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Carbon-Ion Radiotherapy for Non-Small Cell Lung Cancer

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Abstract

Carbon-Ion Radiation (CIRT) is a critical component of contemporary radiotherapy. CIRT has two key benefits over traditional photon radiation modalities in terms of physical and biological considerations. Physical benefits include increased dose distribution to the tumoral region and reduced dose harm to adjacent tissue. The biological benefits include an increase in Double-Strand Breaks (DSBs) in DNA structures, an increase in oxygen enhancement ratio, and improved radiosensitivity as compared to X-ray radiation. CIRT has two advantages: it not only inflicts severe cytotoxic damage on tumor cells, but it also protects adjacent tissue. Lung cancer is the second most frequent cancer in the world, after breast cancer, in terms of annual diagnosis. Lung cancer, on the other hand, is the primary cause of cancer death. Patients with stage I non-small cell lung cancer (NSCLC) who were treated optimally had lobectomy. When paired with surgery, some individuals with comorbidities or concomitant cardiopulmonary insufficiency have been demonstrated to be unable to tolerate the treatment. As a result, radiation may be the best therapeutic option for this patient group. For these situations, radiation options include Stereotactic Body Radiotherapy (SBRT), Volumetric Modulated Arc Treatment (VMAT), and Intensity-Modulated Radiotherapy (IMRT) (IMRT). Although these treatments have shown clinical advantages to certain patients, the associated Adverse Effects (AEs), such as cardiotoxicity and radiation pneumonia, must not be overlooked. Normal tissue damage and toxicity also restrict tumor dosage increases. Because of the tremendous physical and biological benefits provided by CIRT, certain toxicity associated with radiation may be avoided with CIRT Bragg Peak. CIRT provided clinical advantages to lung cancer patients, particularly the elderly. This review discussed the clinical efficacy and research findings for CIRT in Non-Small Cell Lung Cancer (NSCLC).

Keywords: Non-Small Cell Lung Cancer (NSCLC) • Carbon-Ion Radiotherapy (CIRT) • Dose escalation • Efficacy • Toxicity

Introduction

Lung cancer is a prevalent malignant oncologic disorder that affects people all over the world, particularly in industrialized countries and places. According to the 2020 Global Cancer Statistics, 19.3 million new cancer cases were diagnosed in that year, with nearly 10 million deaths from new cases [1]. Breast cancer in female patients has surpassed lung cancer as the most commonly diagnosed cancer in 185 countries worldwide, according to Global Cancer Statistics 2018. According to the data, the number of newly diagnosed female breast cancer cases was 2.3 million (11.7%), followed by lung cancer (11.4%). As a result, lung cancer was the leading cause of cancer incidence and death worldwide at the time. More current data from 2020 indicate lung cancer as the top cause of cancer death, accounting for an expected 1.8 million deaths (18%), followed by colorectal cancer (9.4%). Despite the high prevalence of female breast cancer in 2020 data, the mortality toll for new cases is 68 thousand (6.9%). In conclusion, while female breast cancer is the most commonly diagnosed cancer, lung cancer has a significant part in raising the global cancer mortality burden [2].

Male and female cancer patients have a varied incidence and fatality rate, according to data. Lung cancer is still the largest cause of morbidity and mortality in males, but it ranks only third in terms of incidence in women, trailing breast and colorectal cancer. The highest rates of occurrence are found in high-income countries or areas. The tobacco pandemic and environmental degradation are the primary reasons. Between 2010 and 2014, the 5-year Overall Survival (OS) rates of patients with lung cancer after diagnosis were observed to be 10% to 20% in most countries. However, different countries provide different results. Patients with lung cancer have a good prognosis in some Asian countries, including Japan, Israel, and the Republic of Korea. According to certain studies, there are two major variables contributing to the rise in OS rates. One is early cancer detection and assessment for high-risk individuals using low-dose Computed Tomography (CT) [3]. Another example is effective treatment techniques for people with lung cancer, such as surgery, radiotherapy, chemotherapy target therapy, and extra evaluations. These are key influencing factors on the survival rates of lung cancer patients. Because of the inclusion of numerous therapies including CIRT, the 5-year OS rates for early-stage NSCLC have increased from 20% to 60%-70%. This is particularly true in wealthy countries.

Radiotherapy has emerged as an important treatment option for people with lung cancer. Especially when early-stage patients are geriatric people with coronary artery disease and other problems including liver and kidney function difficulties. This patient group is unable to tolerate surgery or chemotherapy. External beam radiation therapy is the most commonly used treatment modality, and it includes Stereotactic Body Radiotherapy (SBRT), Volumetric Modulated Arc Therapy (VMAT), Intensity-Modulated Radiotherapy (IMRT), and image-guided intensity-modulated radiotherapy. When patients are treated with SBRT, IGRT may provide a routine procedure of position verification [4].

In this circumstance, SBRT will become the recommended treatment option for patients with lung cancer, particularly those with early-stage lung cancer. This is because, as compared to other therapies, SBRT offers additional advantages, such as low toxicity, a quick treatment time, and a therapeutic outcome that is comparable to or even better than surgery. Nonetheless, several acute Adverse Events (AEs) and toxicities must be considered. Although SBRT has demonstrated superior efficacy when compared to other radiotherapy modalities, it may result in radiation-associated pneumonia [5]. Because SBRT requires a high level of positional accuracy, the patient's positioning during treatment is dependent on in-room computed tomography instruments such as the Electronic Portal Imaging Device (EPID) and Cone Beam Computed Tomography (CBCT).

Patients may be given an additional dose of radiation in this instance. Finally, the treatment may result in problems involving Organs At Risk (OARs). CIRT shows considerable promise for cancer therapy when compared to traditional photon radiation techniques. It has two key benefits over X-rays: precise dose distribution and high cell-killing capacity. In this review, we discussed the efficacy and safety of CIRT for lung cancer patients.

The United States was the first country in the world to use heavy ion therapy. Before heavy ion therapy was approved as a cancer treatment, the National Cancer Institute (NCI) of the United States approved long-term funding for translational research on heavy ion therapy. Following the lead of the United States, the Japanese government decided in 1984 to build the Heavy Ion Medical Accelerator (HIMAC) at the National Institute of Radiological Sciences (NIRS) in Chiba, Japan. In 1994, the facility began clinic trials as an autonomous administrative institute, similar to the NCI. Simultaneously, the HIMAC evaluated the efficacy and toxicity of treatment with all types of cancer after CIRT. More than 20,000 patients were treated with CIRT in 2020, with fourteen institutes consistently executing the procedure [6]. The nations in which these institutions are located include Japan (six), Italy (one), Germany (three), China (three), and Austria (one). 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. For example, the first protocol (9303), which began in 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 patient's treatment SCLC [7].

Since 1994, the NIRS has been Japan's first medical center to use CIRT for tumor treatment. The Gunma Heavy Ion Medical Center (GHMC) is the country's first university hospital with a CIRT facility. Carbon-ion beams were chosen for clinical application based on preclinical experiments, although previous particle radiation experiments also played an important role in the curative treatment of cancers. It became clear that dose escalation studies for CIRT were required based on the differential effect and documented toxicity-risk reduction of the surrounding healthy tissue. Despite the fact that carbon-ion beams have a high Linear-Energy Transfer (LET) and a Spread out Bragg Peak (SOBP). The NIRS conducted the 9303 protocol phase I/II trial for stage I NSCLC patients from 1994 to 1998, and the 9701 protocol study from 1997 to 1999. The beginning dosage for the 9303 protocol was 59.4 GyE (3.3 GyE per fraction), while the dose increase for the 9701 protocol was from 68.4 to 79.2 GyE. Both trials concluded that a carbon dose of 86.4 GyE supplied in 18 fractions and one of 72 GyE administered in 9 fractions were the safe doses for the phase II study under the two protocols. Local control rates in the first and second trials, on the other hand, were 64% and 84%, respectively.

Masashi Koto et colleagues. Conducted another research in which 81 patients were divided into two groups: 47 patients (48 lesions) with 18 fractions over 6 weeks, and 34 patients with nine fractions over 3 weeks. The carbon dosage escalation approach was used on test individuals, with increments of 10% from 59.4 to 95.4 GyE and 5% from 68.4 GyE to 79.2 GyE. The findings revealed that 19 of the 82 lesions had a local recurrence. Another study on dose escalation for stage I NSCLC utilizing single-fraction carbon ion radiation included 20 patients who received a dose escalation of 48 GyE to 50 GyE (RBE) with a 58.6-month follow-up. At 5-years, the median LC rate, Overall Survival (OS), and Progression Free Survival (PFS) rate were 95.0%, 69.2%, and 60.0%, respectively. LC improved more than other dosage escalation groups (36 GyE RBE) and less than 36 GyE). Radiotherapy-related toxicity, on the other hand, had not risen when compared to thelower groups. There were no patients with Grade 3 or 4 acute or late pulmonary and skin toxicity.The biological effects of CIRT are clearly distinct from those reported in photon irradiation, according to a dosage escalation research. A substantial amount of clinical data is still needed to establish and verify the best treatment dose and segmentation approach.

Conclusion

Over standard photon radiation, CIRT has two important radiophysical and radiobiological advantages. This characteristic is used by clinical radiologists to treat malignancies that are resistant to standard photon radiation therapy. CIRT not only improves the curative efficacy of tumor treatment, but it also minimizes the irradiationof vulnerable organs. Due to the expensive medical costs and technology of CIRT facilities, there are now just a few units in the globe that can perform CIRT. Japan was a pioneer in the creation of CIRT technology, and their technology is quite advanced. Nonetheless, radiologists have not adequately examined the physical and biological aspects of CIRT. To learn more about the features and efficacy of CIRT, a significant number of randomized phase III trials should be done in the future.

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