Carbon ion radiotherapy in the management of non-small cell lung cancer

Danushka Seneviratne1 | Hitoshi Ishikawa2 | Jingfang Mao3 | Jingjing M. Dougherty1 | Aaron Bush1 | Mathew Thomas4 | Rami Manochakian5 | Yanyan Lou5 | Dawn Owen6 | Terence T. Sio7 | Jessica Kirwan8 | Stephen J. Ko1 | Bradford S. Hoppe1

1Department of Radiation Oncology, Mayo Clinic Florida, Jacksonville, Florida, USA
2QST Hospital, National Institutes for Quantum Science and Technology, Chiba, Japan
3Department of Radiation Oncology, Shanghai Proton and Heavy Ion Center, Fudan University Shanghai Cancer Center, Shanghai, China
4Department of Cardiothoracic Surgery, Mayo Clinic Florida, Jacksonville, Florida, USA
5Department of Medicine, Division of Hematology/Oncology, Mayo Clinic Florida, Jacksonville, Florida, USA
6Department of Radiation Oncology, Mayo Clinic Minnesota, Rochester, Minnesota, USA
7Department of Radiation Oncology, Mayo Clinic Arizona, Phoenix, Arizona, USA
8Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, Florida, USA

Correspondence
Bradford S. Hoppe, Department of Radiation Oncology, Mayo Clinic Florida, Jacksonville, FL, USA.
Email: hoppe.bradford@mayo.edu

Abstract
Despite advancements in local-regional and systemic therapies, non-small cell cancer (NSCLC) remains a leading cause of death worldwide. Among those treated with standard-of-care modalities, 30–60% experience disease recurrence. Carbon ion radiotherapy (CIRT) is a form of densely ionizing radiotherapy with unique physical and biological advantages over traditional photon and proton modalities. CIRT is expected to have a superior biological impact on tumors, and is believed to be less impacted by the presence of tumor hypoxia or cell cycle state. It also shows highly conformal physical dose deposition due to reduced lateral scattering of the particles, limiting the radiation dose delivered to adjacent organs at risk. To implement CIRT as a viable option in the treatment of NSCLC, technical aspects of treatment delivery – including appropriate beam arrangements, dose calculation algorithms, radiobiological models, and methods of motion management – must be thoroughly investigated. Furthermore, randomized clinical trials comparing CIRT versus traditional radiation modalities must be performed to show the benefits and risks associated with this novel treatment modality. This review discusses the rationale for utilizing CIRT in NSCLC, available clinical data to date, and the potential for future investigations that may pave the path for improving outcomes in those diagnosed with NSCLC.

KEYWORDS
carbon ion, high-linear energy transfer, non-small cell lung cancer

1 INTRODUCTION

With nearly 1.79 million deaths per year, non-small cell lung cancer (NSCLC) remains the leading cause of cancer mortality worldwide.1,2 Of the approximately 228,820 new cases of lung cancer diagnosed in the US in 2020, 84% were of the non-small cell variety.2 By 2025, it is projected that radiotherapy will be part of the initial treatment of up to 100,000 patients with lung cancer in the US.3

Early-stage NSCLC is defined as stage I/II disease, whereas locally advanced lung cancer (LA-NSCLC) traditionally refers to stage III disease involving hilar/mediastinal nodal involvement.4 The goal of treatment for patients with stage I–III disease is cure, while...
maintaining appropriate quality of life with limited risk of toxicities. Early-stage disease may be treated with resection in those amenable to surgery, whereas high-dose stereotactic body radiotherapy (SBRT) may be utilized in those considered to be poor surgical candidates. In this early-stage patient cohort, local control rates of 70–90% are observed depending on tumor size, and treatment is typically associated with 1–22% grade 3 or higher toxicity depending on whether the tumor is located peripherally (lower rates of grade 3 toxicity) or centrally (higher rates of toxicity).

Among the patients with locally advanced NSCLC, those with limited stage IIIA nodal disease often have various treatment options, including combined-modality therapy with neoadjuvant chemotherapy/chemoradiation followed by surgery, surgery followed by chemotherapy, or definitive chemoradiation therapy followed by immunotherapy. In contrast, patients with stage IIIIB/IIIC (T1–4 N3 or T4 N2) are typically not amenable to surgery, and are treated with definitive chemoradiation followed by adjuvant immunotherapy with durvalumab. Unfortunately, LA-NSCLC treated with chemoradiation has local control rates of 50–60% and high rates of toxicity (grade 3 or higher acute pulmonary toxicity rates of 10–15%, and grade 3 or higher esophagitis rates of 6–19%). To increase local control rates, the RTOG 0617 trial evaluated whether dose escalation to 74 Gy could result in improved treatment outcomes. Unfortunately, escalating the radiation dose to 74 Gy led to significant morbidity and mortality that adversely affected the overall survival (OS) rates, resulting in 60 Gy being accepted as the standard of care. Furthermore, while the addition of durvalumab has improved OS, 80% of first relapses occurred intrathoracically within the PACIFIC trial, showing poor long-term local disease control with the current standards of care.

Despite best efforts to improve the outcomes of NSCLC patients with multimodality therapy, the observed lackluster control rates and high toxicity of treatment have motivated the investigation of innovative radiation therapy modalities. Although not widely available, one approach that could potentially improve tumor control while limiting normal tissue toxicity is the use of carbon ion radiotherapy (CIRT). CIRT is a high linear energy transfer (LET) radiation treatment that leads to clustered DNA damage resulting in higher cell kill than traditional low LET X-ray-based radiation, such as photons and protons. Investigation of such novel radiotherapy methods is timely, as the first dedicated carbon ion center in the US will be coming to Mayo Clinic Florida in 2027.

The present review aimed to provide an overview of CIRT, including the currently available data on the treatment of NSCLC with particle therapy, and explore the benefits and pitfalls associated with its use in the management of NSCLC.

1.1 Physical and radiobiological advantages of carbon ion radiotherapy

Photons, unlike protons and carbon ions, do not have an electrical charge or mass, and typically deposit dose in a gradually diminishing manner as it passes from the body surface to the deeper tissues. In contrast, particle-based therapies, such as protons and CIRT, deposit a minimal dose on entry into tissue until reaching a point known as the Bragg peak, where most of the energy of the beam is deposited over a relatively short range. Given that the range of dose deposition within the Bragg peak is quite narrow, filters may be used to widen the Bragg peak of carbon ions, using methods similar to those utilized for therapeutic proton treatments. This ensures that the tumor volume is encompassed within the spread-out Bragg peak. The dose distribution of CIRT for a lung cancer are shown in Figure 1.

In addition to interactions with electrons, charged particles also experience repulsion of the Coulomb field by the atomic nuclei. Columbic repulsion leads to multiple deflections in the path of the particle and the creation of a lateral penumbra. In comparison with photons and protons, the lateral penumbra is significantly smaller for carbon ions on account of its significantly heavier mass, leading to greater sparing of tissues adjacent to the target. Another unique aspect of carbon ion radiotherapy is the fact that the heavy ion can split into multiple lighter charged particles that travel in the same direction as the incident particle. This leads to the formation of a "fragmentation tail" beyond that Bragg peak that is typically not observed with proton therapy. Carbon ion radiotherapy is classified as high-LET radiation, in reference to the fact that it leads to clustered DNA damage that forms along a single track of ionizing radiation. Direct DNA damage from such high-LET radiation tends to be disastrous and irreversible, leading to mitotic catastrophe. Often the damage caused by CIRT is so calamitous that chromothripsis (otherwise known as chromosome shattering) occurs, leading to thousands of chromosomal rearrangements and enormous genomic instability within the cells. As CIRT leads to large amounts of direct DNA damage, it relies far less on the presence of oxygen-mediated indirect DNA damage. This increased biological impact associated with high-LET radiation is typically termed relative biological effectiveness (RBE), and is defined as the ratio of the absorbed dose from a given type of radiation to a reference type of low-LET radiation (such as X-rays). Carbon ions are deemed to have an RBE of 2–4. Additionally, unlike low-LET radiation modalities, CIRT-related cell kill has been shown to be less dependent on cell cycle dynamics.

CIRT may be helpful with respect to hypoxia-induced tumor radioresistance. There has been a multitude of efforts to improve the therapeutic efficacy of photons in hypoxic tumors, including the use of dose painting to deliver higher doses of radiation to hypoxic regions and the use of hypoxia-targeted radiosensitizers. Unlike low-LET radiation, CIRT causes DNA damage that is less reliant on the presence of oxygen, leading to similar cell kill in normoxic and hypoxic regions. Therefore, CIRT is postulated to be a highly viable option in the treatment of radioresistant, hypoxic lung tumors. In fact, this concept has been tested in NSCLC preclinical models with considerable success. Klein et al. performed a study involving irradiation of NSCLC cell lines with varying doses of X-rays and carbon ions under normoxic and hypoxic conditions. Although X-rays showed a considerable oxygen effect with very limited cell kill under hypoxic conditions, the relative impact of carbon ions on cell kill was found to be four times that of X-rays under both normoxic and hypoxic conditions.
Another possible advantage of CIRT is its increased potential for immune stimulation. The interaction between radiation therapy and the immune system is highly complex and not fully understood; however, it is generally believed that macromolecular damage associated with radiation leads to production of immunostimulatory epitopes. Given that CIRT leads to immense and catastrophic damage leading to activation of multiple nontraditional cell death cascades, it may provide more varied epitopes for stimulation of cytotoxic T cells. In essence, CIRT may serve as a ‘cancer vaccine’ that can better mobilize the immune system and increase response to immunotherapy, potentially leading to improved patient outcomes, especially in conjunction with immunotherapy.

In addition to the enhanced local control potential, there are preliminary data indicating that particle therapy may reduce the metastatic potential of tumors. Akino et al. demonstrated that metastases-associated gene expression patterns were diminished following treatment of NSCLC cells with CIRT. Studies in human fibrosarcoma cells comparing radiation with photon, proton, and carbon ion beams showed that both proton and carbon ions cause a dose-dependent decrease in cell migration and invasion, whereas X-ray radiation promotes cell migration due to upregulation of αVβ3 integrin. In vivo studies showed that pulmonary metastases formation was reduced in a dose-dependent manner in mice inoculated with osteosarcoma cells treated with carbon ions versus those treated with X-rays. This potential to reduce metastases could further justify the use of CIRT in the treatment of NSCLC, where metastatic spread is a major issue.

1.2 CIRT in the treatment of NSCLC

1.2.1 Early-stage NSCLC

Although SBRT with photons has been established as the standard of care for inoperable early-stage NSCLC with excellent results, there are still some challenges with respect to local-regional control for larger tumors and toxicities for centrally located tumors. Several studies have demonstrated that larger tumors show a higher incidence of local, regional, and distant metastatic disease after SBRT. This may partly be attributable to the larger tumors having areas of hypoxia, making them more radioresistant. Given this, CIRT may offer a more appropriate treatment option for patients with larger early-stage tumors. Furthermore, the dosimetric profile of CIRT may help reduce the risk of toxicity for centrally located tumors by delivering lower doses to the heart, lung, bronchi, esophagus, and major blood vessels.

In a phase I/II study conducted between 1994 and 1999, 50 patients with 51 primary tumors were treated with CIRT with a dose of 72 GyE delivered in nine fractions. After this treatment, the local control rate was found to be 94.7%, and the 5-year OS rate was 50%, with only one grade 3 skin toxicity. In 2004, Koto et al. reported a CIRT dose-escalation study involving 81 patients (82 lesions) with stage I NSCLC. In that study, 47 patients underwent dose escalation from 59.4 to 95.4 GyE over 18 fractions, and 34 patients underwent dose escalation from 68.4 to 79.2 GyE over nine fractions. Among this cohort, 15 patients experienced infield recurrences, and local control was associated with increased radiation dose to the tumor. In a larger study reported by Yamamoto et al., 218 patients received CIRT doses ranging from 28 to 50 Gy. At 5 years, the local control rate was 72.7% and the OS rate was 49.4%, but local control appeared to improve with higher doses. Only one patient developed grade 3 toxicity, which was chest pain. In the GUNMA0701 phase II trial performed between 2010 and 2015, 37 patients with stage I NSCLC were treated with CIRT at a dose of 52.8 GyE for T1 tumors and 60 GyE for T2 tumors. At 5 years, the local control rate was 95.8% and OS rate was 95.8%, and 30.7%, respectively. No patients showed decreased activity of daily living after CIRT, suggesting that CIRT may be appropriate in the treatment of early-stage disease in older patients who are often not considered to be candidates for surgical resection.
greater number of patients with larger tumors. Despite the presence of these larger tumors, the 3-year local control rate was significantly greater at 87.7% in the CIRT group, whereas it was 79.1% in the SBRT group. Similarly, the 3-year OS rate was also greater in those treated with CIRT (80.1%) compared with those treated with SBRT (71.6%). No grade 3 or higher toxicities were observed in either group.39

These prospective and retrospective studies show that CIRT may be safely used to treat early-stage NSCLC, and is potentially even more efficacious than traditional forms of radiotherapy in the treatment of larger tumors. Further studies are required to better characterize the optimal physical radiation dose, RBE, fractionation, and the delivery technique to ensure adequate tumor control in patients with early-stage NSCLC, as well as how to best pair CIRT with systemic therapies.

### 1.2.2 Locally advanced NSCLC

The current standard of care for the treatment of LA-NSCLC is sub-par, and involves the delivery of fractionated radiation therapy concurrently with cytotoxic chemotherapy over the course of 6–7 weeks with poor local-regional control and significant rates of grade 3 hematologic and non-hematologic toxicities.12 The unique properties of carbon ions include its highly favorable dosimetry resulting from the smaller lateral penumbra, Bragg peak characteristics, and its limited entrance and exit doses. These properties allow for a lower dose to the lungs, esophagus, heart, bone marrow, and circulating lymphocytes, ultimately reducing pneumonitis, pulmonary fibrosis, esophagitis, cardiac toxicity, and immune myelosuppression.12,40 Additionally, the increased biological effectiveness of CIRT may potentially preclude (or at least limit) the need for the use of concurrent radiosensitizing chemotherapy, and ultimately reduce chemotherapy-related toxicities. Finally, CIRT can be delivered in a hypofractionated manner, which has not been shown to be safe with IMRT and has only recently been evaluated with protons.41,42

To date, CIRT has been utilized in a small number of patients with locally advanced diseases with promising results.43 In a prospective phase I/II trial of 62 patients with stage IIA-IIIA NSCLC treated with CIRT at a dose of 76 GyE between 1997 and 2012, the 2-year local-regional control and OS rates were found to be 93% and 50.1%, respectively, with no grade ≥3 toxicities after treatment. In a retrospective study of 141 patients with locally advanced NSCLC treated with CIRT between 1995 and 2015, the median dose utilized was 72 Gy (RBE) over 16 fractions without concurrent chemotherapy. In this group, the 2-year local control, PFS, and OS rates were 80.3%, 40.2%, and 58.7%, respectively.43 In a similar analysis, Anzai et al. reported on 65 patients with stage III NSCLC treated with CIRT at the QST Hospital in Japan between 1997 and 2015. The median dose delivered was 72 GyE, and the 2-year local control, PFS, and OS rates were 74%, 38%, and 55%, respectively. As expected, clinical T and N stage, as well as larger clinical target volumes, were significantly associated with worse PFS. These retrospective and prospective studies suggest that CIRT alone, without concurrent chemotherapy, is a potentially successful treatment option for patients with locally advanced disease.

### CONCLUSIONS AND FUTURE DIRECTIONS

CIRT is a form of high-LET radiation therapy that may have several theoretical advantages over traditional low-LET therapies in the treatment of both early-stage and LA-NSCLC. These potential advantages include the ability to achieve high intratumoral radiation doses while sparing adjacent critical structures of the mediastinum, deliver adequate radiation doses in fewer fractions, limit/eliminate the use of concurrent cytotoxic chemotherapy, and increase response to immunotherapy thereby reducing eventual metastatic spread. Available literature to date suggests that CIRT is effective and feasible in the treatment of NSCLC with acceptable toxicity rates. With the development of more technologically advanced methods of CIRT delivery, including the use of pencil beams, Monte Carlo dose calculation algorithms, and advanced motion management techniques, clinicians will likely be able to treat NSCLC lesions more effectively and considerably reduce treatment-related toxicity. As interest in heavy ion therapy continues to grow, randomized control trials are warranted to further investigate the risks and benefits of CIRT in the treatment of NSCLC.

### CONFLICT OF INTEREST

None.

### ORCID

Bradford S. Hoppe https://orcid.org/0000-0002-2312-5418

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