 LN metastases was associated with significantly better PFS. Moreover, LNs with a diameter < 30 mm, having ≤ 3 LN metastases, and a disease-free interval ≥ 16 months after the initial therapy were associated with significantly better OS. These findings support the notion of an oligo-recurrence state in which aggressive local therapy can provide a survival benefit in a specific population. Regarding prognostic factors reported in the literature, Salama et al. reported that patients with ≤ 3 metastases had better PFS and OS than those with 4–5 metastases [21]. Although their cohorts included multisite extracranial oligo-recurrence that were not confined to LNs, our results support their findings. Jerezek-Fossa et al. reported that a larger LN volume compromised LC and predicted a poorer prognosis; an abdominal gross tumor volume of 17 cm³ or smaller predicted favorable PFS; and each additional 1 cm³ was associated with a 1% worsening in PFS [32]. Although LN diameter did not affect the LC rate in our study, it did affect OS. Thus, LN diameter may be a prognostic factor in certain patients with LN oligo-recurrence, as may the

disease-free interval post-primary therapy. Zhang et al. reported that a disease-free interval of more than 12 months was significantly related to longer OS in patients with lung metastases who received SBRT [33]. Furthermore, other researchers have reported that a longer disease-free interval was significantly associated with longer OS in patients with extracranial oligo-recurrence or recurrent hepatocellular carcinoma following SBRT [34, 35]. These results, as well as those of our study, indicate that C-ion RT should be considered in patients with LN oligo-recurrence, particularly in patients with a longer disease-free interval.

The present study has some limitations. First, the study design was retrospective; therefore, various dose fractionation protocols were included. Second, the median follow-up period was short (25 months). Longer follow-up is needed to determine the long-term efficacy and toxicity of C-ion RT.

In conclusion, our study demonstrates that C-ion RT for LN oligo-recurrence appears to be effective and safe. In addition, C-ion RT may improve LC irrespective of tumor status and may produce a survival benefit in patients with LN oligo-recurrence. In particular, patients who have a small number of LN metastases (≤ 3), smaller LN diameter (< 30 mm), and longer disease-free interval (≥ 16 months) are most likely to achieve a survival benefit from C-ion RT.

Acknowledgements We wish to thank the members of the Working Group of Metastatic Tumors, part of the Japan Carbon-Ion Radiation Oncology Study Group, for their constructive criticism and advice. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest No author has any conflict of interest.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

- Hellman S, Weichselbaum RR (1995) Oligometastases. *J Clin Oncol* 13(8):8–10
- Niibe Y, Hayakawa K (2010) Oligometastases and oligo-recurrence: the new era of cancer therapy. *Jpn J Clin Oncol* 40:107–111. <https://doi.org/10.1093/jjco/hyp167>
- Ripley RT, Downey RJ (2014) Pulmonary metastasectomy. *J Surg Oncol* 2014(109):42–46. <https://doi.org/10.1002/jso.23450>
- Ruiterkamp J, Ernst MF (2011) The role of surgery in metastatic breast cancer. *Eur J Cancer* 47:S6–S22. [https://doi.org/10.1016/S0959-8049\(11\)70142-3](https://doi.org/10.1016/S0959-8049(11)70142-3)
- Casiraghi M, De Pas T, Maisonneuve P et al (2011) A 10-year single-center experience on 708 lung metastasectomies: the evidence of the international registry of lung metastases. *J Thorac Oncol* 6:1373–1378. <https://doi.org/10.1097/JTO.0b013e3182208e58>
- Kanemitsu Y, Kato T, Hirai T et al (2004) Preoperative probability model for predicting overall survival after resection of pulmonary metastases from colorectal cancer. *Br J Surg* 91:112–120
- Pawlik TM, Scoggins CR, Zorzi D et al (2005) Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 241:715–724
- Milano MT, Philip A, Okunieff P (2009) Analysis of patients with oligometastases undergoing two or more curative-intent stereotactic radiotherapy courses. *Int J Radiat Oncol Biol Phys* 73:832–837. <https://doi.org/10.1016/j.ijrobp.2008.04.073>
- Tree AC, Khoo VS, Eeles RA et al (2013) Stereotactic body radiotherapy for oligometastases. *Lancet Oncol* 14:e28–e37. [https://doi.org/10.1016/S1470-2045\(12\)70510-7](https://doi.org/10.1016/S1470-2045(12)70510-7)
- Ricco A, Davis J, Rate W et al (2017) Lung metastases treated with stereotactic body radiotherapy: the RSSearch® patient Registry's experience. *Radiat Oncol* 12:35. <https://doi.org/10.1186/s13014-017-0773-4>
- Mahadevan A, Blanck O, Lanciano R et al (2018) Stereotactic Body Radiotherapy (SBRT) for liver metastasis—clinical outcomes from the international multi-institutional RSSearch® Patient Registry. *Radiat Oncol* 13:26. <https://doi.org/10.1186/s13014-018-0969-2>
- Kanai T, Furusawa Y, Fukutsu K et al (1997) Irradiation of mixed beam and design of spread-out Bragg peak for heavy-ion radiotherapy. *Radiat Res* 147:78–85
- Kanai T, Endo M, Minohara S et al (1999) Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. *Int J Radiat Oncol Biol Phys* 44:201–210
- Isozaki Y, Yamada S, Kawashiro S et al (2017) Carbon-ion radiotherapy for isolated para-aortic lymph node recurrence from colorectal cancer. *J Surg Oncol* 116:932–938. <https://doi.org/10.1002/jso.24757>
- Tamaki T, Ohno T, Kiyohara H et al (2013) Carbon-ion radiotherapy for marginal lymph node recurrences of cervical cancer after definitive radiotherapy: a case report. *Radiat Oncol* 8:79. <https://doi.org/10.1186/1748-717X-8-79>
- Shiba S, Okonogi N, Kato S et al (2017) Clinical impact of re-irradiation with carbon-ion radiotherapy for lymph node recurrence of gynecological cancers. *Anticancer Res* 37:5577–5583
- Inaniwa T, Kanematsu N, Matsufuji N et al (2015) Reformulation of a clinical-dose system for carbon-ion radiotherapy treatment planning at the National Institute of Radiological Sciences, Japan. *Phys Med Biol* 60:3271–3286. <https://doi.org/10.1088/0031-9155/60/8/3271>
- NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 data files. <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>. Accessed 20 June 2018
- Choi CW, Cho CK, Yoo SY et al (2009) Image-guided stereotactic body radiation therapy in patients with isolated para-aortic lymph node metastases from uterine cervical and corpus cancer. *Int J Radiat Oncol Biol Phys* 74:147–153. <https://doi.org/10.1016/j.ijrobp.2008.07.020>
- Conde-Moreno AJ, Lopez-Guerra JL, Macias VA et al (2016) Spanish Society of Radiation Oncology clinical guidelines for stereotactic body radiation therapy in lymph node oligometastases. *Clin Transl Oncol* 18:342–351. <https://doi.org/10.1007/s12094-015-1383-y>
- Salama JK, Hasselle MD, Chmura SJ et al (2012) Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. *Cancer* 118:2962–2970. <https://doi.org/10.1002/cncr.26611>
- Kim MS, Choi C, Yoo S et al (2008) Stereotactic body radiation therapy in patients with pelvic recurrence from rectal carcinoma. *Jpn J Clin Oncol* 38:695–700. <https://doi.org/10.1093/jjco/hyn083>
- Kim MS, Yoo SY, Cho CK et al (2009) Stereotactic body radiotherapy for isolated para-aortic lymph node recurrence after curative resection in gastric cancer. *J Korean Med Sci* 24:488–492. <https://doi.org/10.3346/jkms.2009.24.3.488>
- Bignardi M, Navarra P, Mancosu P et al (2011) Clinical outcome of hypofractionated stereotactic radiotherapy for abdominal lymph node metastases. *Int J Radiat Oncol Biol Phys* 81:831–838
- Casamassima F, Masi L, Menichelli C et al (2011) Efficacy of eradicator radiotherapy for limited nodal metastases detected with choline PET scan in prostate cancer patients. *Tumori* 97:49–55
- Bae SH, Kim MS, Cho CK et al (2012) High dose stereotactic body radiotherapy using three fractions for colorectal oligometastases. *J Surg Oncol* 106:138–143. <https://doi.org/10.1002/jso.23058>
- Wang HH, Zaorsky NG, Meng MB et al (2016) Stereotactic radiation therapy for oligometastases or oligorecurrence within mediastinal lymph nodes. *Oncotarget* 7:18135–18145. <https://doi.org/10.18632/oncotarget.7636>
- Napieralska A, Miszczuk L, Stapór-Fudzińska M (2016) CyberKnife stereotactic ablative radiotherapy as an option of treatment for patients with prostate cancer having oligometastatic lymph nodes: single-center study outcome evaluation. *Technol Cancer Res Treat* 15:661–673. <https://doi.org/10.1177/1533034615595945>
- Jereczek-Fossa BA, Fanetti G, Fodor C et al (2017) Salvage stereotactic body radiotherapy for isolated lymph node recurrent prostate cancer: single institution series of 94 consecutive patients and 124 lymph nodes. *Clin Genitourin Cancer*. 15:e623–e632. <https://doi.org/10.1016/j.clgc.2017.01.004>
- Bacorro W, Dumas I, Escande A et al (2018) Dose-volume effects in pathologic lymph nodes in locally advanced cervical cancer.

- Gynecol Oncol 148:461–467. <https://doi.org/10.1016/j.ygyno.2017.12.028>
31. Milano MT, Katz AW, Zhang H et al (2012) Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. *Int J Radiat Oncol Biol Phys* 83:878–886. <https://doi.org/10.1016/j.ijrobp.2011.08.036>
 32. Jerezek-Fossa BA, Beltramo G, Fariselli L et al (2012) Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. *Int J Radiat Oncol Biol Phys* 82:889–897. <https://doi.org/10.1016/j.ijrobp.2010.11.031>
 33. Zhang Y, Xiao JP, Zhang HZ et al (2011) Stereotactic body radiation therapy favors long-term overall survival in patients with lung metastases: five-year experience of a single-institution. *Chin Med J* 124:4132–4137
 34. Sole CV, Lopez Guerra JL, Matute R et al (2013) Stereotactic ablative radiotherapy delivered by image-guided helical tomotherapy for extracranial oligometastases. *Clin Transl Oncol* 15:484–491. <https://doi.org/10.1007/s12094-012-0956-2>
 35. Bae SH, Park HC, Lim DH et al (2012) Salvage treatment with hypofractionated radiotherapy in patients with recurrent small hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 82:e603–e607. <https://doi.org/10.1016/j.ijrobp.2011.09.053>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.