Review

Clinical indications and future directions of carbon-ion radiotherapy: a narrative review

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Abstract

Carbon-ion radiotherapy (CIRT) offers superior dose distributions and greater biological effectiveness than conventional photon-based radiotherapy (RT). Due to its higher linear energy transfer and relative biological effectiveness, CIRT is particularly effective against radioresistant tumors and those located near critical organs. Since the first dedicated CIRT facility was established in Japan in 1994, CIRT has demonstrated remarkable efficacy against various malignancies, including head and neck tumors, skull base and upper cervical spine tumors, non-small-cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), pancreatic cancer, prostate cancer, and bone and soft tissue sarcomas. This narrative review provides a comprehensive overview of the current status of CIRT, highlighting its clinical indications and future directions. According to clinical studies, CIRT achieves high local control rates with manageable toxicity across multiple cancer types. For instance, in head and neck tumors (e.g., adenoid cystic carcinoma and mucosal melanoma), CIRT has achieved local control rates exceeding 80%. In early-stage NSCLC, CIRT has resulted in local control rates over 90% with minimal toxicity. Moreover, CIRT has shown promise in treating challenging cases of HCC and pancreatic cancer, where conventional therapies are limited. Nonetheless, the global adoption of CIRT remains limited due to high costs and complexity. Future directions include conducting randomized controlled trials to establish high-level evidence, integrating new technologies such as ultrahigh-dose-rate (FLASH) therapy, and expanding CIRT facilities globally with strategic planning and cost-effectiveness analyses. If these challenges are addressed, CIRT is poised to play a transformative role in cancer treatment, improving survival rates and the quality of life.

Keywords: Carbon-ion radiotherapy; Charged particle therapy; Bragg peak; review;

Radioresistant tumors

Introduction

Background

Radiotherapy (RT) has long been a cornerstone of cancer treatment. It employs ionizing radiation to damage the DNA in tumor cells, initiating a series of biochemical reactions that result in cell death. Among the various types of ionizing radiation, X-rays and gamma rays are most commonly used, with X-ray therapy being the standard in clinical settings. Despite its prevalent use, X-ray therapy faces significant challenges, particularly in avoiding damage to healthy tissues near the tumor, especially when these tissues are close to vital organs. These challenges have spurred the development of alternative RT methods that offer more favorable dose distributions and improved biological effects.

In recent years, charged particle beam therapy, often referred to as particle therapy, has become a significant advancement in the field of RT. This innovative method includes proton and carbon-ion radiotherapy (CIRT), offering substantial physical and biological advantages over traditional photon-based therapies. Notably, carbon ions have a higher linear energy transfer (LET) and relative biological effectiveness (RBE) than protons, enhancing their effectiveness in controlling tumors, particularly those that are radioresistant or situated near critical organs [1,2]. The establishment of the first dedicated CIRT facility in Japan in 1994 was a pivotal moment in the history of radiotherapy. This development was inspired by earlier research that recognized the therapeutic potential of high-LET radiation. Since then, CIRT has been successfully implemented in a limited number of countries, including China, Germany, Italy, Japan, and Korea, where it has shown remarkable efficacy in treating various malignancies. A recent meta-analysis also confirmed that CIRT is a safe and effective option for achieving local control (LC) in patients with solid tumors [3].

In Korea, the Yonsei Cancer Center has been at the forefront of adopting CIRT,

marking a significant milestone in the nation's medical advancement. The planning for the Heavy Ion Therapy Center at Yonsei Cancer Center began in 2013, leading to the establishment of Korea's first CIRT facility, which became operational in April 2023. This center is globally recognized for its state-of-the-art infrastructure, including the world's first configuration with a fixed beam and two superconducting gantries dedicated to CIRT. The Heavy Ion Therapy Center at the Yonsei Cancer Center represents a decade of meticulous planning and collaboration, with over 200 prostate cancer patients successfully treated by mid-2024. The center has expanded its treatment offerings to include CIRT for pancreatic, liver, and lung cancers starting in May 2024. The Yonsei Cancer Center's commitment to advancing CIRT not only enhances treatment options for Korean patients but also positions the center as a leading institution in the global CIRT community.

Despite the clear therapeutic benefits of CIRT, its global adoption remains limited primarily due to the high costs and complexity associated with establishing such facilities. However, the increasing number of CIRT centers and ongoing clinical research are expanding its applications and accessibility.

Objectives

This review aimed to provide a comprehensive overview of the current status of CIRT, encompassing its physical and biological characteristics, clinical indications, and future directions. By exploring the progress and potential of CIRT, this study sought to highlight its crucial role in advancing cancer treatment and the need for wider implementation of this advanced technology.

Ethics statement

As this study is a literature review, it did not require institutional review board approval or individual consent.

Head and neck tumors

Surgical resection is the primary treatment for head and neck malignancies. However, the complexity of this region often makes it challenging to achieve complete resection without significant morbidity. Consequently, RT is frequently used as either primary or adjuvant therapy. CIRT is particularly effective in these cases due to its superior dose distribution and enhanced biological efficacy. It enables precise targeting of the tumor while sparing radiosensitive structures such as the salivary glands, cranial nerves, and brainstem. CIRT has shown favorable outcomes, especially in treating radioresistant tumors like adenoid cystic carcinoma (ACC) and chordomas, achieving high LC rates with manageable toxicity. Although direct comparative studies with conventional treatments are limited, both CIRT and proton therapy have been successfully used as primary and postoperative treatments, either alone or in combination with photon therapy.

ACC in the head and neck poses significant treatment challenges due to its propensity for perineural invasion and involvement of the skull base, which complicates achieving complete surgical resection. CIRT has emerged as a promising treatment option for managing ACC, especially in patients with postoperative residual disease or unresectable tumors. An initial study [4] from the Heavy Ion Research Center (GSI) in Heidelberg reported 1- and 3-year LC rates of 80.8% and 64.6%, respectively, for patients treated with a combination of photon therapy and a CIRT boost, totaling 72 Gy(RBE). At the National Institute of Radiological Sciences (NIRS) in Japan, a dose-escalation trial identified the maximum tolerated dose as 70.2 Gy(RBE) in 18 fractions, resulting in a 5-year LC rate of 73% [5]. The

COSMIC trial, a phase II study in Heidelberg, reported a 3-year LC rate of 81.9% for ACC, with higher control rates observed in patients with residual disease post-resection [6]. Large-scale studies at the GSI [7] and NIRS [8] confirmed these findings, with 3- and 5-year LC rates of approximately 81% and 73%, respectively, and low incidence of severe toxicity. Additionally, a sub-analysis of a Japanese multicenter study (1402 HN) by the Japan Carbon-Ion Radiation Oncology Study Group (J-CROS) [9] reported 2- and 5-year LC rates of 88% and 68%, respectively. Meanwhile, the 2- and 5-year overall survival (OS) rates were 94% and 74%, respectively, with 15% of the patients experiencing grade 3 or higher toxicities, such as osteoradionecrosis and vision loss. These studies highlight the effectiveness of CIRT in managing ACC, particularly in challenging cases involving residual disease.

CIRT has also shown significant effectiveness in treating head and neck mucosal melanoma, a notably aggressive and radioresistant cancer. Various studies, including both prospective and retrospective analyses from institutions such as the NIRS [5,8], Hyogo Ion Beam Medical Center [10], National Centre for Oncological Hadrontherapy in Italy [11], Gunma University Heavy Ion Medical Center [12], and Heidelberg Ion Beam Therapy Center (HIT) in Germany [13], have documented the benefits of CIRT in this context. A multicenter retrospective study [14] in Japan, which included 260 patients with mucosal melanoma, reported a 2-year LC rate of 83.9% and an OS rate of 69.4%, with grade 3 or higher toxicities occurring in 19% of the patients. At the NIRS, dose adjustments over time, from 70.2 Gy(RBE) in 18 fractions to 57.6 Gy(RBE) in 16 fractions, resulted in a 5-year LC rate of 75% and an OS rate of 35% [5,8]. The HIT in Germany reported a 3-year LC rate of 58.3% and an OS rate of 16.2% for paranasal sinus melanoma [13], highlighting the challenges in treating this type of tumor. In cases of choroidal melanoma, NIRS reported a 5-year LC rate of 92.8% and an OS rate of 80.4%, although 31.6% of patients experienced neovascular glaucoma as a late toxicity [15,16]. These findings demonstrate the potential of CIRT to achieve high LC rates in

challenging melanoma cases, particularly in anatomically complex regions such as the head, neck, and choroid.

Skull base and upper cervical spine tumors

Several studies have demonstrated the effectiveness of CIRT in treating tumors located at the skull base and upper spine, particularly in patients with sarcoma where surgical resection is challenging or incomplete. A prospective study [17] involving 27 patients with unresected sarcomas of mixed histology reported a 3-year LC rate of 91.8% following CIRT administration at a dose of 70.4 Gy(RBE) in 16 fractions. However, 23.1% of these patients experienced late radiation-related complications of grade 3 or higher. Similarly, another prospective study [18] conducted at Gunma University included 10 patients with unresectable bone or soft tissue sarcomas at the skull base. These patients received CIRT at the same dosage and reported a 3-year LC rate of 72.9%. These studies underscore the potential of CIRT to achieve substantial LC in regions that are difficult to treat, although concerns about late toxicity remain unresolved.

Chordomas and chondrosarcomas of the skull base have been significant targets for charged-particle therapy due to their complex anatomical locations and the high radiation doses needed for effective treatment [19,20]. At HIT, a retrospective study [21] conducted in 155 patients with skull base chordomas treated with 60 Gy(RBE) in 20 fractions reported 5-year and 10-year LC rates of 72% and 54%, respectively. Another follow-up study [22] at HIT involving 111 patients treated with 66 Gy(RBE) in 22 fractions reported a 5-year LC rate of 65%. In Italy, a study carried out at the National Centre for Oncological Hadrontherapy reported a 5-year LC rate of 71% in 135 patients treated with 70.4 Gy(RBE) in 16 fractions for skull base chordoma [23]. For chondrosarcoma, German studies [24-26] demonstrated a 3-year LC rate of 96.2% and a 10-year LC rate of 88% in patients treated with 60 Gy(RBE) in 20

fractions, with a low incidence of severe toxicity. These findings underscore the efficacy of CIRT in managing these rare but challenging tumors, providing long-term control with an acceptable safety profile.

Non-small-cell lung cancer

RT is a crucial treatment modality for lung cancer and the second most common treatment in Korea [27]. CIRT has become a viable and effective treatment option for localized non-small-cell lung cancer (NSCLC), especially in patients who are not suitable candidates for surgery due to comorbidities or advanced age. Since its introduction for NSCLC in November 1994, CIRT has shown effectiveness in treating early-stage NSCLC, particularly in tumors located peripherally and in selected cases of central tumors. CIRT offers potential advantages over traditional treatments for patients who need to minimize radiation exposure to the lungs, such as those suffering from interstitial lung disease (ILD). Multiple studies have confirmed the efficacy of CIRT in improving LC with an acceptable toxicity profile (Table 1).

At the NIRS in Japan, several hypofractionation and dose-escalation studies explored the optimal dosing regimens for CIRT in stage I NSCLC. An initial dose of 59.4 Gy(RBE) in 18 fractions was progressively refined to 72 Gy(RBE) in nine fractions, 52.8 Gy(RBE) in four fractions, and even a single-fraction dose of 50 Gy(RBE). These studies [28-32] reported a 3-year OS rate of approximately 70%–80% and a 3-year LC rate exceeding 90% in patients with stage IA tumors, although the LC rate was lower in patients with stage IB tumors. The incidence of grade 2 or higher toxicity was less than 2%. Recent phase I/II Japanese studies [31] and other recent studies [33] have identified 50 Gy(RBE) as the optimal dose for dose-escalated, single-fraction CIRT, demonstrating its feasibility as a treatment option with high LC and low toxicity rates. In a Japanese multicenter study (J-CROS-LUNG) [34], 95 patients with

inoperable stage I NSCLC received CIRT using regimens such as 64–72 Gy(RBE) in 12–16 fractions, 54–64 Gy(RBE) in four fractions, and 50 Gy(RBE) in one fraction. This study reported a 3-year LC rate of 87.3%, an OS rate of 59.3%, and a 3-year cumulative incidence of grade 2 or higher radiation pneumonitis of 3.2%. A retrospective, single-institutional study [35] directly comparing CIRT and stereotactic body radiotherapy (SBRT) for early-stage NSCLC found that CIRT achieved significantly higher 3-year OS rates (80.1% vs. 71.6%) and LC rates (87.7% vs. 79.1%) than SBRT. Furthermore, a cost-effectiveness analysis at Gunma University [36] suggested that while CIRT is cost-effective for stage I NSCLC, careful resource management could enhance its economic viability. These outcomes highlight CIRT's potential to achieve high LC with low toxicity, particularly in patients with limited surgical options.

CIRT has shown promising results in treating locally advanced NSCLC (LA-NSCLC), despite the inherent challenges associated with this stage of the disease. In a phase I/II study [37] at NIRS involving 62 patients with stage IIA–IIIA NSCLC treated with CIRT at a dose of 76 Gy(RBE), the 2-year LC and OS rates were 93% and 52%, respectively. Notably, patients with N0 disease exhibited a 2-year LC rate of 100% and an OS rate of 69%, with cases pf no grade 3 or higher toxicity observed following treatment with 72 Gy(RBE). A retrospective study [38] of 141 patients with LA-NSCLC treated with a median dose of 72 Gy(RBE) in 16 fractions reported 2-year LC and OS rates of 80.3% and 58.7%, respectively. In a Japanese multicenter study [39] of patients with LA-NSCLC, the 2-year LC and OS rates were 81.8% and 62.2%, respectively, with no reported adverse effects higher than grade 2. Similarly, Anzai et al. [40] analyzed 65 patients with stage III NSCLC treated at NIRS with a median dose of 72 Gy(RBE), resulting in 2-year LC and OS rates of 74% and 55%, respectively. These studies suggest that CIRT, even without concurrent chemotherapy, may be a viable treatment option for patients with LA-NSCLC, achieving substantial LC and survival rates. However, further research is needed to clarify the role of CIRT in combination with systemic treatments, such as

chemotherapy or immunotherapy.

Treating NSCLC in patients with ILD presents significant challenges due to the risk of acute exacerbation. However, recent research indicates that proton therapy [41] or CIRT may be safe and effective options. A retrospective study [42] of 124 patients with stage I NSCLC, including 26 with ILD, found that although patients with ILD had a lower OS (59.7% vs. 83.2%), CIRT did not significantly increase the incidence of severe side effects. Additionally, a multi-institutional study [43] of 30 patients with ILD reported a 3-year LC rate of 88.1%, with only 3.3% experiencing grade 2 or higher radiation pneumonitis. These findings suggest that CIRT could be a viable treatment for early-stage NSCLC in patients with ILD.

Hepatocellular carcinoma

CIRT has demonstrated significant potential in treating hepatocellular carcinoma (HCC), proving effective not only in early-stage cases but also in more complex situations where alternative treatments are limited. It is particularly beneficial for patients with large tumors, tumors in difficult anatomical locations such as near the porta hepatis or major blood vessels, and for those with compromised liver function. In cases where surgical resection or photon therapy may present significant risks, CIRT offers a safer alternative. Moreover, CIRT is a viable treatment option for patients experiencing recurrent HCC following previous interventions like transarterial chemoembolization (TACE) or radiofrequency ablation (RFA), where it is critical to minimize additional liver damage.

In 2004, the NIRS conducted a prospective phase I trial [44] to explore the impact of increasing the dose from 49.5 Gy(RBE) to 79.5 Gy(RBE) in 15 fractions. The trial found no severe adverse effects and reported an 81% LC rate at both 3 and 5 years. Subsequent phase I

and II trials [45] established 52.8 Gy(RBE) in four fractions as the recommended dose, with no cases of dose-limiting toxicity. Gunma University reported a 92.3% LC rate at 2 years and 76.5% at 4 years using doses of 52.8 Gy(RBE) and 60 Gy(RBE) in four fractions, with only grade 3 hepatobiliary toxicity reported in two patients [46,47]. A multi-institutional retrospective study [48] conducted by the J-CROS Group in 174 patients with HCC treated with CIRT (48–60 Gy(RBE) in two to four fractions) reported a 3-year LC rate of 81.0% and a 3-year OS rate of 73.3%, with only a few patients experiencing grade 3 or higher acute or late toxicity. Recent studies have refined the dosing strategy, using two or four fractions for tumors distant from the gastrointestinal tract and 12 or more fractions for those closer to the gastrointestinal tract to minimize adverse effects [49-52].

The majority of existing literature on CIRT has focused primarily on its usage, with only a limited number of small retrospective studies comparing it to other treatment modalities. Shiba et al. [50] compared CIRT with TACE after propensity score matching. They found that CIRT led to significantly better 3-year OS (88% vs. 58%, $P<0.05$) and LC (80% vs. 26%, $P<0.01$) rates. Fujita et al. [53] compared the efficacy of CIRT and RFA in early-stage HCC in a study of 560 patients. CIRT was associated with significantly lower cumulative intrasubsegmental recurrence rates than RFA (2 years: 12.6% vs. 31.7%; 5 years: 15.5% vs. 49.6%), although the local recurrence, progression-free survival, and OS rates were similar between the groups. Notably, no grade 3 or higher adverse events were reported in the CIRT group, while 1.2% of the patients in the RFA group experienced grade 3 adverse events. Additionally, a comparative study by Komatsu et al. [54] reported similar outcomes between CIRT and proton beam therapy, with 5-year LC and OS rates of 93% and 36.3%, respectively, for CIRT.

CIRT has demonstrated significant potential in managing complex HCC cases, where

conventional RT may pose considerable risks. Studies have demonstrated that CIRT can effectively minimize radiation-induced liver disease while still achieving high LC rates, even in patients with compromised liver function or large tumors. Hiroshima et al. [55] reported a low incidence of grade 3 toxicity in patients with Child-Pugh B liver function treated with CIRT. Meanwhile, Tomizawa et al. [52] reported no grade 4 toxicity in patients who underwent re-irradiation with CIRT for intrahepatic HCC recurrence. Furthermore, CIRT has proven effective in treating HCC located near critical structures such as the caudate lobe and porta hepatis, maintaining high LC rates and reducing the incidence of adverse effects in these challenging scenarios [56,57].

Pancreatic cancer

Pancreatic cancer is known for its resistance to conventional RT and its generally poor prognosis, underscoring the urgency for more effective treatment approaches. The pancreas's close proximity to radiosensitive organs like the stomach and bowel restricts the amount of radiation that can be safely administered using photon therapy. CIRT has not only shown a strong biological rationale *in vitro* [58,59], but has also yielded promising clinical results, especially in cases of locally advanced pancreatic cancer. Recent studies have further investigated the potential of CIRT in treating resectable and borderline resectable pancreatic cancers, aiming to improve surgical outcomes and decrease recurrence rates.

CIRT has emerged as a promising alternative for treating locally advanced pancreatic cancer, where conventional treatments often show limited efficacy. A phase 1/2 prospective clinical trial conducted at the NIRS [60] assessed the maximum tolerated dose of CIRT combined with gemcitabine. The study reported a 2-year local progression-free rate of 83% and a 2-year OS rate of 48% for patients receiving more than 45.6 Gy(RBE). A multicenter

study (J-CROS 1403) [61] reported a median survival of 21.5 months, with a 2-year OS rate of 46% and a 2-year local recurrence rate of 24%. Notably, only 1% of patients experienced late grade 3 gastrointestinal toxicity, and no cases of severe toxicity were observed. Additionally, a study from Gunma University [62], which analyzed patients treated with concurrent chemotherapy (±neoadjuvant or adjuvant multiagent chemotherapy), reported a 2-year LC rate of 76.1%, a 2-year OS rate of 56.6%, and a median survival of 29.6 months. These findings suggest that CIRT may improve outcomes in patients with locally advanced pancreatic cancer. However, further research is needed to comprehensively define its role and determine the optimal combination strategies with chemotherapy.

For resectable or borderline resectable pancreatic cancers, CIRT has been investigated as a preoperative treatment to enhance surgical outcomes and decrease recurrence rates. Promising results have emerged from studies conducted by Japan's NIRS. A phase I trial [63] demonstrated that 90% of patients could undergo R0 resection after receiving CIRT at 30–36.8 Gy(RBE) in eight fractions, with no local recurrences reported. The 5-year OS rate of patients who underwent surgery was 52%. Based on these findings, a subsequent phase II study [64] reported that 89% of patients underwent surgery after receiving CIRT, with a 5-year LC rate of 92.3% and an OS rate of 49%. Ongoing trials, such as the PIOPPO study in Italy [65], will further explore the efficacy of CIRT combined with chemotherapy in improving surgical outcomes for this group of patients.

Prostate cancer

For prostate cancer, RT is crucial for achieving optimal tumor control while minimizing gastrointestinal and genitourinary toxicities. While photon therapy is widely used, charged-particle therapies such as proton therapy and CIRT offer improved dose distribution and a lower

incidence of side effects. This advantage is similar to what is observed in breast cancer [66,67]. The low alpha/beta ratio in prostate cancer makes it particularly amenable to hypofractionated treatment schedules [68]. Hypofractionated CIRT has shown high rates of biochemical recurrence-free survival (bRFS) with reduced toxicity compared to photon therapy. Although direct comparisons are limited, current studies suggest that CIRT may offer significant benefits in the treatment of prostate cancer.

Since 1995, CIRT has been administered to over 4,100 prostate cancer patients in Japan, with its use refined through numerous clinical trials. Initial phase I/II trials at NIRS escalated the doses from 54 Gy(RBE) to 72 Gy(RBE) across 20 fractions [69,70]. The second trial (protocol 9703) established 66 Gy(RBE) as the recommended dose [70,71]. A subsequent phase II trial (protocol 9904) [72] validated this regimen and reported 4-year bRFS rates of 87% in low-risk patients and 88% in high-risk patients. In this group, 5% experienced grade 2 genitourinary toxicity, 2% had gastrointestinal toxicity, and there were no grade 3 or higher events. Further research led to a reduction in dose to 63 Gy(RBE) in 20 fractions and subsequently to 57.6 Gy(RBE) in 16 fractions, achieving a 5-year bRFS rate of 88.5% with fewer cases of grade 2 genitourinary toxicity [73]. In 2010, protocol 1002 [74] adopted 51.6 Gy(RBE) in 12 fractions as the standard, with 5-year bRFS rates of 95.1%, 90.9%, and 91.1% in low-, intermediate-, and high-risk groups, respectively, and late grade 2 genitourinary and gastrointestinal toxicity in only 6.3% and 0.4% of patients, respectively. A Japanese multicenter study (J-CROS1501PR) [75] involving 2,157 patients further validated these outcomes, with 5-year RFS rates of 92%, 89%, and 92% in the respective risk groups and a lower incidence of grade 2 genitourinary and gastrointestinal toxicity.

In Germany and Italy, CIRT for prostate cancer has demonstrated favorable safety and efficacy outcomes. A clinical trial [76] at the HIT in Germany reported that CIRT was

associated with a lower incidence of genitourinary and gastrointestinal toxicities compared to proton therapy. Among those treated with CIRT, 28.9% experienced grade 1 cystitis, 13.3% experienced grade 2 cystitis, 11.1% experienced grade 1 proctitis, and 2.2% experienced grade 2 proctitis. In Italy, a trial that combined CIRT with photon therapy for patients at high risk of prostate cancer indicated that this combined approach might offer better outcomes than photon therapy alone [77,78]. Additionally, quality of life assessments from studies conducted in Germany, Japan, and China [76,79,80] showed that CIRT had a minimal long-term impact on the quality of life. These studies reported transient acute genitourinary toxicity and no cases of significant gastrointestinal toxicity, reinforcing its safety and efficacy in prostate cancer.

Bone and soft tissue sarcoma

Sarcomas are known for their radioresistance and often develop in anatomically challenging locations, which complicates surgical resection. As a result, RT plays a pivotal role, especially for patients with unresectable tumors or residual disease. While traditional photon therapy is commonly employed, there is a growing preference for charged-particle therapies, such as CIRT, due to their enhanced efficacy. CIRT has demonstrated effectiveness in treating sarcomas, particularly those that are radioresistant or situated in complex anatomical areas. There is substantial evidence supporting the effectiveness of CIRT in improving LC and OS rates in patients with various types of sarcomas (Table 2).

CIRT has demonstrated significant efficacy in treating various types of bone sarcomas, particularly those that are inoperable or resistant to conventional therapies. In a study involving 188 patients treated with CIRT, Imai et al. [81,82] reported a 5-year LC rate of 77.2% and a 5-year OS rate of 81% in patients treated with CIRT at a dose of 64–73.6 Gy(RBE). More recent studies have also reported a 2-year LC rate exceeding 80% in patients with sacral chordomas

or chondrosarcomas [83,84]. Furthermore, Shiba et al. [85] found that patients with inoperable bone sarcomas treated with CIRT exhibited a 3-year LC rate of 62% and an OS rate of 51%. For the treatment of primary spinal sarcomas, Matsumoto et al. [86] demonstrated that CIRT delivered at a dose of 64 Gy(RBE) in 16 fractions achieved a 5-year LC rate of 79% and an OS rate of 52%. The effectiveness of CIRT has also been prospectively evaluated in primary spinal sarcomas [87] or localized primary sarcomas of the extremities [88]. Moreover, it has shown potential in pediatric and young adult patients with bone tumors [89,90], providing effective treatment without significant growth disturbances or secondary malignancies, as observed in studies from the NIRS in Japan and HIT in Germany. These results collectively illustrate CIRT's ability to provide effective tumor control with a manageable toxicity profile across various challenging bone sarcomas.

CIRT has shown promising results in treating retroperitoneal sarcoma, a particularly challenging subtype of soft tissue sarcomas due to their proximity to critical structures like the gastrointestinal tract. Since 1997, CIRT has been used at the NIRS to manage unresectable retroperitoneal sarcomas that are not extensively attached to the intestines and measure less than 20 cm, employing a dose of 70.4 Gy(RBE) delivered in 16 fractions over 4 weeks. Serizawa et al. [91] reported a 5-year LC rate of 69% and an OS rate of 50% in patients with unresectable retroperitoneal sarcomas with no gastrointestinal complications or grade 2 or higher toxicity. This finding suggests that CIRT is an effective treatment option for these cases. Additionally, Imai et al. [92] evaluated 128 patients with unresectable axial soft tissue sarcomas treated with CIRT at doses of 64–73.6 Gy(RBE). They reported a 5-year LC rate of 54% and a 5-year OS rate of 46%, with grade 3 or higher late adverse events occurring in four patients.

Although the administration of high-dose CIRT is associated with the risk of late toxicity, particularly osteoradionecrosis and soft tissue necrosis, its ability to achieve high LC

rates in both bone and soft tissue sarcomas makes it an invaluable treatment option. The use of surgical spacers for tumors located near the gastrointestinal tract has proven to be an effective strategy for reducing the risk of severe complications [93,94], thereby enabling safer delivery of CIRT and improving patient outcomes.

Future directions

CIRT has demonstrated significant clinical efficacy across various types of malignancies and offers distinct advantages over conventional therapies due to its unique physical and biological properties. However, the lack of high-level evidence, especially from randomized controlled trials, challenges the establishment of CIRT's superiority over conventional therapies. To further solidify CIRT's role in modern oncology, it is crucial to address these gaps by conducting well-designed randomized controlled trials that directly compare CIRT with conventional therapies. In addition to these trials, adopting a multifaceted approach that includes long-term clinical cohort studies and the establishment of robust multicenter registries is essential. These initiatives will provide a deeper understanding of CIRT’s clinical benefits across diverse patient populations, refine patient selection criteria, and optimize treatment protocols. Moreover, future advancements in CIRT will be influenced by translational research. Key areas of exploration include the integration of ultrahigh-dose-rate (FLASH) therapy, which could further enhance the therapeutic window of CIRT by reducing the risk of normal tissue toxicity. Additionally, investigating the immunogenic effects of particle therapy could reveal potential synergies with emerging immunotherapies. As CIRT facilities continue to expand globally, particularly in leading countries such as Japan, the United States, Europe, and Korea, this growth must be managed through strategic planning and comprehensive cost-effectiveness analyses. These efforts should be complemented by initiatives to standardize treatment

protocols and facilitate international collaboration to ensure that the benefits of CIRT are accessible to a broad range of patients worldwide. By addressing these challenges and capitalizing on new research opportunities, CIRT is expected to play a transformative role in cancer treatment.

Conclusion

The establishment of Korea's first CIRT center at the Yonsei Cancer Center, along with the development of additional CIRT centers in Korea and abroad, offers a significant opportunity to gather compelling evidence that could substantiate the clinical advantages of CIRT and broaden its uses. By coordinating clinical and translational research with carefully devised expansion strategies, CIRT is well-positioned to improve survival rates, enhance the quality of life for cancer patients, and potentially decrease the risk of secondary malignancies. These advancements highlight the pivotal role of CIRT as a critical modality in modern cancer treatment, setting the stage for its incorporation into worldwide oncological practices.

Authors' contributions

Project administration: Lee IJ

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Funding acquisition: Choi SH and Lee IJ

Writing – original draft: Choi SH

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Conflict of interest

The authors declare that they have no potential conflicts of interest.

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Data availability

Not applicable

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Table 1. Clinical studies and outcomes of patients with NSCLC treated with CIRT

Author (year)	Study design	No. of patients	CIRT dose	LC	OS	Acute toxicity	Late toxicity
Early-stage NSCLC							
Miyamoto et al. (2003) [26]	Phase I/II	81	59.4–95.4 Gy(RBE)/9–18 fr	first trial: 64% second trial: 84%	5-yr 42%	Gr3 RP = 3	
Miyamoto et al. (2007) [27]	Phase II	50	72 Gy(RBE)/9 fr	5-yr 94.7%	5-yr 50% (IA 55.2%, IB 42.9%)	No Gr3≤ toxicity Gr 2 skin = 1, Gr 2 RP = 1	Gr 3 skin = 1 Gr 2 skin = 1 Gr 2 lung = 2
Miyamoto et al. (2007) [28]	Phase II	79	52.8 Gy(RBE)/4 fr for stage IA, 60 Gy(RBE)/4 fr for stage IB	5-yr 90%	Overall: 5-yr 45%, stage IA: 5-yr 62%, stage IB: 25%	No Gr3≤ toxicity Gr 2 skin = 5 Gr 2 lung = 1	No Gr3≤ toxicity Gr 2 skin = 1 Gr 2 lung = 1
Yamamoto et al. (2017) [29]	Phase I/II	218	28–50 Gy(RBE)/1 fr	36–50 Gy(RBE): 3-yr 84.2%, 5-yr 80.5% 28-34 Gy(RBE): 3-yr 63.7%, 5-yr 54.4%	36-–50 Gy(RBE): 3-yr 76.2%, 5-yr 56.8% 28–34 Gy(RBE): 3-yr 50.7%, 5-yr 32.8%	No Gr3≤ toxicity Gr 2 toxicity = 2% Gr 3 chest wall pain = 1 (50 Gy(RBE))	

Saitoh et al. (2019) [30]	Phase II	37	52.8–60 Gy(RBE)/4 fr	Overall: 2-yr 91.2%, 5-yr 88.1% T1: 2-yr 91.3%, 5-yr 86.7% T2: 2-yr 90%, 5-yr 90%	Overall: 2-yr 91.9%, 5-yr 74/9% T1: 5-yr 80% T2: 66.7%	No Gr 4≤ toxicity, Gr 3 RP = 1, Gr 2 RP = 1	
Ono et al. (2020) [31]	Retrospective	57	50 Gy(RBE)/1 fr	3-yr 96.4%, 5-yr 91.8%	3-yr 91.2%, 5-yr 81.7%	No Gr 3≤ toxicity Gr 2 rib fracture = 4 (7.0%) Gr 2 peripheral motor neuropathy = 2 (3.5%)	
Kubo et al. (2023) (J-CROS-LUNG) [32]	Multicenter prospective observational registry study	95	72 Gy(RBE)/16 fr ~50 Gy(RBE)/1 fr	3-yr 87.3%	3-yr 59.3%	No Gr 4≤ toxicity, 3-yr Gr2≤ RP rate = 3.2%, Risk factor for RP = FEV1 <0.9L, dose ≥67 Gy(RBE)	
Locally advanced NSCLC							
Takahashi et al. (2015) [35]	Phase I/II	62	68–76 Gy(RBE)/16 fr	2-yr 93.1% (cT3–4N0 only: 2-yr 100%)	2-yr 51.9% (cT3–4N0 only: 2-yr 69.3%)	Gr 2 RP = 6.5% Gr 3 RP = 1.6%	Gr 3 tracheoesophageal fistula = 1 No grade 4/5 toxicity

Hayashi et al. (2019) [36]	Retrospective	141	54–76 Gy(RBE)/12–16 fr	2-yr 80.3%, 3-yr 75.4%	2-yr 58.7%, 3-yr 47.5%	Gr 2 skin = 13.5%	Gr 4 mediastinal hemorrhage = 0.7% Gr 3 RP = 3.5% Gr 3 bronchial fistula = 7%
Karube et al. (2017) [37]	Retrospective	64	52.8–60 Gy(RBE)/4 fr, 64–70.4 Gy(RBE)/16 fr	2-yr 81.8%	Overall: 2-yr 62.2% N0: 2-yr 67.8% N1-N2: 2-yr 62.2%	Gr 2 lung infection = 3 Gr 2 lung reaction = 4 Gr 2 skin reaction = 3 Gr 2 chest wall pain = 1	NR
Anzai et al. (2020) [38]	Retrospective	24	64–76 Gy(RBE)/16 fr	2-yr 73.9%, 3-yr 70.2%	2-yr 54.9%, 3-yr 42%	No Gr 3≤ toxicity	Gr 4 mediastinal hemorrhage = 1 Gr 3 RP = 4 Gr 3 bronchial fistula = 1

Abbreviations: CIRT, carbon-ion radiotherapy; FEV1, forced expiratory volume in 1 s; fr, fractions; Gr, grade; J-CROS, Japan Carbon–Ion Radiation Oncology Study Group; LC, local control; NR, not reported; NSCLC, non-small-cell lung cancer; OS, overall survival; RBE, relative biological effectiveness; RP, radiation pneumonitis; yr, year

Table 2. Clinical studies and outcomes of patients with bone and soft tissue sarcomas treated with CIRT

Author (year)	Study design	Tumor type and location	No. of patients	CIRT dose (Gy(RBE))	LC	OS	Acute toxicity	Late toxicity
Bone sarcoma								
Imai et al. (2016) [79]	Retrospective	Sacral chordoma	188	64–73.6	5-yr 77.2%	5-yr 81.1%	NR	Gr 3 peripheral nerve toxicity = 6, Gr 4 skin = 2
Imai et al. (2017) [80]	Retrospective	Chondrosarcoma	73	64–73.6	5-yr 53%	5-yr 53%	NR	Gr 3≤ toxicity = 8, Gr 3 skin = 3, bone fracture = 4, bone necrosis = 1
Wu et al. (2019) [81]	Retrospective	Chordoma or chondrosarcoma	21	57–80	1-yr 93.8%, 2-yr 85.2%	1-yr 100%, 2-yr 100%	Gr 1 skin = 14.2%, Gr 1 myelosuppression = 33.3% No Gr 2≤toxicity.	No severe late toxicity

Bostel et al. (2020) [82]	Retrospective	Primary or recurrent sacrococcygeal chordoma	68	60–70.4	Overall: 1-yr 90%, 2-yr 80%, 3-yr 65%, 5-yr 53% Primary: 1-yr 96%, 2-yr 88%, 3-yr 77%, 5-yr 62% Recurrent: 1-yr 68%, 2-yr 54%, 3-yr 27%, 5-yr 27%	Overall: 1-yr 97%, 2-yr 97%, 3-yr 86%, 5-yr 74%	NR	Radiogenic toxicity = 40(59%) (14 received at least 80GyE) Gr 3≤ = 21%, Sacral insufficiency fractures = 49%
Shiba et al. (2021) [83]	Retrospective	Bone sarcoma	53	64–70.4	Overall: 3-yr 88.6%, 5-yr 73.8% Chordoma: 3-yr 92.5%, 5-yr 84.8% Non-chordoma: 3-yr 82.2%, 5-yr 54.8% Osteosarcoma: 3-yr 87.5% Chondrosarcoma: 3-yr 60%	Overall: 3-yr 79.7%, 5-yr 79.7% Chordoma: 3-yr 91.3%, 5-yr 91.3% Non-chordoma: 3-yr 60.7%, 5-yr 60.7% Osteosarcoma: 3-yr 36.5% Chondrosarcoma: 3-yr 59.3%	No Gr 3≤toxicity. Gr 1 dermatitis = 21 Gr 2 dermatitis = 6 Gr 1 neuropathy = 6 Gr 2 neuropathy 2	Gr 3 dermatitis = 5 Gr 3 GI tract = 1 Gr 3 infection =5 Gr 3 dermatitis = 3 Gr 3 GI tract = 1 Gr 2 neuropathy = 12 Gr 2 urinary = 3 Gr 2 bone fracture = 4
Matsunobu et al. (2012) [84]	Retrospective	Trunk osteosarcoma	78	52.8–73.6	5-yr 62%	5-yr 33%, <70 Gy(RBE) = 56% ≥70Gy(RBE) = 27%	Gr 3 skin = 3	Gr 3 skin/soft tissue = 4 Gr 4 skin/soft tissue = 3 Bone fracture

								requiring surgery = 2
Matsumoto et al. (2013) [85]	Retrospective	Primary spinal sarcoma	47	52.8–70.4	5-yr 79%	5-yr 52%	Gr 3 skin = 1	Gr 3 skin 1, Gr 4 skin ulcer 1, Vertebral body compression = 7 (more common in ≥70.4GyE)
Sugahara et al. (2012) [86]	Phase I/II	Extremity sarcoma	17	52.8–70.4	3-yr 76%, 5-yr 76%	3-yr 68%, 5-yr 56%	Gr 1 skin = 16 (94%)	Gr 3 myelopathy =1 Gr 2 skin = 1 (6%) Gr 2 neuropathy = 4 (24%)
Pediatric/young adult sarcoma								
Mohamad et al. (2018) [87]	Retrospective	Unresectable truncal osteosarcoma	26	52.8–73.6	3-yr 70%, 5-yr 63%	3-yr 50%, 5-yr 42%	none	Gr 3~4 = 4 (1 Gr 3 skin, 1 Gr 4 skin, 2 neuropathy)

Combs et al. (2009) [88]	Retrospective	Skull base chordoma or chondrosarcoma	17	60–66.6	Only 1 tumor progression (60 months after CIRT)	NR	only mild (Gr 1 or 2) focal alopecia = 1 (6%), skin = 1 (6%)	No severe late toxicity, 2 hormone deficiency requiring hormone substitution, No secondary malignancy
Soft tissue sarcoma								
Serizawa et al. (2009) [89]	Retrospective	Unresectable retroperitoneal sarcoma	24	52.8–73.6	2-yr 77%, 5-yr 69%	2-yr 75%, 5-yr 50%	Gr 1 skin = 83%, Gr 2 skin = 17%	Gr2 neurotoxicity = 21% No Gr3≤ toxicity
Imai et al. (2018) [90]	Phase I/II	Unresectable axial soft tissue sarcoma (deep 96%, subdeep 4%)	128	64–73.6	3-yr 68%, 5-yr 65%	3-yr 60%, 5-yr 46%	NR	Gr3≤ = 4 Gr 3 spinal cord injury =1 Gr 3 peripheral nerve injury =1 Gr 4 colon injury = 1 Gr 3 skin = 1

Abbreviations: CIRT, carbon-ion radiotherapy; fr, fractions; GI, gastrointestinal; Gr, grade; Gy(RBE), gray (relative biological effectiveness); LC, local control; NR, not reported; OS, overall survival; RBE, relative biological effectiveness; yr, year