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Review Article

Carbon-ion radiotherapy for urological cancers

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Abbreviations & Acronyms
ADT = androgen deprivation therapy
bRF = biochemical relapse-free
CIRT = carbon-ion radiotherapy
eGFR = estimated glomerular filtration rate
FACT-P = functional assessment of cancer therapy for prostate cancer patients
GI = gastrointestinal
GU = genitourinary
HIMAC = The Heavy Ion Medical Accelerator in Chiba
HRQOL = health-related quality of life
IMRT = intensity-modulated radiation therapy
JASTRO = Japanese Society for Radiation Oncology
J-CROS = Japan Carbon-ion Radiation Oncology Study Group
LBNL = Lawrence Berkeley National Laboratory
LET = linear energy transfer
NA = not assessed
NIRS = National Institute of Radiological Sciences
PBT = proton beam therapy
QOL = quality of life
QST = National Institutes for Quantum Science and Technology
RBE = relative biological effectiveness
RCC = renal cell carcinoma
RPS = retroperitoneal sarcoma
RT = radiotherapy
SBRT = stereotactic body radiotherapy
SOBP = spread-out Bragg peak

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Abstract: Carbon-ions are charged particles with a high linear energy transfer, and therefore, they make a better dose distribution with greater biological effects on the tumors compared with photons and protons. Since prostate cancer, renal cell carcinoma, and retroperitoneal sarcomas such as liposarcoma and leiomyosarcoma are known to be radioresistant tumors, carbon-ion radiotherapy, which provides the advantageous radiobiological properties such as an increasing relative biological effectiveness toward the Bragg peak, a reduced oxygen enhancement ratio, and a reduced dependence on fractionation and cell-cycle stage, has been tested for these urological tumors at the National Institute for Radiological Sciences since 1994. To promote carbon-ion radiotherapy as a standard cancer therapy, the Japan Carbon-ion Radiation Oncology Study Group was established in 2015 to create a registry of all treated patients and conduct multi-institutional prospective studies in cooperation with all the Japanese institutes. Based on accumulating evidence of the efficacy and feasibility of carbon-ion therapy for prostate cancer and retroperitoneal sarcoma, it is now covered by the Japanese health insurance system. On the other hand, carbon-ion radiotherapy for renal cell cancer is not still covered by the insurance system, although the two previous studies showed the efficacy. In this review, we introduce the characteristics, clinical outcomes, and perspectives of carbon-ion radiotherapy and our efforts to disseminate the use of this new technology worldwide.

Key words: carbon-ion radiotherapy, local control, prostate cancer, renal cell carcinoma, toxicity.

INTRODUCTION

CIRT has unique biological and physical properties among the different RTs, and it has been used to treat prostate cancer since 1995[1] and RCC since 1997[2] at the NIRS (currently QST). Both diseases are known as radioresistant to RT using a conventional fractionation due to the low alpha-beta ratio of the cancer cells based on the linear-quadratic model.[3,4] RPSs is also known to be radioresistant tumors, and CIRT was applied to them since 1997.[5] To overcome resistance to RT, high-dose irradiation with a hypofractionation using carbon-ion beams seems to be a reasonable approach because these beams can deliver high doses to the tumors while sparing the surrounding organs at risk, such as the GI tracts. According to long-term and careful follow-up studies of CIRT, the feasibility and efficacy of CIRT using reduced fraction numbers have been tested in these cancers step by step.[6–8]

Beam delivery and treatment planning techniques for CIRT are improving; the size of CIRT accelerators is decreasing to reduce the cost, and the number of facilities practicing CIRT has been recently increased. At the present, 14 institutes have implemented CIRT worldwide, seven of which are in Japan (Figure 1). The J-CROS was established in 2014 to create a registry of all treated patients and to conduct multi-institutional prospective studies in cooperation with all CIRT-practicing Japanese institutes, with the aim of establishing coverage of CIRT by the national health insurance system. CIRT is a treatment covered by the health insurance for prostate cancer and RPS but is only used as an advanced medical

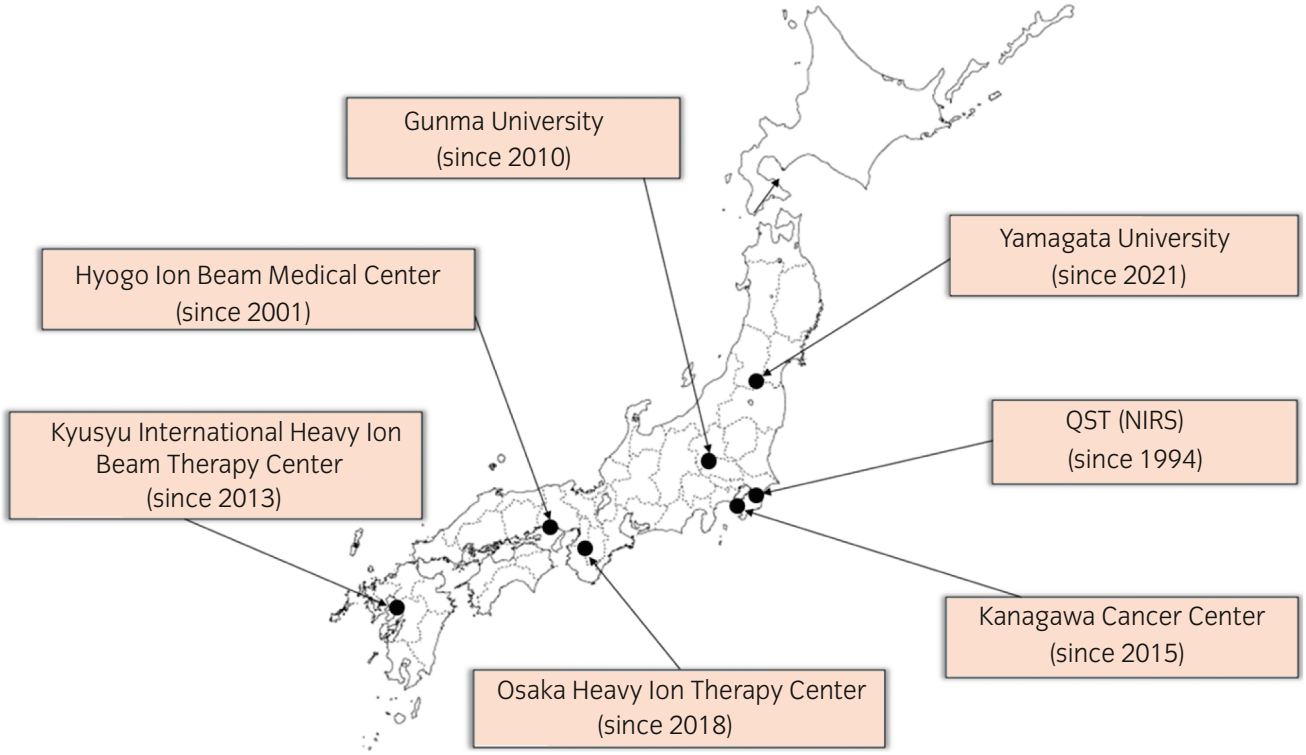

FIGURE 1 Carbon-ion therapy institutes in Japan

treatment for many other types of cancers including RCC. Thus, the working group of the JASTRO has been prospectively investigating the collected data and systematically reviewing the clinical outcomes of individual cases obtained from published data.

In this review, we summarize the history and biological and physical characteristics of CIRT, as well as the clinical outcomes of CIRT for urological malignancies and describe our perspectives.

HISTORY AND CHARACTERISTICS OF CARBON-ION THERAPY

History of carbon-ion radiotherapy

CIRT is regarded as an innovative technology in oncology. Although the number of centers performing this treatment is still limited, major paradigm shifts in RT for a variety of cancers including urological malignancies have steadily progressed.

The basic concept of the charged particle therapy was advocated by Robert Wilson in 1946.[9] He proposed that accelerated protons are the most practical particle for medical purposes in terms of beam range in that era. He also claimed that heavier particles, such as alpha particles or energetic carbon atoms, which have less straggling and angular spread, will be the most desirable and will eventually become therapeutically practical. PBT was first implemented at the LBNL in 1954 and treatment with helium ions was initiated in 1957, although it was limited to the superficial lesions.[10] Clinical studies using heavier ions, such as silicon, neon or carbon were also begun at the LBNL in 1974, and the favorable outcomes were obtained in certain cases.[11] However, the cost of developing and delivering heavy ions could not be justified in the limited patients' experience, and the studies were terminated in 1992.

In Japan, Umegaki proposed fast neutron therapy, which has high radiological effects on tumor cells, and it was implemented at the NIRS in 1971.[12] Favorable results were obtained in salivary gland tumors, Pancoast tumors, and some sarcomas, but severe adverse events due to insufficient dose concentration of the fast neutron beams occurred.[12] Therefore, heavy-ion therapy, which has both a high biological effect and localized dose distribution, was desired, and the construction of a dedicated facility was achieved in 1984. The HIMAC was completed in 1994, and phase I/II clinical studies using carbon-ion beams were begun. Of the several types of ion species, carbon ions were selected because they have optimal properties in terms of the most effective dose-localization in the body, both physically and biologically.[13]

In clinical studies at the QST, the treatment efficacy of CIRT was investigated in a variety of tumors, and consequently, effective and safe treatment techniques were established for most indications. Particularly, several tumors including locally advanced tumors of the histologically non-squamous cell type, such as adenocarcinoma, adenoid cystic carcinoma, malignant melanoma, and bone and soft tissue sarcomas, appeared to respond favorably to carbon ions. In addition, the efficacy of treatment regimens using a hypofractionation was confirmed in many tumor types, particularly those in parallel organs, such as the lung or liver.[14] Clinical experience at the QST was evaluated by the review panel consisting of radiation oncologists, radiobiologists, and

medical physicists from the U.S. and Europe.[15] Peer review of the clinical outcomes at the QST suggested that CIRT improves the outcomes of several common cancers with poor prognoses, in addition to the favorable results in some rare cancers, such as bone and soft tissue sarcomas. The panel recommended prioritization of shortening the fractionation schedules, reducing the size and cost of the technology and equipment, and research on improving patient throughput, including the use of a rotating gantry.[15] Prior to the recommendation of the panel, the QST attempted to shorten the treatment period even for cancers at the kidney and prostate. Moreover, the QST is also working on the development of downsized facilities, scanning irradiation and a rotating gantry in collaboration with accelerator vendors in Japan. In fact, a rotating gantry with scanning irradiation of carbon-ion beams became available in a new treatment facility of the QST in 2017, which would be advantageous for the treatment of many cancers close to the radiosensitive organs.

Physical properties of carbon-ion beams

Energetic charged particles deliver the irradiation doses to matter via the electromagnetic interactions causing ionization energy loss in a stopping process. The stopping power, known as the theoretical mean value of the LET, increases with depth by inverse speed squared and reaches a maximum at a range to form the Bragg peak in depth–dose distribution.[16] The dosimetric properties of charged-particle beams are essentially governed by the electric charge and mass of the particles. As shown in Table 1, a proton has a positive elementary charge (e) and is approximately 1840 times bigger than an electron. A carbon ion has six elementary charges and is approximately 11.9 times bigger than the proton. For charged particles traversing at a certain speed, the kinetic energy is proportional to the mass, the stopping power is proportional to the charge squared, and scattering angles are proportional to the charge/mass ratio. A low charge/mass ratio means carbon ions travel in a straighter trajectory through matter, which is desirable for targeting tumor but, at the same time, renders it difficult to bend the path of the ions magnetically in the accelerator systems. In addition, the carbon-ion range is approximately one-third the proton range at the same speed, such that carbon ions must be accelerated faster than protons to obtain the range required for tumor treatment.

A fully stripped accelerated carbon ion, or a carbon-12 nucleus, is a composite of six protons and six neutrons and may incidentally fragment into lighter nuclei via nuclear interactions as it penetrates through matter.[17] For example, of 290 MeV/nucleon carbon ions, approximately 50% will fragment before reaching the 16 cm depth in water. The loss of carbon ions by fragmentation lowers the Bragg peak, and the resulting fragments display a long tail in the depth–dose distribution curve. That is a major disadvantage of carbon ions, especially for the treatment of deep-seated tumors.

TABLE 1 Particle mass and charge for common therapeutic radiations

Particle type	Symbol	Mass	Charge	Composition
Photon	γ	0	0	Elementary
Electron	e^-	0.511	−1	Elementary
Proton	p	938.3	+1	$u\ u\ d$ (quarks)
Neutron	n	939.6	0	$u\ d\ d$ (quarks)
Carbon-ion	$^{12}C^{6+}$	11 175	+6	$6\ p + 6\ n$

In a modern CIRT systems, carbon ions accelerated at a designated variable energy are delivered to cancer patients in the form of a pencil beam typically 5 mm in both diameter and Bragg peak size to form a local high-dose spot area, which is scanned sequentially over a target volume.[18] The beam delivery sequence is designed using a treatment planning system to achieve an optimal dose distribution in the patient, whose physical structure has been modeled numerically by CT imaging. As explained in the following section, the high-LET nature of carbon-ion beams effectively enhances the radiation dose to cells, especially at the Bragg peak. The enhancement factor, or the RBE, is considered in the dose optimization algorithms of treatment planning systems to prescribe curative doses. For all positions, the number of carbon ions to be delivered is optimized to form a SOBP of a uniform RBE-weighted dose covering the tumor, as shown in Figure 2.[19]

Biological properties of carbon-ion beams

Charged particle beams of protons and carbon ions offer a more localized dose distribution to a tumor compare with conventional photons and electrons due to their intrinsic physical properties such as an advantageous depth-dose profile known as the Bragg peak and little lateral scattering.[20] In addition, the high-LET nature of carbon ions provides the advantageous radiobiological properties compare with those of photons, electrons, and protons, such as an increasing RBE toward the Bragg peak, a reduced oxygen enhancement ratio, and a reduced dependence on fractionation and cell-cycle stage.[21] Furthermore, favorable responses have been reported for high-LET carbon ions such as an increased immune response and reduced angiogenesis and metastatic potential.[22] These physical and radiobiological properties make carbon ions attractive for treating radioresistant tumors.

What causes the differences in radiobiological effects of radiations? The radiobiological effects following energy transfer by radiation proceed in the following steps: *physical processes* ($<10^{-15}$ s) including ionization, excitation, and transportation of secondary electrons, *chemical processes* ($<10^{-3}$ s) including dissociation of excited/ionized molecules, diffusion and reaction of generated radical species, and *biological processes* ($<10^{9}$ s) including all subsequent processes such as enzymatic repair, cellular and tissue responses, mutations, and carcinogenesis. Figure 3 shows the spatial dose distributions on a microscopic scale delivered via the physical processes pertaining to the same 1-Gy macroscopic dose exposures to radiation with different LET values; 100-keV electrons with a LET of 0.5 keV/μm, 270 and 15 MeV/u carbon ions with LETs of 13 and 118 keV/μm, respectively.[23] The diameter of the circle in each panel is 10 μm (approximately the size of a cell nucleus). The 100-keV electrons (right figure) yield an almost homogeneous microscopic dose distribution within the cell nucleus, inducing simple DNA

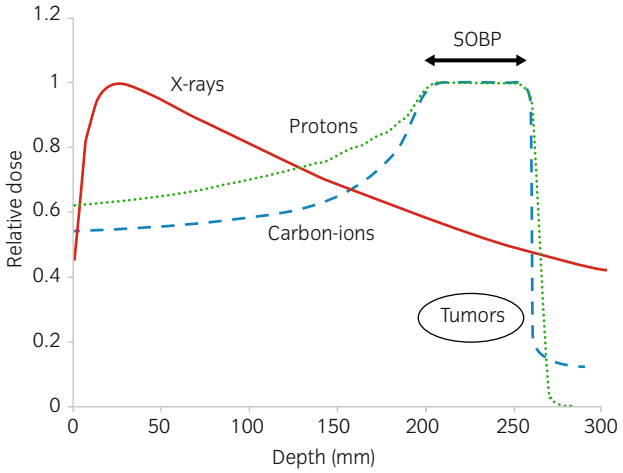

FIGURE 2 A schema of treatment doses for X-ray, proton, and carbon-ion beams, where the proton and carbon-ion beams are optimized to cover a tumor with SOBP. Reprinted from Figure 1 of a reference reported by Ishikawa et al.[19] © 2019 The Authors

damage that is easy to repair. In contrast, stopping carbon ions with a high LET (left figure) causes track cores with high local doses exceeding 10 Gy, inducing clustered DNA damages around the track cores that are difficult to repair. It should be noted that 270 MeV/u carbon ions (middle figure) show reduced local doses at track cores causing reduced DNA damages, compared with stopping carbon ions. Thus, the difference in the microscopic dose distributions delivered in the initial physical processes at the atomic or molecular level may lead to the differences in radiobiological effects at the cellular, organ, and eventually systemic levels after radiation exposure, resulting in the advantageous radiobiological properties of carbon ions.

To effectively use the advantageous physical and radiobiological properties of carbon ions in cancer treatments, a clinically relevant dose, defined as the product of the physical dose and the clinical RBE, must be calculated for treatment planning systems. The RBE of heavy ions depends on various physical and biological parameters, including LET, ion species, dose level, type of tissue or cell, oxygen conditions, and endpoint of interest. For practicality, the survival of human salivary gland tumor cells under aerobic conditions was selected as the endpoint of the RBE definition in Japan.[24,25] The LET and ion-species dependencies were accounted for by taking the specific energy z absorbed by a microscopic subcellular structure 'domain' for expressing the RBE of heavy ions, as the quantity directly relates to ionizing densities in microscopic sites.[26,27] In CIRT planning, the spatial distribution of z in patients is calculated for the therapeutic carbon-ion beam, and the uniform clinical dose distribution is designed throughout the tumor volume using dose-optimization algorithms. Since the RBE of therapeutic carbon-ion beams varies along the SOBP, a uniform clinical dose in the tumor results in a varying physical dose along the SOBP, as shown in Figure 4.

CLINICAL OUTCOMES OF CARBON-ION THERAPY FOR UROLOGICAL CANCERS

Prostate cancer

Since 1995, CIRT for prostate cancer has been provided to more than 4100 prostate cancer patients as of November 2021 (Table 2).[1,28] In the initial study (protocol 9402), 35 patients with histologically confirmed adenocarcinoma of the prostate were enrolled through December 1997, and the dose was escalated from 54 Gy (RBE) to 72 Gy (RBE) in 20 fractions.[28] In the study, patients with T2b–T3N0M0 were eligible. In addition, patients who underwent staging pelvic lymphadenectomy and were diagnosed as pN1 (single and non-fixed lymph node metastasis) were also eligible as T2b–T3pN1M0 prostate cancer. On the other hand, Gleason scores and initial PSA values were not restricted to the eligibility in

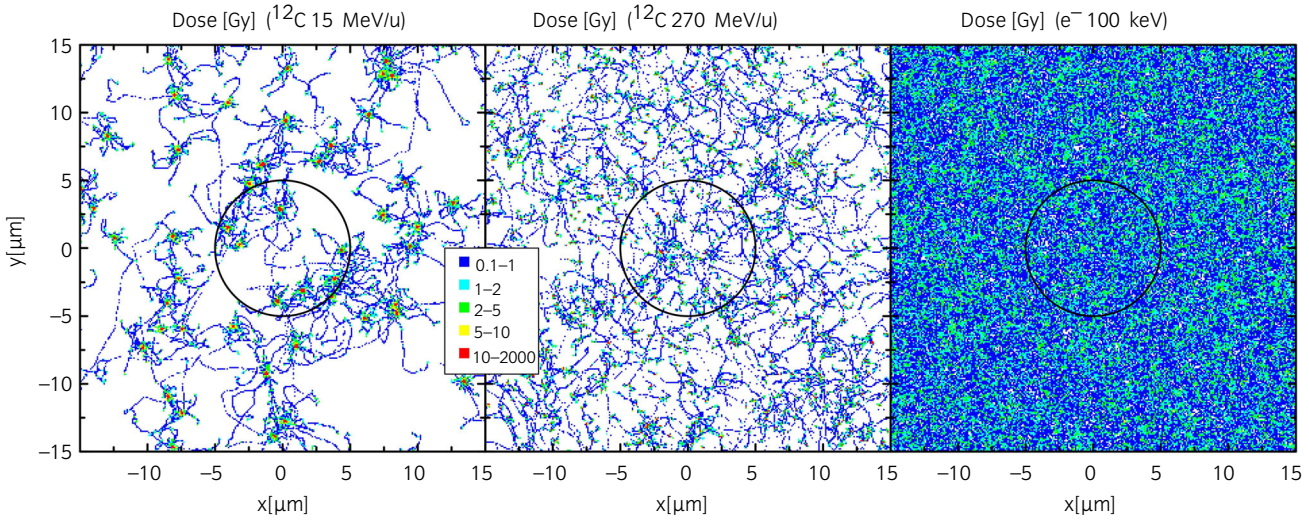

FIGURE 3 Microscopic spatial dose distributions pertaining to the irradiations delivering the same macroscopic dose of 1 Gy: 15 MeV/u stopping carbon ions with LET of 13 keV/μm (left), 270 MeV/u high-energetic carbon ions with LET of 118 keV/μm (middle), and 100 keV electrons with a LET of 0.5 keV/μm (right). The diameter of the circle in each panel is 10 μm. Reprinted from Figure 2 of a reference reported by Krämer et al.[23] © 2012 The Authors and IOP Publishing

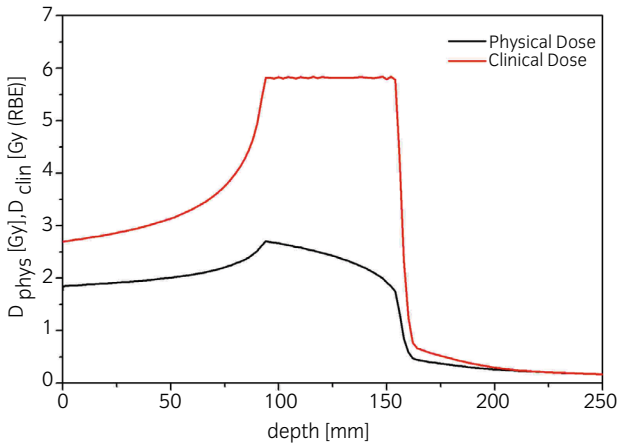

FIGURE 4 Physical (black) and clinical dose distribution (red) of therapeutic carbon-ion beams for a tumor volume located at 94–154 mm depth. The uniform clinical dose of 5.8 Gy (RBE) was designed at the tumor volume

all studies at our institute. That study established the tolerable dose to the rectum and the basic methodology for CIRT for prostate cancer. The second study (protocol 9703) was initiated in January 1998, and T1b–T2aN0M0, T1b–T3pN0M0 prostate cancer was treated with CIRT alone, while T2b–T3bN0M0 or T2b–T3pN1M0 prostate cancer was treated with CIRT combined with ADT. A total of 97 patients were enrolled in these studies and a recommended dose of 66.0 Gy (RBE) was determined for both locally advanced and early-stage tumors.[28,29]

Based on these results, a phase II study (protocol 9904) was started in April 2000 to validate the feasibility and efficacy of CIRT using the shrinking field technique and the recommended dose fractionation (66.0 Gy (RBE) in 20 fractions over 5 weeks) determined from the phase I/II studies.[30] In that study, patients were divided into two groups according to their risk classification, such as T stage, initial prostate specific antigen level, and Gleason score. Patients were eligible if their tumors were histologically confirmed as adenocarcinoma of the prostate and staged as T1b–T3N0M0,0 and patients with pN0 or a solitary and non-fixed regional lymph node metastasis (pN1) were also eligible as T1b-3pN0-1 M0. On the other hand, exclusion criteria of the study were the history of pelvic RT or other treatments for prostate cancer, performance status of 3–4, and presence of concurrent active malignancies. A total of 176 patients were enrolled, and local control was achieved in all but one patient. The 4-year bRF rate was 87%, and grade 2 GU and GI events were observed in only 2% and 5% of patients, respectively without grade 3 or higher morbidities.[30]

After the phase II study, a lower dose of 63.0 Gy (RBE) in 20 fractions was successfully evaluated for the purpose of reducing late toxicities. Consequently, the appropriate treatment technique and recommended dose in 20-fraction CIRT was established and confirmed around 2006.[30] The results of the phase II trial also suggested dividing the high-risk group into two subgroups: intermediate-risk and true high-risk groups. It was also recommended that true high-risk patients should undergo combined treatment with CIRT and long-term ADT, whereas CIRT combined with a short course of neoadjuvant and concurrent ADT should be applied to patients in the intermediate-risk group. Hereby, a treatment strategy of the 20-fraction CIRT according to the risk factors was established.[30,31] Furthermore, studies including various patient backgrounds and treatment factors relates to reduced GU and GI disorders found that anticoagulation and high rectal doses increased the risk of rectal bleeding, and that prolonged ADT worsened GU symptoms.[30,31]

At an α/β ratio of 1.5 Gy for prostate cancer, 63 Gy (RBE) in 20 fractions is equivalent to 83.7 Gy in 2 Gy

TABLE 2 Clinical outcomes of high-dose RT for prostate cancer

				5-year bRF (%)			Late toxicity (%)	
Author (year)	No. of patients	Total dose	Fractions (Gy)	Low-risk	Intermediate-risk	High-risk	GI	GU
IMRT								
Kupelian[37] (2007)	770	70	28	94	83	72	6	7
Cahlon[38] (2008)	478	86.4	48	98	85	70	7	16
Guckenberger[39] (2014)	150	73.9–76.2	32–33	88	80	78	4.8	22.4
Leing[40] (2017)	123	60–66	20–22	100	56–89	56	7.3	12.2
Shimizu[41] (2017)	138	72.6–74.8	33–34	95	92	77	10.9	7.2
SBRT								
King[42] (2013)	1100	35–40	5	95	84	81	NA	NA
Fuller[43] (2018)	259	38	4	100	81–90	NA	3.4	14.7
Vuolukka[44] (2020)	213	36.25	5	100	87.5	80	NA	NA
PBT								
Bryant[45] (2016)	1327	72–82	36–41	99	94	74	0.6‡	2.9‡
Iwata[46] (2018)	1291	70–80/63–66	35–40/21–22	97†	91†	83†	4.1	4.0
Takagi[47] (2020)	2021	74	37	99–100	90–93	76–88	4.0	2.2
CIRT								
Ishikawa[1] (2012)	927	63–66/57.6	20/16	90	97	88	1.9	6.3
Nomiya[36] (2016)	2157	63–66/57.6/51.6	20/16/12	92†	89†	92†	0.4	4.6

†Biochemical relapse-free survival. ‡Grade 3.

fraction. Further hypofractionation was attempted since it was expected to be beneficial for prostate cancer considering the characteristics of carbon-ion beams and prostate cancer. CIRT of 57.6 Gy (RBE) in 16 fractions, which was estimated to be almost equivalent to 63.0 Gy (RBE) in 20 fractions, was applied to a portion of patients in 2003 and then expanded to all patients in 2007.[32] The 5-year bRF rate of patients treated with 16-fraction CIRT was 88.5% and was comparable with that of 20-fraction CIRT (90.2%). The incidence of grade 2 GU toxicities was lower with 16-fraction than 20-fraction CIRT.[32] Thus, the 57.6 Gy (RBE) in 16 fractions was more suitable for prostate cancer compared with the recommended dose of 63.0 Gy (RBE) in 20 fractions. Based on the success with further hypofractionation from 20 to 16 fractions, a new clinical trial of hypofractionated CIRT (protocol 1002) was planned in 2010.[33] This protocol used a total dose of 51.6 Gy (RBE) in 12 fractions, which has been used as the standard dose fractionation in subsequent protocols. Patients who met all the following conditions were included in the study: histologically diagnosed prostate adenocarcinoma, without any previous surgery or radiotherapy for prostate cancer, and T1b–T3bN0M0. The bRF rate in that study was comparable with those in the 20-fraction and 16-fraction protocols, and the 5-year rates of grade 2 late GI and GU toxicities were 0.4% and 6.3%, respectively. Regarding the irradiation technique, the CIRT beam delivery method was changed from passive to scanning in 2012, which further improved the dose distribution of CIRT for prostate cancer (Figure 5).[34,35] Since October 2018, we have started 4-fraction CIRT with the aim of further ultra-hypofractionation (protocol 1891, UMIN000032340). This trial consists of starting with a total dose of 36 Gy (RBE) and then increasing the dose, while confirming no severe toxicities, until eventually reaching 44 Gy (RBE). A total of 60 patients were enrolled by October 2020, and we are currently in the post-treatment follow-up stage.

The numbers of CIRT facilities and patients treated with CIRT were gradually increasing in Japan (Figure 6). With these increases, there is a growing momentum for clinical research using CIRT among other facilities. In the field of prostate cancer, the Gunma University Heavy Ion Medical Center and Ion Beam Therapy Center, SAGA HIMAT Foundation participated in a multi-institutional prospective study in addition to NIRS (J-CROS1501PR). The study enrolled 2157 patients treated with CIRT for prostate cancer.[36] The 5-year bRF survival rates of the low-, intermediate-, and high-risk groups were 92%, 89%, and 92%, respectively. The results of late adverse events were also favorable, and the incidences of grade 2 GU and GI toxicities were 4.6% and 0.4%, respectively, and there were no grade 3 or higher GU/GI toxicities. Table 2 summarizes clinical outcomes of IMRT, SBRT, PBT, and CIRT for prostate cancer,[1,36–47] and the bRF of the high-risk prostate cancer patients and the incidence of GI toxicity after CIRT were relatively better than those after other modalities.[1,36–47]

Since the treatment outcomes for prostate cancer have improved, researchers have paid more attention to treatment-related changes in QOL. We initially investigated 150 patients after CIRT using the self-administered FACT-P questionnaire and found that the change in HRQOL from before to after CIRT was minimal.[48] Updated data after long-term follow up obtained from 417 patients confirmed the minimal changes in HRQOL after 60 months and revealed that the use of ADT, presence of adverse events, and biochemical failure were related to lower scores.[49] Comparisons of adverse events and QOL between PBT and IMRT have also been conducted, with several studies reporting higher rates of acute GU adverse events in the IMRT group.[50,51] No difference in adverse events or post-treatment change in QOL between CIRT and PBT was observed in a prospective randomized trial,[52] and based on these favorable outcomes, particle therapy for prostate cancer became covered by the national health insurance in Japan from April 2018.[19]

Renal cell carcinoma

In Japan, the incidence of renal cancer has been increasing, with approximately 30 000 new diagnoses and over 9000 deaths in 2018.[53] RCC accounts for the majority of renal cancers, and the standard of care for patients with localized RCC is surgery to remove the tumor, by either partial or radical nephrectomy.[54] However, RCC predominantly affects the

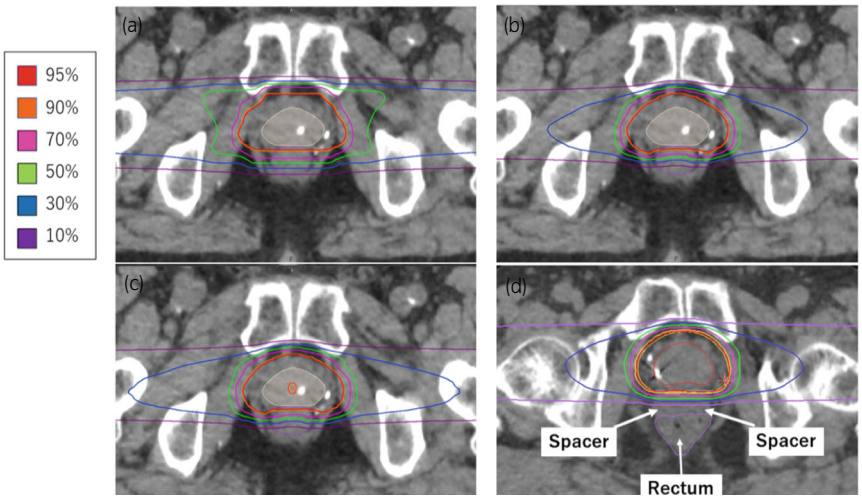

FIGURE 5 Difference in dose distributions of CIRT for prostate cancer. Compared with using passive scattering beams (a), irradiated doses and volumes at the rectum and bone can be reduced using spot scanning beams (b). In the prospective study for ultra-hypofractionated CIRT, the urethra doses are constrained using the inverse treatment planning method (c). The rectal dose can be also much reduced using a commercial rectal spacer (d)

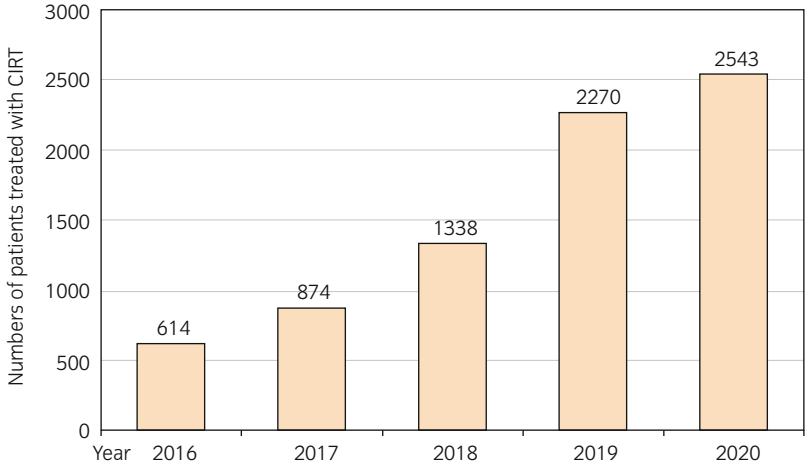

FIGURE 6 Trends in the numbers of CIRT institutes and treated patients with prostate cancer

older population, and some patients have contraindications to surgery due to comorbidities, while others refuse to undergo surgery. Both RFA and cryoablation may be offered as treatment options, but they have limited effects in some patients depending on tumor size and location and require access to the kidney via percutaneous or laparoscopic approaches.[55,56] Furthermore, both techniques may encounter issues in patients taking continuous anticoagulative medications.

RT is another non-surgical treatment option, but normal tissues surrounding the tumor are radiosensitive in addition to the kidney. Furthermore, RCC as well as prostate cancer may be radioresistant to standard fractionation, and such tumors theoretically benefits from dose escalation with hypofractionation using a large fractional dose, because the estimated α/β ratio of RCC is lower than those of other tumors based on the linear-quadratic model.[4] Therefore, in the last decade, SBRT using photons has been performed in RCC patients with contraindications for surgery, RFA, or cryoablation,[57] and the usefulness of SBRT in small-sized tumors is well confirmed. As with SBRT for stage I non-small cell lung cancer,[58] the normal tissues surrounding the kidney irradiated with a low- to intermediate-dose of SBRT will increase with increasing tumor diameter. To control the radioresistant tumors by hypofractionated RT without increasing the rate of late adverse effects such as GI bleeding and chronic renal dysfunction, CIRT for RCC has been started as a pilot study using 16 fractions at our institute.[2]

The first report to analyze the initial experience with CIRT involved 10 RCC patients (seven with stage I and three with stage IV).[2] The patients received a total dose of 64–80 Gy (RBE) in 16 fractions over 4 weeks with a fractional dose of 4, 4.5, or 5.0 Gy (RBE).[2] After a median follow-up of 57 months for the eight surviving patients, the 5-year rates of local control and overall survival were 100% and 74%, respectively, and no cases of cancer recurrence was observed at the last follow-up. In addition, one patient had complete response, including the disappearance of tumor; six patients had partial response with ≥50% decrease in tumor volume; and three patients had stable disease with either ≤50% decrease or ≤25% increase in tumor volume. Furthermore, there was no case of grade 2 or more severe GI bleeding. These results were confirmed by long-term follow-up, which indicated no grade 3 renal dysfunction in the patients without chronic kidney disease after CIRT.[59] Regarding a change in tumor size, imaging studies showed that the tumors transiently increased for several months after CIRT but were gradually shrunk thereafter (Figure 7). Therefore, the patients were carefully examined during the follow-up to avoid interpretation of local failure.

In April 2013, a phase I/II study of CIRT was initiated to establish 12-fraction CIRT for RCC and to investigate the rates of acute and late adverse effects, local control rate, and survival.[7] Five patients received 66 Gy (RBE) without any dose-limiting toxicity, and thus the dose was escalated to 72 Gy (RBE) for the next three patients. Although the trial was censored in March 2017 because of poor patient accrual, grade 2 or severe late adverse effects outside of the kidney were not observed. After a median follow-up of 50 months, the average decrease in the eGFR, reflecting renal function, was 10.8 ml/min/1.73 m^2. Three patients had partial response and the remaining five patients had stable disease according to the modified response evaluation criteria in solid tumors,[60] and all tumors were locally controlled at the last follow-up.

Table 3 summarizes the treatment outcomes of RCC according to RT modality.[7,59,61–66] Although studies of particle beam therapy using protons and carbon ions included relatively higher populations of advanced tumor cases compared with the SBRT series, no severe GI toxicities was observed. Furthermore, the average decrease in the eGFR rate after CIRT was comparable with that after SBRT for small-sized tumors. At our institute, a new phase I/II study for 4-fraction treatment of CIRT within a week has been ongoing since 2017. Study registration was completed successfully, and follow-up is ongoing for all 10 eligible patients. In the near future, the optimal fractionation schedule for 4-fraction CIRT will be determined, and CIRT and PBT may be the standard for treating inoperable patients with large (>4 cm) tumors.

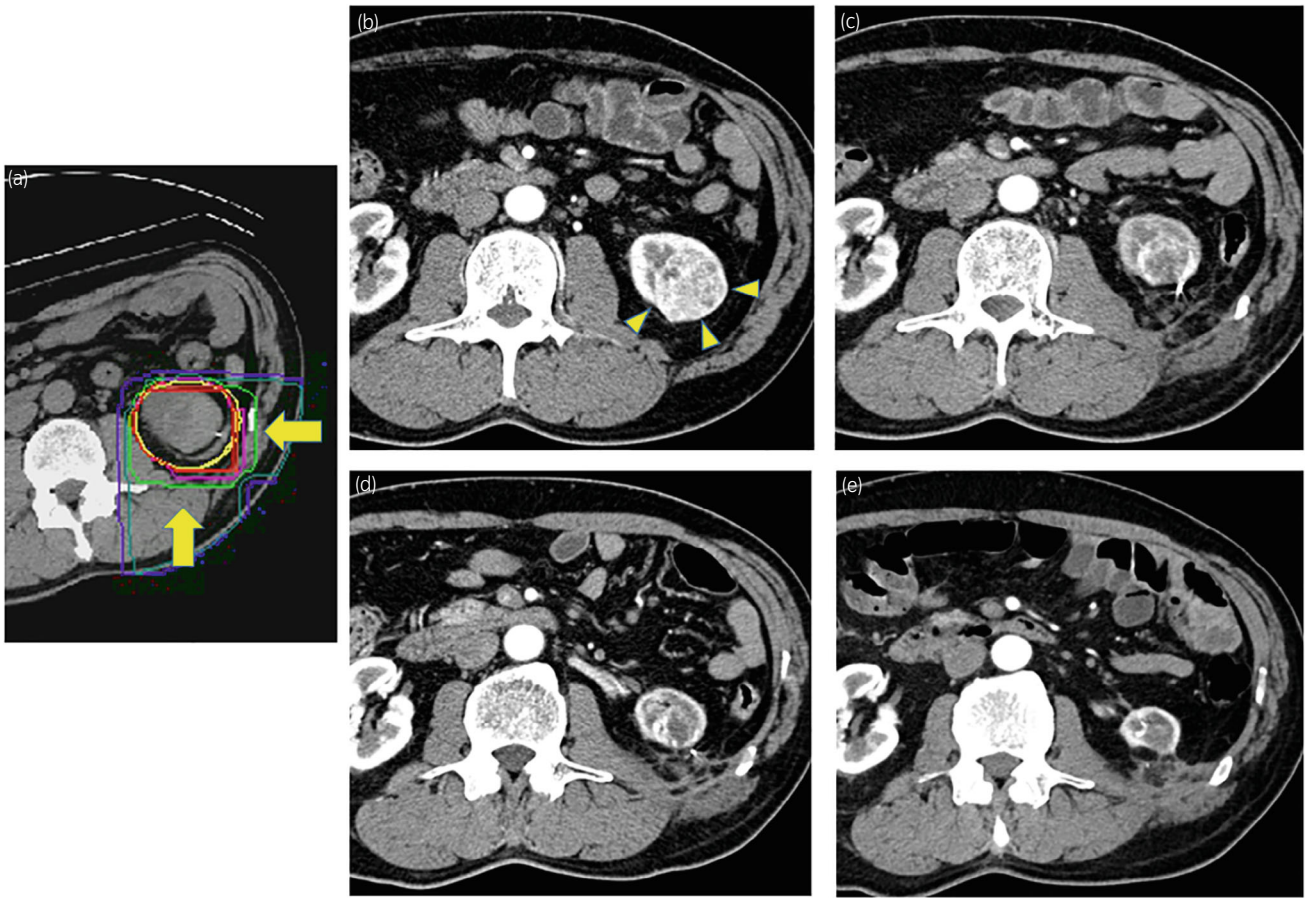

FIGURE 7 A representative RCC case after CIRT. Dose distribution of CIRT (a), and changes in a tumor on CT images at before (b) and 1 (c), 3 (d), and 10 (e) years after CIRT

Retroperitoneal sarcoma

RPSs are rare malignancies accounting for 1–2% of solid malignancies, and 10–20% of all sarcomas are originated from the retroperitoneum.[67] RPSs frequently occur in the 5th decade of life,[68] and liposarcoma and leiomyosarcoma are common among the many subtypes.[69] The mainstay of treatment for RPSs is surgery, and 70% of patients underwent surgical resection. However, complete resection cannot be sometimes achieved due to the structural complexity of the retroperitoneum and large tumor size, and RT was performed for 25% of patients with RPSs, combined with surgery.[70] On the other hand, the published data of phase I and II trials and retrospective trials were not enough to make the effectiveness of perioperative RT clear.[71,72] A multicenter randomized phase III study (STRASS: EORTC-62092) was conducted to evaluate the efficacy of perioperative RT, but the 3-year abdominal-free survival rates in the surgery group and surgery plus perioperative RT group were 58.7% and 60.4%, respectively.[71]

CIRT has been applied to unresectable gross RPSs at NIRS since 1997.[5] The eligibility is that tumor is not widely attached to the intestines and the tumor size is within 20 cm. The irradiated dose was set to be 70.4 Gy (RBE) in 16 fractions over four weeks. Recently, the outcomes of 50 RPSs treated with CIRT were updated, and the 3-year rate of overall survival was 60%, which is almost equal to that after surgery for operable patients.[71,72] In addition, Grade 3 or severe adverse events were observed only in 8% of the patients. Although the reported analysis was retrospective data, CIRT may be an option for unresectable gross RPSs (Figure 8).

FUTURE PROSPECT

As new approaches to improve the clinical outcomes of CIRT for prostate cancer and RCC, image-guided and real-time tumor tracking RT using fiducial markers in the prostate and kidney are currently available. Furthermore, the dose to the urethra using inverse treatment planning with carbon ions (Figure 5c) and the dose to the rectum using SpaceOAR injections (Boston Scientific Corp., Marlborough, MA, USA; Figure 5d) can be reduced to improve the incidence of adverse events after prostate cancer treatment. In addition, a kind of bioabsorbable spacer sheet to make a distance between tumors and intestines was approved by the Japanese public insurance in 2019.[9] The spacer sheets will significantly assist the safety and effectiveness of CIRT for RCC and RPSs.

QST is now developing a compact equipment called "Quantum Scalpel" (Figure 9), which can deliver not only

TABLE 3 Clinical outcomes of RCC according to RT methods

Author (year)	Study	No. of patients		Size	Age (years)	Follow-up	OS (%)	LC (%)	eGFR	GI toxicity
		All	Non-T1	(mm)		(months)			(ml/min/1.73 m^2)	(≥grade 3)
X-ray (SBRT)										
Ponsky[61] (2015)	Prospective	19	NA	57.9 cm^3	77†	13†	72 (3y)	100 (3y)	NA	10.5%
Siva[62] (2017)	Prospective	37	2.7%	48†	78†	24†	92 (2y)	100 (2y)	−11.0 (2y)	3.0%
Siva[63] (2018)	Retrospective	223	NA	43‡	72‡	NA	82/71 (2/4y)	98/98 (2/4y)	−5.5 (3.6y)	1.3%
Funayama[64] (2019)	Prospective	13	0%	19†	72†	48.3†	92/71 (2/3y)	92/92 (2/3y)	−16.3 (2y§)	0%
Peddada[65] (2019)	Prospective	21	4.8%	29†	71†	78†	88 (5y)	100 (5y)	−6.8	0%
PBT										
Fukumitsu[66] (2020)	Retrospective	22	9.1%	35†	67†	37†	95 (3y)	100 (3y)	−7.2 (3y§)	0%
CIRT										
Kasuya[59] (2018)	Retrospective	19	15.8%	36†	67†	79†	89 (5y)	94 (5y)	−6.1	0%
Kasuya[8] (2019)	Prospective	8	12.5%	43†	69†	50†	88 (3y)	100 (3y)	−10.8	0%

†Median, ‡mean, §estimated.

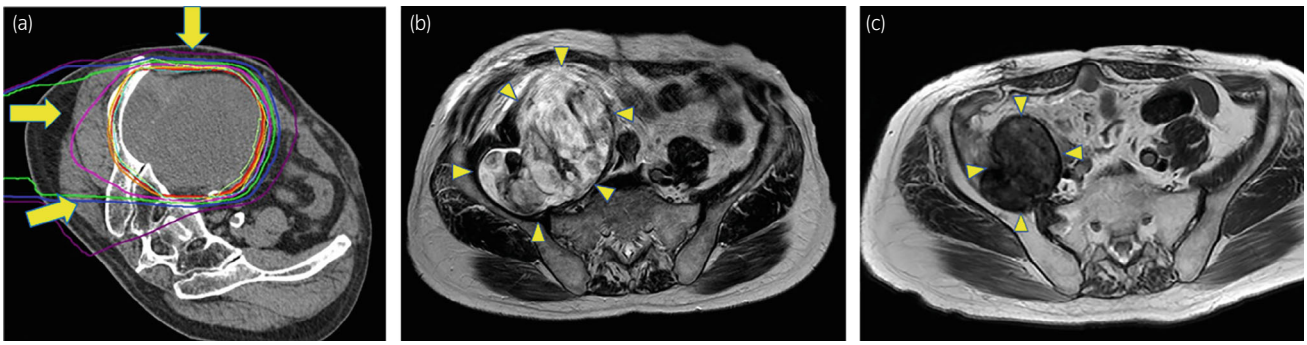

FIGURE 8 A large retroperitoneal sarcoma (13.6 × 11.5 cm) of a 78-year-old male treated with CIRT at a total irradiation dose of 70.4 Gy (RBE) in 16 fractions (a). The red, pink, green, blue lines indicated 97, 70, 50, 30% of the total dose. The tumor located in the right pelvic retroperitoneum (b), and it has gradually shrunk and the tumor size was 7.5 × 5.9 cm at 2 years after CIRT (c)

carbon-ion beams but also helium-ion, oxygen-ion, and neon-ion beams to radioresistant tumors including prostate cancer and RCC. A clinical study of CIRT using a mixture of several ion types for non-squamous cell head and neck carcinomas was initiated in September 2020, and new studies for CIRT of pancreas cancer, prostate cancer, and RCC will be started in the near future. The injector length is about 5 m using a laser-driven ion accelerator and the size of the synchrotron in the Quantum Scalpel is 7 m in diameter, of which the footprint is $1/40^{th}$ that of the HIMAC at QST and $1/10^{th}$ that of conventional equipment installed at other Japanese institutes. We will begin construction of the superconducting synchrotron prototype at QST in Chiba. The rotating gantry will be 7 m in size using the new superconducting technology, and CIRT will become a more attractive treatment due to significantly reduced construction and running costs and the equipment size.

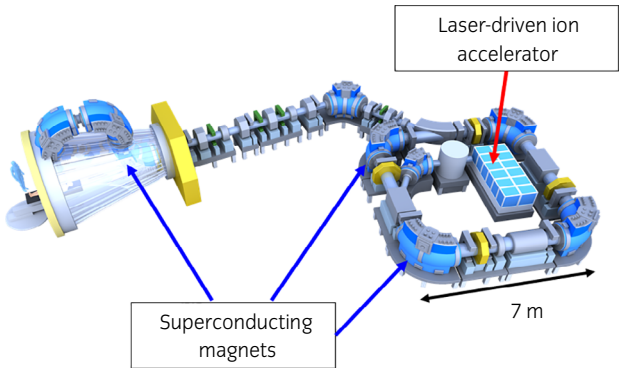

FIGURE 9 Schematic perspective view of Quantum Scalpel

CONCLUSION

In conclusion, the evidence that CIRT is feasible and effective for many types of cancers including prostate cancer and RCC is accumulating, but Japanese health insurance covers CIRT only for limited diseases such as prostate cancer, unresectable sarcomas, and head and neck cancers. Theoretically, carbon ions are high-LET charged particles that contribute to improving local control and reducing the toxicity because local failure and treatment-related toxicities occur in a dose-dependent manner. To reduce the cost of CIRT construction and broaden the use of CIRT as a cancer treatment, we are developing a new

compact-sized equipment using several heavy ion types and are continuing clinical trials and a registry of all treated patients via the J-CROS. If the national health insurance covers CIRT for many types of cancers including RCC, randomized trials comparing CIRT with other cancer therapies including photon-based RT are feasible, to support CIRT as a representative therapy for urological cancers.

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AUTHOR CONTRIBUTIONS

Hitoshi Ishikawa: Conceptualization; data curation; funding acquisition; methodology; visualization; writing – original draft. Yuichi Hiroshima: Data curation; writing – original draft. Nobuyuki Kanematsu: Visualization; writing – original draft. Taku Inaniwa: Visualization; writing – original draft. Toshiyuki Shirai: Data curation; visualization. Reiko Imai: Resources; writing – original draft. Hiroyoshi Suzuki: Validation; writing – review and editing. Koichiro Akakura: Validation; writing – review and editing. Masaru Wakatsuki: Data curation; writing – review and editing. Tomohiko Ichikawa: Project administration; writing – review and editing. Hiroshi Tsuji: Project administration; supervision.

CONFLICT OF INTEREST

Nobuyuki Kanematsu and Taku Inaniwa have received their share of royalties for patents and other intellectual properties for the carbon-ion radiotherapy equipment from Accelerator Engineering Corporation, Mitsubishi Electric Corporation, Toshiba Corporation, Elekta AB, RaySearch Laboratories AB, and Hitachi Ltd, but these royalties are unrelated to the current work. The other authors declare no conflict of interest for this article.

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