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Review Article

Carbon-ion Radiotherapy for Colorectal Cancer

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Abstract

Heavy-ion radiotherapy (RT) is a kind of particle RT, and carbon-ion beam constitutes the primary delivery method of heavy-ion RT. Unlike the conventional photon modalities, particle RT, in particular carbon-ion radiotherapy (CIRT), offers unique physical and biological advantages. Particle therapy allows for substantial dose delivery to tumors with minimal surrounding tissue damage. In addition, CIRT in particular possesses biological advantages such as inducing increased double-strand breaks in DNA structures, causing irreversible cell damage independently of cell cycle or oxygenation, more so than proton or photon. It can be expected that CIRT is effective on radioresistant cancers such as colorectal cancers (CRCs). We introduced the results of CIRT for local recurrent rectal cancer, lung metastasis, liver metastasis, and lymph node metastasis.

Keywords

colorectal cancer, carbon-ion radiotherapy (CIRT), lung metastasis, liver metastasis, lymph node metastasis

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Introduction

Compared to photon beam therapy, particle beams (proton and heavy-ion beams) have the physical advantage of better dose distribution, allowing for more accurate targeting of the tumor and further normality around the target. Increasing the total dose by appropriately controlling the target dose is possible. In addition, since the heavy particle beam accelerates heavier particles than the proton beam, it is characterized by a strong ionizing action on the target substance and a high cell-killing effect.

Since 1994, the National Institute of Radiological Sciences (currently the National Institutes for Quantum and Radiological Science and Technology (QST)) has treated solid cancers using carbon-ion beams generated from a heavy-ion accelerator (Heavy Ion Medical Accelerator (HIMAC) in Chiba, Japan). In 2003, the Ministry of Health, Labor, and Welfare approved advanced medical treatment, and after 27 years, 12,710 cases were treated by March 2020. From these results, it has been shown that CIRT is effective against adenocarcinoma and sarcoma, which were previously considered to be radioresistant, and that short-term irradiation is possible[1].

This time, we will introduce the clinical outcomes and prospects centering on carbon-ion radiotherapy (CIRT) for colorectal cancer (CRC), especially rectal cancer.

History of Particle Therapy

The use of particles in radiotherapy (RT) was first proposed by physicist Robert Wilson in RT in 1946[2]. Proton beam therapy was first used in clinical practice at the Lawrence Berkeley National Laboratory (LBL) in California in 1954. Heavy ions were clinically used in 1957, and patients

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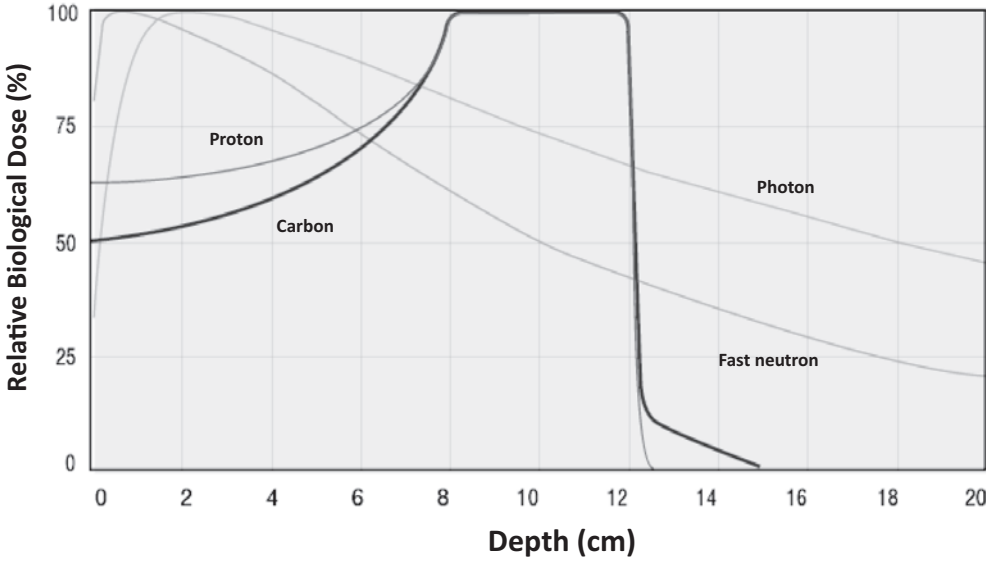

Figure 1. Depth dose distribution of various ion beams.

were treated with helium ions at LBL[3]. Unfortunately, the treatment was shut down in 1992 due to financial constraints. Then, in 1994, the QST in Japan began the clinical application of carbon ions using the HIMAC in Chiba, the world's first heavy-ion facility dedicated to medical treatment.

Currently, there are 12 facilities for CIRT in operation, 6 of which are in Japan, with 6 facilities under construction in the world.

Characteristics of Heavy-ion Beams in Cancer Treatment

Physical and biological advantages

We have summarized the physical and biological advantages of carbon-ion beams for cancer treatment over photon and proton beams[4], which are briefly described below.

A) Physical advantages (comparison of particle beams (heavy-ion and proton beams) and X-ray)

Figure 1 shows the deep dose distribution from the skin in the body due to various radiations used for treatment. X-rays deposit most of their energy near the surface of the skin, while particle beams, such as protons and heavy-ion beams, deposit more energy as they increase in depth. The penetration depth of these beams achieves a sharp maximum peak at the end of their range. This peak of dose distribution is called the Bragg peak (Figure 1)[5,6]. The position and width can be adjusted according to the shape and position of the tumor using a special filter, making it possible to concentrate the effect of particle beams only on cancer, thus targeting cancer cells. Due to the characteristics of the particle beams, effectively avoiding the organs (gastrointestinal (GI) tract, bladder, spinal cord, etc.) around the cancer, which are highly sensitive to radiation, and irradiating the cancer with a sufficient dose to control the tumor are possible.

B) Biological advantages (comparison of heavy particle and proton beams)

The other characteristic of heavy-ion beams has useful biological properties. The cell-killing effect of proton is almost the same as that of X-ray.

To understand the radiobiological properties of heavy-ion beams, understanding that linear energy transfer (LET) values are high when comparing heavy ions with either photons or protons[7] is important. LET is defined as the transfer of energy from a radiation beam to a medium that passes per unit length. LET with a high heavy-ion beam has a significantly effective biological effect at the DNA level on cancer cells. As a result, heavy-ion beams are described as high-LET radiation. High-LET radiations have high relative biological effectiveness (RBE). X-rays and protons have a low cell-killing effect on (1) cells in the DNA synthesis stage (S phase)[8], (2) hypoxic cells[9,10], and (3) cancer stem cells[11], but heavy-ion beams also act on those resistant cells. That is, the heavy particle beam is characterized by expressing a cell-killing effect independently of the characteristic of the target cell.

In view of these unique properties of carbon-ion beams, a kind of heavy-ion beams, it is theoretically possible to perform hypofractionated RT using significantly smaller numbers of fractions than have been used in conventional RT. QST has accumulated data from clinical trials using hypofraction CIRTs for various tumors. The analysis of these data showed that the characteristics of CIRT could be used to complete treatment in a short time without increasing normal tissue damage. Currently, the average number of

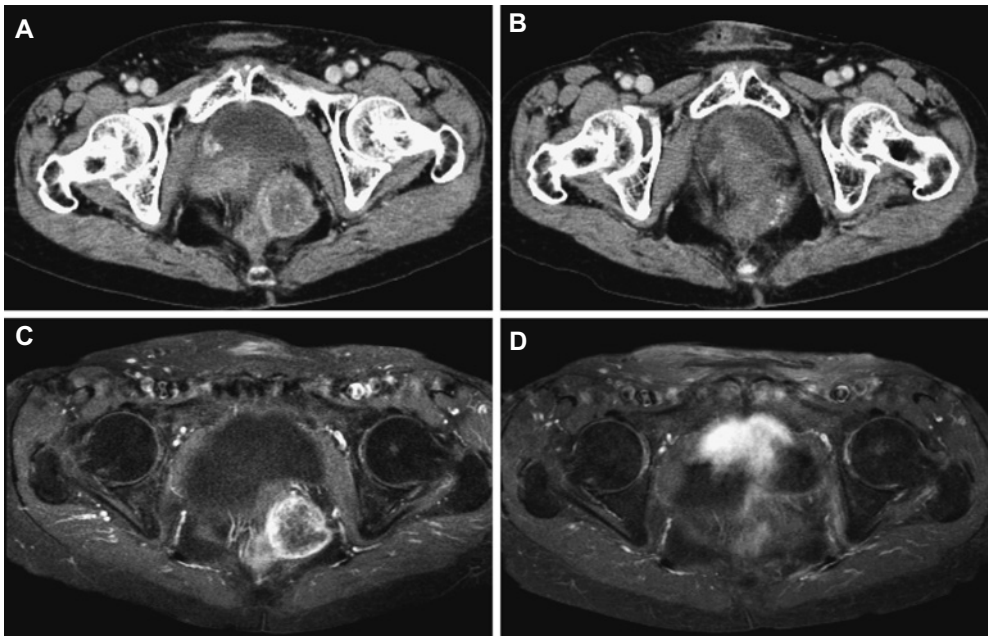

Figure 2. Locally recurrent rectal cancer 3 years after resection (70-year-old female).
(A) Computed tomography (CT) scan before CIRT. (B) CT scan 2 years after CIRT. (C) Magnetic resonance imaging (MRI) before CIRT. (D) MRI scan 2 years after CIRT demonstrated disappearance of the mass.

fractions per patient and duration of treatment at QST are 12 fractions and 3 weeks, respectively.

To summarize the characteristics of heavy particle radiation, (1) the dose distribution is excellent and (2) it has a high biological effect and therefore exhibits a high cytocidal effect even on X-ray-resistant cells.

1. Postoperative Recurrence of Rectal Cancer

Although total mesorectal excision, radiation, and/or chemoradiation therapy have reduced the incidence of local recurrence (LR) of rectal cancer, it still occurs in 4%-13% of patients[12,13]. The majority of rectal cancers are adenocarcinomas, and postoperative recurrence has a high proportion of hypoxic cells, which are considered to be radioresistant[14]. In addition, recurrent lesions are often close to radiosensitive organs such as the intestinal tract and bladder. From these facts, heavy-ion beams, which avoid high radiosensitive organs and have high cytocidal effects on radioresistant cells, were expected as a treatment for postoperative recurrence of rectal cancer.

A phase I/II dose escalation study of CIRT was performed. Between April 2001 and February 2016, a total of 235 patients (245 lesions) received CIRT for locally recurrent rectal cancer (LRRC) (Figure 2)[15,16]. The median patient age was 60.9 years (range, 20-80 years). Relapse locations included the presacral region (n = 102), pelvic side walls (n = 91), perineum (n = 30), and surrounding soft tissue (n = 22).

The total dose of CIRT ranged from 67.2 to 73.6 Gy (RBE) and was administered in 16 fixed divisions over 4 weeks (4.2-4.6 Gy (RBE)/fraction). One grade 3 (G3) GI adverse event was observed as a normal tissue reaction (GI ulcer). No other serious acute reaction (≥ G3) was observed. Two late G3 skin adverse events were observed; one was G3 GI obstruction. The local control (LC) rate of 244 lesions in all cases was 90% at 3 years and 88% at 5 years. The overall survival (OS) rate of 235 patients was 67% at 3 years and 46% at 5 years. With the 73.6 Gy (RBE) (n = 203) currently in clinical use, the 5-year LC and survival rates were 89% and 52%, respectively. In the literature (Table 1), recent developments in chemotherapy have improved survival, but the reported 5-year survival rate for LRRC treated with resection remains 20%-40%[17-22]. CIRT is a safe and effective treatment for the management of LRRC, providing good LC and the benefits of survival without unacceptable morbidity.

We verified whether similar results could be obtained at other facilities.

The QST, the Gunma University Heavy Ion Medical Center (GHMC, Gunma, Japan), and the Ion Beam Therapy Center, SAGA HIMAT Foundation (HIMAT, Saga, Japan) participated in this multi-institutional study on LRRC[23]. We retrospectively analyzed data from patients with LRRC

Table 1. Comparison of Outcome for Locally Recurrent Rectal Cancer Treated with Radiotherapy or Chemoradiotherapy.

Author	Year	Number	Radiation	Dose	Chemotherapy	Survival Rate			MST
						2 y	3 y	5 y	
Murata [17]	1997	17	RT	12–60 Gy		20%	10%		6 M
Hu JB [18]	2006	25	3DCRT	60 Gy	None	24%			16 M
		23	3DCRT	60 Gy	FOLFOX	50%	14%		23 M
Km MS [19]	2008	23	SBRT	30–51 Gy	FOLFOX	82%	53%	23%	37 M
Lee JH [20]	2011	22	CRT	54.6–66.5 Gy	5FU CP11 L-OHP	74%	52%	41%	48 M
		45			Surgery				
Jo S [21]	2015	22	CRT	45–75.6 Gy (57.6 Gy)	FOLFOX	82%	52%	25%	
Cai G [22]	2015	71	IMRT	55–61 Gy	CAPE+CPT11		37%		29 M
QST [16]	2016	203	CIRT	73.6 GyE	None	90%	74%	52%	66 M

CRT, conformal radiation therapy; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiotherapy

treated with C-ion RT at three heavy-ion RT facilities in Japan from November 2003 to December 2014. Overall, 224 patient data were collected. The median follow-up period from the initiation of C-ion RT was 62 months (range, 6-169 months). The OS rates were 73% at 3 years and 51% at 5 years. The LC rates were 93% at 3 years and 88% at 5 years. G3 normal tissue toxicity was observed in three patients: GI toxicity in one and pelvic infections in two. G3 late normal tissue toxicity was observed in 12 patients: skin damage in 2, GI toxicity in 2, neuropathy in 1, and pelvic infections in 7. No G4 or G5 acute or late normal tissue toxicity was observed. The results of this multicenter analysis showed that CIRTs for LRRC can provide satisfactory therapeutic effects with less severe normal tissue toxicity.

C-ion RT for locally recurrent rectal cancer in patients with prior pelvic irradiation

Recently, preoperative RT and chemoradiotherapy have been used to reduce the LR rate[24,25]. In addition, high-precision RT, such as intensity-modulated RT, is often used for LR. The surrounding normal tissues may have already received doses near the organ- or end point-specific tolerance dose during the primary treatment. Therefore, re-irradiation was difficult to use at a sufficient dose to control the tumor due to the fear of serious adverse late effects in normal tissue, particularly of the intestine and bladder, and was often a palliative treatment. To improve long-term LC and survival, we have treated patients with LRRC, who have a history of prior pelvic X-ray irradiation, with CIRT at our institute since 2005.

From 2005 to 2015, 67 patients were treated with CIRT re-irradiation for LRRC[26]. All patients received prior X-ray RT with a median dose of 50.0 Gy (range, 20-74 Gy). Prior radiation was given for recurrence prophylaxis (neoadjuvant or adjuvant) in 32 patients and for treatment of recurrence in 35 patients. The total dose of CIRT was 70.4 Gy (RBE) and was administered in 16 fixed fractions over 4 weeks (4.4 Gy (RBE)/fraction). There were four G3 pelvic infections, two G3 pain, and one G3 skin reactions. All were observed prior to CIRT. Late G3 toxicities occurred in 13 (19%) patients. There were nine late G3 infections and three late G3 skin reactions. Four of the late G3 infections were observed prior to CIRT. The overall LC rates at 3 and 5 years were 85.9%. The 3- and 5-year OS rates were 64.5% and 42.3%, respectively.

The literature reports a 3-year survival rate for LRRC in patients with prior pelvic irradiation treated with conventional RT, who were unable to undergo postirradiation surgery, of 20%-27% (Table 2), with a survival rate of 60%-67% in those able to receive surgery[27-29]. All patients in this cohort were ineligible for surgery, and in this trial, their results appeared mirror those of patients able to undergo resection, with acceptable morbidity.

2. Liver Metastasis

The most common metastatic liver tumor is derived from CRC. Among liver metastases from various primary tumors, liver metastasis from CRC is expected to improve the prognosis by surgical resection. Therefore, the guidelines state that the current standard treatment for liver metastases from CRC is resection. On the other hand, since the recurrence rate after resection of liver metastases is high, chemotherapy is necessary, and for this reason, local therapy with less invasiveness and high efficacy is desired.

At the QST, we conducted the clinical trial of hypofractionated CIRT for liver metastasis from CRCs (Figure 3)[30]. Since 2006, we have been conducting a prospective single-arm dose escalation phase I study for CRC liver metastasis using single-fraction CIRT. Twenty-nine patients re-

Table 2. Comparison of Outcome of Re-irradiation for Locally Recurrent Rectal Cancer Treated with Radiotherapy with/without Surgery.

Ref	Author	Year	Number	Total Dose	Toxicity ≥G3	3-y Survival	3-y LC
			RT only		Acute	RT only	
			+Surgery		Late	+Surgery	
27	Mohiuddin	2002	69	70–108 Gy	21%	20%	44%
			34		22%	60%	
28	Das P	2010	32	64–109 Gy	4%	27%	33%
			18		26%	66%	
29	DS Sun	2012	54	52–57 Gy	18%	45.1% (including surgery)	31%
			18	36 Gy	13%		
26	QST	2020	96	90–144 Gy (RBE)	11%	66.4%	81%
					19%		

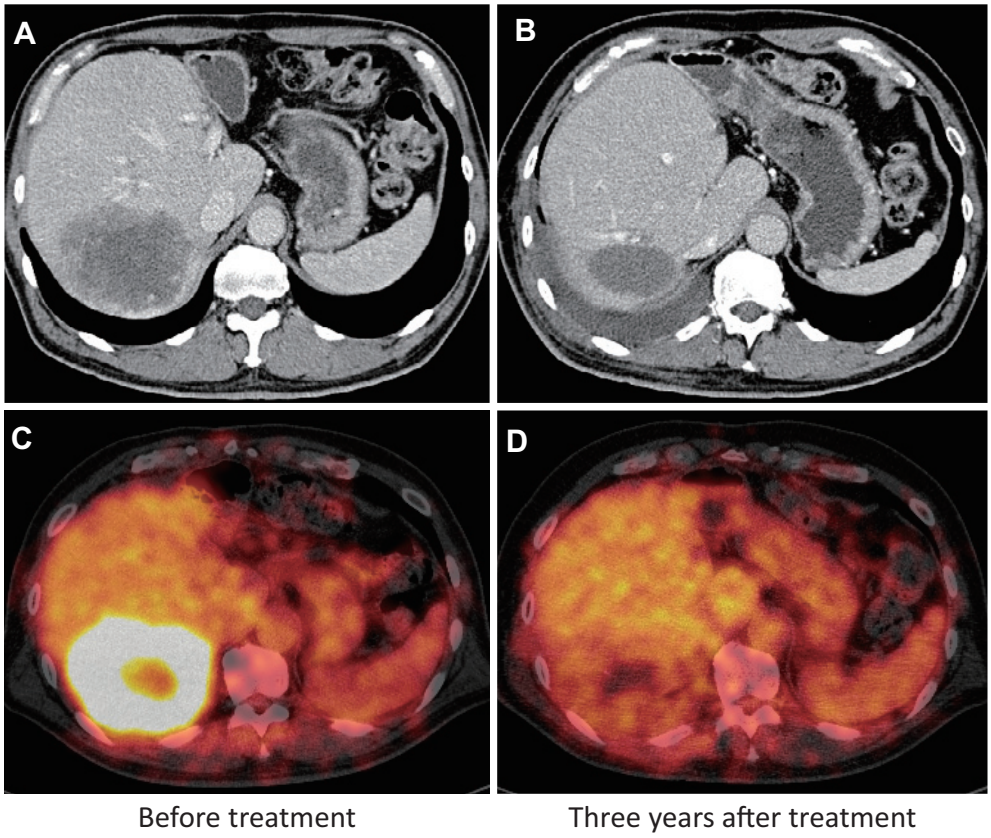

Figure 3. Liver metastasis 3 years after sigmoid colon cancer resection (61 years old).
(A) Computed tomography (CT) scan before CIRT. (B) CT scan 2 years after CIRT. (C) Positron emission tomography (PET) imaging before CIRT. (D) PET scan at years after CIRT demonstrated disappearance of the mass.

ceived a single-fraction CIRT. The prescribed doses were as follows: 36 Gy (RBE) (n = 3), 40 Gy (n = 2), 44 Gy (n = 4), 46 Gy (n = 6), 48 Gy (n = 3), 53 Gy (n = 8), and 58 Gy (n = 3). The 3-year actuarial OS rate of all 29 patients was 78%. The LC rate at 3 years in the higher dose (≥53 Gy) group was 82%. No cases of ≥G3 acute toxicity attributed to CIRT were observed. However, late G3 liver toxicity due to biliary obstruction was observed in two patients who received 53 Gy (RBE). Single-fraction CIRT for liver metastasis from CRC is a safe and effective treatment.

Recently, stereotactic body RT (SBRT), a type of high-precision RT using X-rays, has also been used for the treatment of liver metastasis. LC by SBRT has a 2-year rate in the range of 60%-90%. The median planning target volume

(PTV) using CIRT was 50 cm^3, which was larger than other reports using SBRT that reported a median PTV size of 25-35 cm^3[31-35]. For patients, single-fraction treatment was expected to be effective in maintaining quality of life.

3. Lung Metastasis

We evaluated the efficacy and safety of CIRT for oligo-recurrent lung metastasis from CRC[36].

From May 1997 to October 2012, 34 patients (44 lesions) treated with CIRT for oligo-recurrent lung metastases from CRC were analyzed. All patients were not indicated for surgical treatment due to functional medical reasons such as cardiopulmonary hypofunction or patient refusal. The CIRT used respiratory-gated technology using four coplanar beam angles. The median dose of CIRT was 60 Gy (RBE) (range, 44-64.8 Gy (RBE)), and irradiation was performed in four fractions. We analyzed LC rates, survival, and treatment-related normal tissue damage by CIRT. The median follow-up was 23.7 months. Both the 2- and 3-year LC rates were 85.4%. The 2- and 3-year OS rates were 65.1% and 50.1%, respectively. Univariate analysis showed relatively low survival in a subset of patients younger than 63 years or with early metastases (less than 36 months after primary site resection), but these factors were not significantly correlated with OS (P = 0.13 and P = 0.19). There was no treatment-related G3-G5 normal tissue toxicity.

In the recent years, many papers show that SBRT has an excellent LC effect on the treatment of lung metastasis[37-43]. However, given that CRC metastases are less sensitive to radiation, escalated doses may be needed to achieve the same results as surgery. Norihisa et al. escalated the dose of SBRT for oligo-recurrent lung metastases to increase LC[37], but G3-G5 toxicity was observed in 15% of patients[44]. CIRTs for oligo-recurrent lung metastases provide high survival rate and good LC effects comparable to surgical resection. In addition, it should be noted that all patients were safely treated, although most patients were medically comorbid and elderly. CIRT is considered to be the least invasive approach, even in patients with recurrent lung metastases, due to its high dose concentration. CIRT is one of the most effective nonsurgical treatments for lung metastases from CRC.

4. Lymph Node Metastasis

Para-aortic lymph node (PALN) metastases from CRC belong to distant metastases, and chemotherapy is recommended as standard treatment[45]. However, the frequency of isolated PALN metastases from CRC is low (1.3%)[46], and many reports indicate that isolated cases of PALN metastases after curative resection can expect long-term survival[46,47]. We retrospectively evaluated and reported the safety and efficacy of CIRT for isolated PALN metastases[48].

We analyzed 34 patients who underwent CIRT for PALN metastases after CRC resection from June 2006 to August 2015. The median total dose was 52.8 Gy (RBE) (range, 48-52.8 Gy (RBE)) and was given in 12 fixed fractions over 3 weeks. The median follow-up period for all patients was 24.4 months (range, 7-82.8 months). In the evaluation of local response, 13 patients (38.2%) achieved a complete response after treatment. The 3-year LC rate was 70.1%. The 2- and 3-year OS rates were 83.3% and 63.0%, respectively, with a median survival of 41.7 months. Twelve patients survived for longer than 3 years. No G3 or higher normal tissue damage was observed.

Although chemotherapy has been significantly developed in the recent years, the median survival time of isolated PALN recurrence cases is about 13 months, and the prognosis cannot be evaluated as good. Many reports have shown that cases with resected isolated PALN metastases can achieve long-term survival[49,50]. CIRT achieved as good LC and survival as surgery. In addition, it should be noted that no G3-G5 normal tissue disorders were observed, and it can be evaluated that the treatment is extremely minimally invasive. This suggests that CIRT is a less invasive and more therapeutic tool for PALN after CRC resection.

Future Prospects of CIRT

In 2011, we built a new treatment building and introduced 3D scanning technology for the treatment of respiratory movement targets. In 2017, we implemented the world's first rotating gantry using superconducting technology[51]. These techniques are expected to not only improve treatment outcomes but also dramatically increase the number of patients that can be treated per day. They also provide a wider range of treatment indications and improved QOL for treated patients due to faster completion of treatment.

Recently, the combination of new therapies, such as molecular-targeted therapies, with RT has demonstrated improved outcomes for CRC[52]. These new drugs may not only enhance the antitumor effect of radiation but also increase damage to normal tissues.

Heavy-ion RT allows the concentration of sufficient therapeutic dose to the target while minimizing normal tissue dose. Therefore, even when used in combination with these molecular-targeted agents, it is expected that there is very little possibility of increasing normal tissue damage due to the extremely low dose of normal tissue. Even with heavy-ion RT combined with chemotherapy for pancreatic cancer, the incidence of normal tissue damage was extremely low compared to photon irradiation[53]. Thus, heavy-ion RT can be expected to improve LC without increasing toxicity.

Recently, with the development of immune checkpoint in-

hibitors, the abscopal effect of radiation activating immunity has become a hot topic. The abscopal effect is a phenomenon in which unirradiated metastatic lesions shrink after irradiation when a local tumor is treated with radiation[54]. Experiments with mice have demonstrated that treating mouse tumors with CIRT suppresses metastasis and abscopal effect[55,56]. Ebner et al. presented two cases of patients who demonstrated an abscopal effect response following CIRT for metastatic recurrent CRC[57]. Recently, the effectiveness of immunotherapy for CRC has been shown[58]. RT has also been shown to enhance the effectiveness of immunotherapy for GI cancer[59].

Heavy-ion beams are expected to increase these immunotherapies more than photon beams[60]. Currently, multi-ion irradiation using multiple particles, such as oxygen ion, helium ion, and carbon ion, to further enhance the LC effect on tumors[61] and the immunity of heavy-ion RT to further control the suppression of distant metastasis is under development. We are planning to use it in combination with other treatments centered on therapy.

Conflicts of Interest

There are no conflicts of interest.

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