Value of carbon-ion radiotherapy for early stage non-small cell lung cancer

Hanguang Ruan [a,b,c], Juan Xiong [d,*]

[a] Department of Radiation Oncology, Graduate School of Medicine, Gunma University, 3-39-22, Showa-machi, Maebashi, Gunma 371-8511, Japan
[b] Gunma University Heavy Ion Medical Center, 3-39-22, Showa-machi, Maebashi, Gunma 371-8511, Japan
[c] Department of Radiation Oncology, The Third Hospital of Nanchang, No 1248 Jiuzhou Avenue, Nanchang City 300002, China
[d] Department of Radiation Oncology, Jiangxi Cancer Hospital, 519 East Beijing Road, Nanchang City 330029, China

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ABSTRACT

Carbon-ion radiotherapy (CIRT) is an important part of modern radiotherapy. Compared to conventional photon radiotherapy modalities, CIRT brings two major types of advantages to physical and biological aspects respectively. The physical advantages include a substantial dose delivery to the tumoral area and a minimization of dose damage to the surrounding tissue. The biological advantages include an increase in double-strand breaks (DSBs) in DNA structures, an upturn in oxygen enhancement ratio and an improvement of radiosensitivity compared with X-ray radiotherapy. The two advantages of CIRT are that the therapy not only inflicts major cytotoxic lesions on tumor cells, but it also protects the surrounding tissue. According to annual diagnoses, lung cancer is the second most common cancer worldwide, followed by breast cancer. However, lung cancer is the leading cause of cancer death. Patients with stage I non-small cell lung cancer (NSCLC) who are optimally received the treatment of lobectomy. Some patients with comorbidities or combined cardiopulmonary insufficiency have been shown to be unable to tolerate the treatment when combined with surgery. Consequentially, radiotherapy may be the best treatment option for this patient category. Multiple radiotherapy options are available for these cases, such as stereotactic body radiotherapy (SBRT), volumetric modulated arc therapy (VMAT), and intensity-modulated radiotherapy (IMRT). Although these treatments have brought some clinical benefits to some patients, the resulting adverse events (AEs), which include cardiotoxicity and radiation pneumonia, cannot be ignored. The damage and toxicity to normal tissue also limit the increase of tumor dose. Due to the significant physical and biological advantages brought by CIRT, some toxicity induced by radiotherapy may be avoided with CIRT Bragg Peak. CIRT brought clinical benefits to lung cancer patients, especially geriatric patients. This review introduced the clinical efficacy and research results for non-small cell lung cancer (NSCLC) with CIRT.

Introduction

Lung cancer is a common malignant oncologic condition affecting patients all over the world, and especially those in developed countries and areas. According to the 2020 Global Cancer Statistics, in that year there were 19.3 million newly diagnosed cancer cases, and almost 10 million deaths from new cases [1]. Among all, breast cancer in female patients was shown to have surpassed lung cancer as the most diagnosed cancer in 185 countries worldwide, compared to the same data from Global Cancer Statistics 2018 [1]. The record indicated that the number of newly diagnosed cancer cases of female breast cancer was 2.3 million (11.7%), followed by lung cancer (11.4%). However, according to the same source, lung cancer was the most diagnosed cancer for female and male patients combined, as newly diagnosed cases amounted to 2.1 million (11.6%) and deaths reached 1.8 million (18.4%). As a result, it can be evinced that lung cancer was the leading cause of cancer incidence and death worldwide at that time. The more recent data from 2020 confirm lung cancer as the leading cause of cancer death, with an estimated 1.8 million deaths total cases (18%), followed by colorectal cancer (9.4%) [2]. Despite the significant incidence of female breast cancer in the 2020 statistics, the death toll for new cases is a total of 68 thousand (6.9%). In conclusion, although female breast cancer is seen to be the most diagnosed cancer compared to other forms of cancer (Figs. 1A, 1B), lung cancer plays a key role in increasing the burden of worldwide cancer mortality.

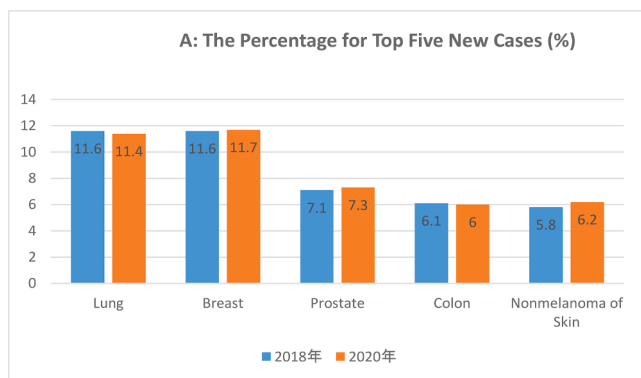Data shows a different incidence and mortality rate between male

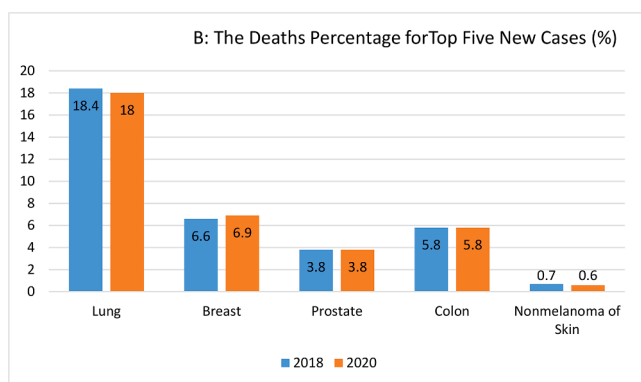**Fig. 1A.** The Top Five New Cases for 36 Cancers on the GLOBOCAN(%).

Fig. 1B. Deaths Cases for The Top Five New Cases on the GLOBOCAN(%).

and female cancer patients. In terms of morbidity and mortality, lung cancer is still the leading form of cancer in men, whereas it ranks only third in terms of incidence in women, following breast and colorectal cancer. The highest incidence rates are observed in high income countries or area. The related causes are mainly the tobacco epidemic and environmental pollution [3,4]. The 5-years overall survival (OS) rates of patients with lung cancer after diagnosis was observed to be 10% to 20% in most countries between 2010 and 2014. However, different countries show unique results. Some Asian countries, such as Japan, Israel and Republic of Korea, indicate that patients with lung cancer have high OS rates. Some studies indicate that there are two important factors leading to the increase of OS rates. One is early cancer diagnosis and assessment through low-dose computed tomography (CT) for high-risk individuals. Another is effective treatment approaches for diagnosed lung cancer patients, such as surgery, radiotherapy, chemotherapy target therapy and additional assessments. These are significant influencing factors on lung cancer patients' OS rates [1,5-7]. The 5-year OS rates for early-stage NSCLC has increased from 20% to 60%-70% due to the involvement of multiple treatments and CIRT. This situation is especially true in developed countries [8-10].

Radiotherapy has become a major therapeutic option for patients with lung cancer. Especially when early-stage patients are geriatric patients affected by coronary diseases and other disorders such as liver and kidney function complications. This patient category cannot tolerate surgery and chemotherapy. The common administration modality of radiation treatment is via external beam, which mainly includes stereotactic body radiotherapy (SBRT), volumetric modulated arc therapy (VMAT), intensity-modulated radiotherapy (IMRT), and image-guided intensity-modulated radiotherapy (IGRT). IGRT sometimes offers a routine procedure of position verification when patients are treated with SBRT [11-20]. In this case, SBRT will become the preferred choice of treatment for patients with lung cancer, especially for early-stage lung

cancer. This is because SBRT, compared to other treatments, carries more advantages which include mild toxicity, short treatment time, and therapeutic effect which has shown a level of efficacy that is similar to or even better than surgery [11,12,14]. Notwithstanding, some acute adverse events (AEs) and toxicities cannot be ignored. Although SBRT has shown better efficacy compared to other modalities of radiotherapy, radiation-associated pneumonia could result from its administration. Since SBRT requires a high level of positional accuracy, the patient's positioning relies on in-room computed tomography instruments, such as the electronic portal imaging device (EPID) and cone beam computed tomography (CBCT) at the time of treatment, so as to reach the required level of positioning accuracy during radiotherapy. In this case, patients may receive an additional dose of radiation [21-24]. Finally, the treatment may cause complications with organs at risk (OARs). Compared to the conventional photon radiotherapy modalities, CIRT holds great promise for cancer therapy. Namely, it shows two significant advantages over X-rays, such as sharp dose distribution and strong cell-killing capacity [25-27]. In this review, we introduced the efficacy and safety of CIRT for patients with lung cancer.

Landscape of carbon-ion radiotherapy worldwide

The first country to carry out heavy ion therapy worldwide was the United States. Before heavy ion therapy was approved as a treatment for cancer patients, the National Cancer Institute (NCI) of the US had cleared long-term support to translational research on heavy ion therapy. Although heavy ion therapy was shown to have abundant evidence of significant physical and biological benefits, in many institutes or hospitals worldwide most patients could not receive heavy ion therapy because of the prohibitive costs involved with the creation and maintenance of the necessary facilities. After the US, the Japanese government decided to construct the Heavy Ion Medical Accelerator (HIMAC) at the National Institute of Radiological Sciences (NIRS) in Chiba, Japan in 1984. The institution then started clinic trials as an independent administrative institute like the NCI in 1994. At the same time, the HIMAC assessed efficacy and toxicity of the treatment with all kinds of cancer after CIRT [9,10]. In 2020 more than 20,000 patients were treated by CIRT and fourteen institutions were regularly performing CIRT. The nations in which these institutions are located include Japan (six), Italy (one), Germany (three), China (three), and Austria (one) [9,28] (Fig. 2). Currently, Japan is the country with the largest number of CIRT facilities, followed by Germany and China. Since 1994, the NIRS has been using carbon ions to treat tumors, and some clinical trials involving CIRT for the treatment of lung cancer are conducted in the institution [29]. For example, the first protocol (9303), which began in
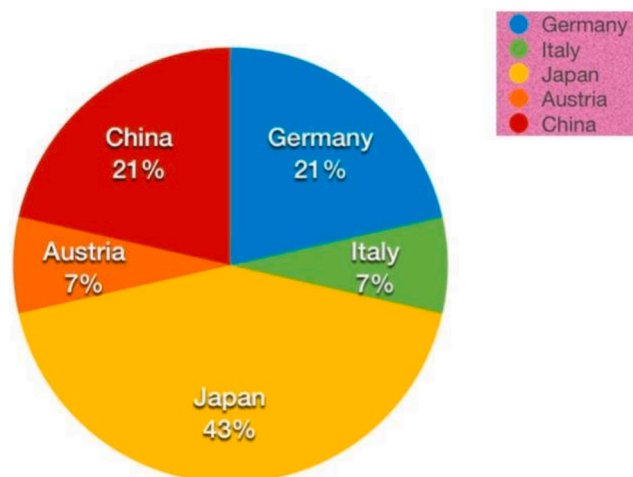

Fig. 2. Institution Perform Carbon Ion Radiotherapy (up to 2020) (%).

October 1994, and ended in August 1998. Another protocol (9701) began in September 1997 and ended in February 1999. The two protocols are both about dose escalation for early-stage patients treatment SCLC [30]. In regards with the current developmental stage of CIRT, Japan holds the largest and most advanced CIRT technology carried out by hospitals or research institutions.

Outcomes of clinical applications

Dose escalation

The NIRS was the first medical center for tumor treatment in Japan that to employ CIRT since 1994. The second one is the Gunma Heavy Ion Medical Center (GHMC), which is the first university hospital with a CIRT facility in Japan. For its clinical use, carbon-ion beams were selected based on preclinical experiments, while the past experiments with particle radiotherapy also played a pivotal role in the curative treatment of tumors [29]. It became apparent that it was necessary to carry out dose escalation studies for CIRT according to the differential effect and described toxicity-risk reduction of the surrounding healthy tissue. Although carbon-ion beams employ a high linear-energy transfer (LET) and spread out Bragg peak (SOBP).

From 1994 to 1998, the NIRS carried out the 9303 protocol phase I/II trial for stage I NSCLC patients, and from 1997 to 1999, the 9701 protocol study respectively. For the 9303 protocol the starting dose was 59.4 GyE (3.3 GyE per fraction), while for the 9701 protocol the dose escalation was conducted from 68.4 to 79.2 GyE. The conclusions of both trials were that the implementation of a carbon dose of 86.4 GyE administered in 18 fractions and one of 72 GyE in 9 fractions were identified as the safe dose for the phase II study under the two protocols. On the other hand, the local control rates in the first and second trials were 64% and 84%, respectively [30]. Masashi Koto et al. inducted another trial in which 81 patients have been divided into two groups, one group was made of 47 patients (48 lesions) with 18 fractions over 6 weeks, and another group comprised 34 patients with nine fractions over 3 weeks. Test subjects were administered the carbon dose escalation method from 59.4 to 95.4 GyE by a 10% increment and from 68.4 to 79.2 GyE by a 5% increment, respectively. The result showed that a local recurrence in 19 subjects (23.2%) of 82 lesions [31]. Another study about dose escalation for stage I NSCLC using single-fraction carbon ion radiotherapy saw 20 patients receiving a dose escalation of 48 to 50 GyE (RBE), with a follow up after 58.6 months. The median LC rate, overall survival (OS) rate and progression free survival (PFS) rate at 5-years was 95.0%, 69.2%, and 60.0%, respectively. Compared with other dose escalation groups (36 GyE(RBE) and less than 36 GyE), LC tended to improve more. However, the radiotherapy related toxicity had not increased compared to the lower groups. There were no patients with Grade 3 or 4 lung and skin acute and late toxicity [32]. From a dose escalation study, the biological effects of CIRT are obviously different from those of observed in photon radiotherapy. The optimal therapeutic dose and segmentation method still needs a large amount of clinical data to be confirmed and verified.

Fraction modalities and clinical efficacy

Radiotherapists have carried out a series of studies on fraction modalities and dose of CIRT with NSCLC patients. Fraction modalities include single-fraction, and hypofractionated [33-35]. One study (NO: UMIN000033402) was the first to report long-term results of single-fraction passive CIRT in patients (57 patients) with early-stage NSCLC treated with single-fraction carbon ion radiotherapy 50GyE (RBE). By the median follow-up time of 61 months, the 3-and 5-year LC rates were 96.4% and 91.8%. The 3-and 5-year OS rates were 91.2% and 81.7%, respectively. However, there was no patient with ≥ grade 2 pneumonitis. The results of this study using the fraction modalities showed that single-fraction passive CIRT can serve as an alternate treatment for

patients with early-stage NSCLC, especially with special populations that are inoperable due to conditions such as heart blood-vessel complications and/or medically inoperable patients [36].

The dates for a 10-year study that looked to use single-fraction SBRT for medically inoperable peripheral early-stage lung cancer had been announced. A total of 229 patients were recruited in this study, and were prescribed a dose of either 34 Gy or 30 Gy, with a follow-up of minimum 6 months after receiving single-fraction SBRT. The results showed that the median OS was 44.1 months. 2-year local, nodal, and distant failure rates were 7.3%, 9.4%, and 12.2%, respectively. A dose was not a determining factor for outcomes. In terms of adverse effect, at the end of the follow-up period, a total of 55.9% patients had survived. Two (0.9%) patients developed grade 3 toxicities. The incidence rate of grades 1 to 2 pneumonitis was 7%, but chest-wall toxicity was 12.7%, which was higher than in previous studies. The study also revealed none had grade 4/5 toxicities [12]. The adverse events of single-fraction SBRT was higher than CIRT. After comparing the two studies and considering the resulting adverse events, single-fraction SBRT may be the preferable alternative option for inoperable lung cancer patients.

A prospective phase II study (GUNMA0701) confirmed the efficacy and safety of hypofractionated carbon ion radiotherapy with stage I NSCLC patients. Test subjects were treated with a dose of 52.8 Gy and 60 GyE (RBE) (4f/over 1 week) for T1 and T2a tumors, respectively. All 37 patients were followed up after at least 2 years and the median time was a period of 56.3 months. If after this period the patient was alive, the follow-up time was extended to 62.2 months. The primary endpoint LC rate showed that 2-year, 3-year, and 5-year LC rates were 91.2%, 88.1%, and 88.1%, respectively. Subgroup analysis indicated that the 2-year and 5-year LC rates were 91.3% and 86.7% for patients with T1 tumors, which was similar to that of patients with T2a tumors in both local control groups (P = 0.75). However, univariate survival analysis revealed patients with smoking habits exhibited lower 2-year LC rates than non-smoking patients (82.4% vs 100.0%, P = 0.03). In this study no patient showed grade 4 toxicity, but one patient experienced a grade 3 pneumonitis from an original severe emphysema. Other patients with lung diseases such as bronchiectasis atypical mycobacteriosis developed grade 2 pneumonitis. Cumulative incidence of pneumonitis of grade 2 or higher severity was 5%.

The conclusion of the study was that CIRT may be effective and safe as a local treatment option for patients with larger or inoperable tumors [37].

A retrospective, single-institutional study carried out a direct comparison of benefits deriving from CIRT and SBRT. This was the first study to carry out this modality of research. The 3-year OS and LC rates were the primary point. The results showed an OS rate of 80.1% in CIRT and 71.6% in SBRT (p = 0.0077), and an LC rate of 87.7% and 79.1% (p = 0.037) respectively. The 3-year and 5-year PFS rates did not identify any statistically significant differences (p = 0.14). The recorded OS and LC rates were 60.4% and 55.3% in the CIRT group, and 62.5% and 29.8% in the SBRT group respectively [8]. The study showed that CIRT was an option for early-stage NSCLC patients.

A study about cost-effectiveness of CIRT versus SBRT for stage I NSCLC patients treated with CIRT or SBRT was carried out at Gunma university, Japan [38]. The results showed that, although CIRT is a cost-effective approach, reducing costs by carefully evaluating the necessity and validity of examinations and hospitalizations would make CIRT a more cost-effective approach.

The effect of radiation pneumonitis and clinical efficacy

Radiation pneumonitis (RP) is a frequent toxicity occurrence when lung cancer patients receive photon radiation beam therapy because of its multiple-fraction doses and surrounding healthy lung tissue damage [12,14,39-43]. The local therapy modality is SBRT for early inoperable NSCLC, because in case of patients showing medical contraindications such as old age, some cardiovascular diseases, and lung complications,

SBRT is the recommended treatment alternative to surgery. However, in many institutions of China and worldwide, only photon-radiation beam facilities are available, hence the RP incidence rate remained high with NSCLC patients after local radiotherapy SBRT, even though some techniques such as IGRT, VMAT, IMRT were introduced in a timely manner [11,12,19,44-47]. A total of 339 eligible medically inoperable NSCLC patients received lung SBRT from 2002 to 2015. The primary endpoint and aim of the study was to predict the relationship between risk factors and incidence rates of grade 2 or above radiation pneumonitis (RP2). The study results showed that RP2 rates were recorded in 10% of patients. These rates were found to be occurring especially in patients with a history of lung primary diseases such as respiratory comorbidities. Other risk factors included previous thoracic radiation, right lung location, mean lung doses of total or ipsilateral lung, and total lung volume receiving 20 Gy and so on. In this study, a model using dose volume histograms (DVH) established that the patients should have had no previous lung radiation and that the mean dose of total and ipsilateral lungs should be kept at less than 6 Gy and 20 Gy, in order to ensure keeping the RP2 rate under 10% [48].

At the NIRS, Japan, a phase II study recruited 28 patients (from a total of 129 patients) with lung cancer aged 80 years and older who were under CIRT. The aim of this study was to analyze the 5-year LC rate, 5-year OS rate and activity of daily living (ADL) during CIRT. The 5-year LC rate was 95.8%, and the 5-year OS rate was 30.7%. In addition, it was found that the patients' ADL had not decreased while undergoing CIRT treatment. The efficacy of this fraction modality was equivalent to the one detected under SBRT. The study demonstrated that CIRT was safe and effective for elderly patients aged 80 and above with stage I NSCLC [49]. For octogenarian patients with locally advanced non-small-cell lung cancer (LA-NSCLC), a study on CIRT with a median dose of 72.0 GyE (RBE), The prescribed dose ranged from 68.0 to 76.0 GyE in 12–16 fractions, 4 days per week, had been carried out at Osaka University, Japan. Which evaluated 32 patients who underwent CIRT alone between 1997 and 2015. The 2-year LC, PFS, and OS rates were 83.5%, 46.7%, and 68.0%, respectively. In terms of AEs, no patient suffered grade 4 RP. Grade 3 RP and Grade 2 RP were recorded in 1 patient (3.1%), and 3 patients (9.4%) respectively [50]. The incidence of RP in geriatric patients was lower than the one recorded under photon beam radiotherapy [40,51-53]. For patients with Coexisting Interstitial Lung Disease (ILD), will the use of CIRT affect the outcome of treatment and increase complications? There is one study that illustrates this possibility. Before treatment, 124 patients with stage I NSCLC patients were divided into two groups: one group was composed of patients without ILD (98 patients) and group had patients with ILD (26 patients). In the non-ILD group (control), the 3-year OS and cause-specific survival (CSS) rates were 83.2% and 90.7%. In the ILD group (Experiment) the recorded rates were 59.7% and 59.7%, thus pointing out that there are significant differences between the two categories in terms of OS rate and CSS rate (p = 0.002 and p less than 0.001 respectively). The resulting RP incidence in the non-ILD group was three patients (3.0%) and in the ILD group was two patients (7.6%). However, no significant differences for the resulting RP incidences were reported in regard to (p = 0.29) [54]. In conclusion, it seems clear that CIRT does not aggravate the occurrence of RP after radiotherapy with carbon ion beam in NSCLC patients, and its incidence is sometimes even lower than that recorded after SBRT [8,10,28,55,56]. Many oncologists of radiation therapy regard CIRT as safe and effective despite combined interstitial lung disease and old age (Table 1) [8,30,32,36,37,49,54,57,58].

Future and challenges of carbon ion radiotherapy

Compared to conventional photon external beam radiation, carbon ion radiotherapy has a superior dose distribution. Physical advantages include a substantial dose delivery to the tumoral area and a minimal dose damage to the surrounding tissue. Biological advantages include increasing double-strand breaks (DSBs) in DNA structures, enhancing oxygen enhancement ratio and improving radiosensitivity compared with photon radiation.

According to the data and results of the published studies, patients with lung cancer who received CIRT have better local control and overall survival. Although CIRT is a local treatment method, it shows significant radiophysical and radiobiological advantages over photon radiotherapy. From the perspective of the current development trend of radiotherapy and comprehensive cancer therapy, nevertheless, there are still many directions for further research in CIRT. The future development of CIRT is mainly carried out in the three aspects of radiophysics, radiobiology, and clinical research.

The greatest radiophysical advantage of CIRT is that the tumor tissue receives an adequate dose distribution and the surrounding tissue suffers minimal damage. In order to achieve the two main treatment goals, the oncologist used four-dimensional CT (4DCT) to overcome target inaccuracy caused by respiratory movement. Some studies showed that using daily computed tomographic images can overcome the influence of treatment interfractional anatomical dose changes in daily radiation. A study verified that tumor matching (TM) is better than bone matching (BM) in daily dose distributions with hypofractionated particle therapy for early stage NSCLC [59]. Selecting a particle beam angle played an important role in satisfying dose distribution of clinical target volume and organs at risk. Some studies indicate that the tumor location is more effective than beam angle selection in early stage NSCLC, especially in patients with large tumors. However, in cases of locally advanced lung cancer, results differ in regard to affecting dose distribution of clinical target volume and organs at risk by selecting beam angles corresponding to the minimal WET change to compare with the original treatment plan [60-63]. In addition, in order to reduce insufficient dose coverage for clinical target volume and excessive irradiation for organs at risk, beam direction and angles should be considered due to the uncertainty of anatomical changes.

Radiotherapy sensitivity and resistance are not only related to the total dose and segmentation method of radiotherapy, but also to the intrinsic biological behavior of tumors and the mechanism of radiation action on tumors. The latter is the domain of radiobiology. The hallmarks of DNA damage structure and the repair pathway following heavy-ion irradiation are a primary research topic. The mechanism however is unclear, when high-LET heavy-ion irradiation induce dicentrics, translocations, and large deletions [64,65]. Radiotherapy immunity is a cancer treatment hotspot. Similar studies have been reported in carbon ion radiotherapy. Lots of researchers carried out the study by means of cancer microenvironment immune response when patients accepted radiotherapy. The primary point of studies are CD8 + T cell infiltration and programmed death ligand 1 (PD-L1) expression. In some studies, PD-L1 expression was significantly increased after patients received heavy ion therapy [66-69]. This conclusion indicates that PD-L1 may be a potential therapeutic target for patients with heavy ion radiotherapy. Whether immune checkpoint inhibitors can enhance the sensitivity of carbon ion radiotherapy is still undetermined, but we believe that this kind of treatment and radiotherapy is one of the prospective directions for future research. The relationship between gene mutation and CIRT has also been reported. The study showed that patients who received carbon ion radiation therapy had significantly higher rates of mutations in certain susceptibility genes than those who did not. Some scholars have also carried out studies on the clinical efficacy and adverse reactions of gene mutation-targeted drugs combined with CIRT. This study showed that the combination of targeted drugs improved the efficacy of radiotherapy in patients without increasing the occurrence of adverse events [70-73]. Carbon ion radiotherapy to change the tumor microenvironment of patients after treatment is a popular direction of current research. How to detect, analyze, and use this microenvironmental change to further understand the biological impact of carbon ions on tumors will be the focus of our next work for carbon ion related workers. At present, the data of phase III clinical studies on the effect of carbon ions on lung cancer patients is very

Table 1
Clinical study and outcome in early stage non-small cell lung cancer patients treated with CIRT.

Authors	Institution	Year	patients	Study type	Primary endpoint	Dose and Fraction modalities	Median of follow-up	Clinical outcome
Tadaaki Miyamoto et al.[8]	NIRS, (HIMAC) Japan	1994	81 patients. early stage	Prospective, phase I/II trial, dose escalation	LC and OS rates	86.4 GyE at 18 fractions (9303 protocol) and 72 GyE at 9 fractions (9701 protocol)	60 months	The 5-year infield LC rate and a total control rate (including margin) 79% and 76%, respectively. The 5-year overall and cause-specific survivals were 42% and 60%, respectively. The frequency of grade III lung reaction was 3.7% (3/81) and that of grade II plus III was 9.8% (8/ 81) (9303 protocol). Grade III pneumonitis occurred in one patient with IPF among 12 patients who were treated at the second stage (9701 protocol).
Naoyoshi Yamamoto et al.[30]	NIRS, (HIMAC) Japan	2003	218 patients. early stage	Prospective, dose escalation	LC, PFS and OS rates	single-fraction, 36 GyE or more two groups (0201 protocol)	57.8 months	All patients the OS and LC rate at 5-years were 49.4% and 72.7%. The two groups showed significant differences in LC,OS and PFS. No patients with grade 3 or higher reactions, and less than 2% had a grade 2 reaction., one patient had grade 3 chest wall pain late toxicity.
Toshio Sugane et al.[32]	NIRS, (HIMAC) Japan	1999	28 patients aged 80 years and older. early stage	Prospective,phase II study	LC and OS rates	12 lesions received a 72.0 GyE in 9 fractions, 11 lesions received 52.8 GyE, and 6 received 60.0 GyE in 4 fractions	60 months	The 5-year LC rate was 95.8%, and the 5-year OS rate was 30.7%, All were at grade 0 for early reactions. late reactions, 1 lesion at grade 0 and 28 lesions at grade 1
Jun-ichi Saitoh et al.[36]	GHMC Gunma, Japan	2010	37 patients, early stage	Prospective phase II study (GUNMA0701)	LC, PFS, and OS rates	T1 tumors was 52.8 GyE, T2 tumors was 60.0 GyE four fractions over 1 week.	56.3 months overall and 62.2 months in the surviving patients,	The 2-years and 5-years actuarial LC rates were 91.2% and 88.1% The 2-years and 5-years actuarial OS rates were 91.9% and 74.9%. either severe emphysema or bronchiectasis experienced lung toxicity ≥ grade 2.
Takashi Ono et al.[37]	QST Hospital, Chiba, Japan	2011	57 patients early stage	Retrospectively study	LC, and OS rates	single-fraction 50GyE	61 months	The 3- and 5-year overall survival rates were 91.2% and 81.7%, respectively. The 3- and 5-year local control rates were 96.4% and 91.8%, respectively. No case of ≥ grade 2 pneumonitis was recorded.
Naoko Okano et al.[49]	GHMC Gunma, Japan	2010	124 patients, (26 Interstitial lung disease) early stage	Single-institution retrospective study (HS2019-233).	OS and cause-specific survival rates	52.8 GyE and 60.0 GyE in four fractions.	60 months	The 3-year OS and cause-specific survival rates were 83.2% and 90.7%, respectively, in the non-ILD group, and 59.7% and 59.7%, respectively. RP worse than Grade 2 was observed in three patients (3.0%) in the non-ILD group and two patients (7.6%) in the ILD group.

Table 1 (*continued*)

Authors	Institution	Year	patients	Study type	Primary endpoint	Dose and Fraction modalities	Median of follow-up	Clinical outcome
Yuhei Miyasaka et al.[54]	GHMC Gunma, Japan	2010	89 patients, early stage	retrospective, single-institutional, and contemporaneous comparison study	LC, PFS, and OS rates	CIRT of 52.8 or 60.0 GyE, SBRT of 48 GyE	60.5 months and 64.4 months	The 3-year and 5-year OS rates were 80.1% and 73.4% in the CIRT group, and 71.6% and 46.3% in the SBRT group, respectively. The 3-year and 5-year PFS rates were 60.4% and 55.3% in the CIRT group, and 62.5% and 29.8% in the SBRT group. The 3-year and 5-year LC rates were 87.7% and 85.5% in the CIRT group, and 79.1% and 55.3% in the SBRT group. One patient in each treatment group developed grade 3 radiation pneumonitis.
Mio Nakajima et al.[57]	NIRS, (HIMAC) Japan	2004	29 patients, diagnosed with ILD (NSCLC)	retrospective study (NIRS-9404)	LC and OS rates	72 GyE, 16 fractions	26.8 months	The OS rates at 3 and 5-years was 46.3 and 30.4% (57.2 and 42.4% for stage I disease), respectively. Eighteen of 29 patients (62.1%) OS longer than 2 years. Two patients were diagnosed with AE of their ILD
Masataka Karube et al.[58]	Tokyo University Hospital, Quantum and Radiological Sciences and Technology	2007	29 patients, recurrences after initial treatment, early stage	retrospective study	LC, PFS, and OS rates	60GyE initial treatment and 66.0GyE in 12 fractions as reirradiation	unaccounted	Two-year OS, LC, and PFS rates after reirradiation were 69.0%,66.9% and 51.7%. No severer than grade 2 adverse effects except one (3.4%) grade 3 bacterial pneumonia.

HIMAC: Heavy Ion Medical Accelerator in Chiba; NIRS: National Institute of Radiological Sciences, Chiba, Japan; GHMC: Gunma Heavy Ion Medical Center; LC: local control;

OS: overall survival; PFS: progression-free survival; IPF: idiopathic pulmonary fibrosis; RP: radiation pneumonitis; ILD: interstitial lung disease.

limited, and most of the studies are carried out by single centers or regional medical centers. The biggest reason for this result is that CIRT is not very popular globally, and the prohibitive cost of medical bills and lack of technology are the biggest obstacles. The physical and biological characteristics of CIRT are different from those of traditional photon radiotherapy, and the premise of clinical research is based on the above characteristics. The focus of future clinical research is on how CIRT can be combined with other systemic treatments, chemotherapy, and targeted therapy to improve clinical efficacy.

Conclusion

CIRT has two major radiophysical and radiobiological advantages over traditional photon radiotherapy. Clinical radiologists use this property to treat tumors that are resistant to conventional photon radiation therapy. CIRT not only improves the curative effect of tumor treatment, but also reduces the excessive irradiation of organs at risk. Due to the high medical cost and technology of CIRT facility, at present not many units can perform CIRT in the world. Japan is relatively early in the development of CIRT technology, and their technology is relatively advanced. Even so, the physical and biological characteristics of CIRT have not been thoroughly studied by radiologists. A large number of randomized phase III trials should be conducted in the future to further reveal the characteristics and efficacy of CIRT.

Author contributions

All authors were involved in the process of collecting and reading the papers, and unanimously agreed to the manuscript. None of the authors have any conflict of interest to disclose.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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