

## Overview

## Clinical Indications for Carbon Ion Radiotherapy

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## Abstract

Compared with photon and proton therapy, carbon ion radiotherapy (CIRT) offers potentially superior dose distributions, which may permit dose escalation with the potential for improved sparing of adjacent normal tissues. CIRT has increased biological effectiveness leading to increased tumour killing compared with other radiation modalities. Here we review these biophysical properties and provide a comprehensive evaluation of the current clinical evidence available for different tumour types treated with CIRT. We suggest that patient selection for CIRT should move away from the traditional viewpoint, which confines use to deep-seated hypoxic tumours that are adjacent to radiosensitive structures. A more integrated translational approach is required for the future as densely ionising C-ions elicit a distinct signal response pathway compared with sparsely ionising X-rays. This makes CIRT a biologically distinct treatment compared with conventional radiotherapy.

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## Introduction

More than half of all cancer patients receive radiotherapy during the course of their illness, but only a small percentage of those are treated with particle therapy [1,2]. Most patients who receive particle radiotherapy are treated with proton beams, with a relatively smaller number receiving heavier ions, including carbon [3]. Compared with photon therapy, particles have physical advantages warranting a superior dose distribution, which allows a more accurate tumour targeting and dose escalation with better sparing of nearby organs. Within the field of particle therapy, different nuclei have different physical and biological properties [4]. Carbon ions, for

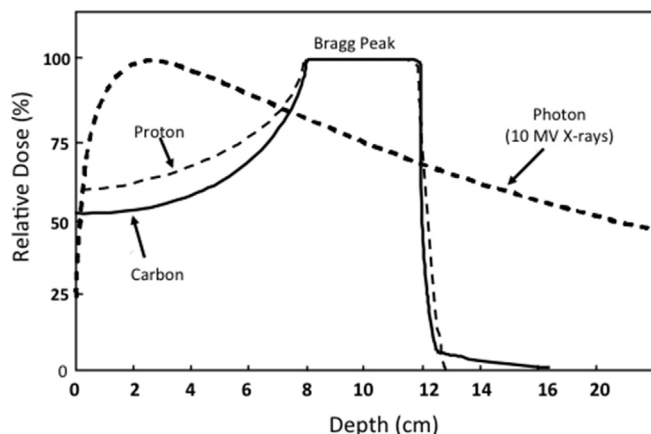
example, have a better dose distribution and increased biological effectiveness compared with protons.

## A Brief History

The use of particles in radiotherapy was initially proposed in 1946 by physicist Robert Wilson [5]. It was several years before the first patient received proton beams at the Lawrence Berkeley National Laboratory in California in 1954. The patient had a pituitary gland tumour. The first case series with proton radiotherapy was published in 1958 [6]. Starting in 1975, physicians at the Lawrence Berkeley National Laboratory treated hundreds of patients with other ions, including carbon ions, for various indications. Unfortunately, the programme was shut down in 1992 due to financial constraints. The accumulated experience from the USA together with a growing community of particle therapy advocates from Europe and Japan led to the treatment of thousands of patients with proton and other particle beams. In 1994, the National Institute of Radiological Sciences

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**Fig 1.** Percentage depth dose curves for carbon, proton and photon beams showing clear physical advantages for carbon ion beams.

(NIRS) treated the first patient with carbon beams at the Heavy Ion Medical Accelerator in Chiba, marking the second birth of carbon ion radiotherapy (CIRT). Soon after, in 1997, the Gesellschaft für Schwerionenforschung (GSI) started a treatment programme in Darmstadt, Germany, followed by the Heidelberg Ion Therapy Center in 2009. Currently, more than 11 CIRT centres are in operation (Japan [five], Germany [two], Italy [one], China [two], and Austria [one]) [7] and several others are under construction.

## Physical and Biological Advantages

We have previously reviewed the physical and biological characteristics of carbon ion beams for cancer treatment [8,9]. Here, we will only briefly review some of the major properties of CIRT, how these characteristics contribute to their enhanced clinical efficacy and how they should be considered in designing clinical trials.

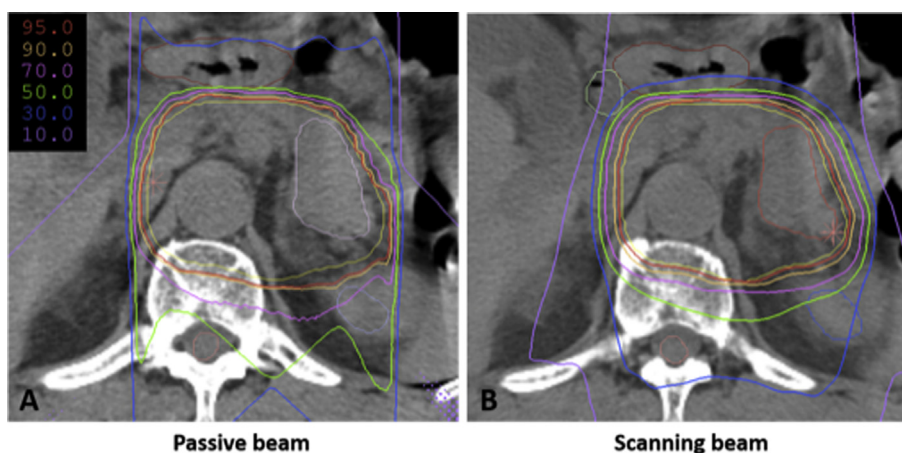
### Physical Advantages

Given their physical charge, mass and high initial energy, heavy particles such as carbon ions transfer their energy in

matter as a function of depth. As such, and in contrast to photons where the maximum dose ( $D_{\max}$ ) is close to the skin surface, little ionisation energy is deposited at or near the surface with CIRT, but rather most energy is deposited at a well-defined depth with a relatively well-defined range. This peak of dose distribution is called the Bragg peak. By manipulating the beam line and/or weighting different energies, the whole depth of any particular tumour can be irradiated with CIRT with a high peak-to-plateau ratio and no exit dose. This extended Bragg peak is called the spread-out Bragg peak [10,11] (Figure 1). Carbon beams have less Coulomb interactions and subsequently sharper lateral penumbra compared with proton beams [9]. These physical characteristics impart a superior dose distribution to CIRT that is not paralleled in other radiotherapy modalities. This has been repeatedly shown in dosimetric studies [12–14] with even more improved dose distribution with scanning compared to passive beams (Figure 2). Notably, this advantageous dose distribution is not perfect given the range uncertainty at the distal end of the Bragg peak [15] and its sensitivity to set-up variation, and inter-fractional anatomic change [16] and tumour motion [17]. Nonetheless, CIRT is believed to have the capacity of delivering higher energy to deep-seated tumours while simultaneously sparing nearby radiosensitive structures better than photon- or proton-based therapies.

### Biological Advantages

To better understand the radiobiological characteristics of CIRT, it is important to mention their superior linear energy transfer (LET) values when compared with either photons or protons. LET is defined as the energy transfer from a radiation beam to the medium it traverses per unit length. This increased LET of carbon beams leads to significantly different biological effects at the DNA level. This measure of biological potency is termed relative biological effectiveness (RBE), which is the ratio of dose from a particular radiotherapy modality needed to cause the same amount of tumour kill as a reference dose, which is usually X-rays of 250 kVp. Thus, RBE for photons is 1. Although RBE



**Fig 2.** Dose distribution by passive (A) and scanning (B) beams using carbon ion radiotherapy for pancreas cancer showing a clear reduction in the dose to the spinal cord and left kidney with scanning beams.

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