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RADIATION THERAPY PHYSICS

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Carbon Ion Radiotherapy

Authors:
Angel CHAVIRA
Tracy CHEN
Emeline HANNA
Kaiwen HU

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1 Introduction

Carbon ion radiotherapy (CIRT) is a type of particle therapy that uses carbon ion beams for cancer treatment. It is a form of external beam radiotherapy that delivers radiation through beams of energized carbon ions to tumor sites while sparing surrounding healthy tissues.

The start of particle therapy dates back to 1946, when Robert R. Wilson introduced the idea of using high-energy particles in radiology [1]. In the 1950s, the development of high-energy medical linear accelerators allowed this concept to be used clinically. Around the same time in 1954, Lawrence Berkeley National Laboratory (LBL) began treating patients with particle therapy using protons. Between the 1970s to 1990s, LBL expanded its trials to include the clinical use of other charged particles (helium, carbon, neon, etc). The trials were halted in 1992 due to concerns regarding the use of certain particles. Nonetheless, in 1994, with much of the knowledge developed in LBL, Japan opened its first CIRT facility in Chiba. Three years later, Germany opened the first CIRT facility in Europe. Between the 2000s to 2010s, several additional facilities were built in Europe and Asia in Italy, Japan, and China. Currently, the first CIRT facility in North America is under planning [2].

1.1 Physical Advantages

For heavy charged particles like carbon ions, the depth dose curve is characterized by a slow initial dose increase to a steep rise at the Bragg peak followed by a sharp dose fall off as shown in Figure 1. This allows for a more precise dose localization than lighter particles such as electrons. Due to the heavier mass, carbon ion beams have smaller lateral scattering and range straggling, which allows for better dose conformation. Another unique characteristic of the carbon ion beam is that it produces a dose tail at the distal side that emits carbon isotopes, which is useful for the verification of the range and quality of the applied dose without needing to apply additional dose for checking [3].

1.2 Radiobiological Advantages

As discussed in the previous section, carbon ion beams are characterized by a low linear energy transfer at the entrance that increases in proportion with depth until it reaches the maximum at the Bragg peak. Another advantage of this phenomenon is that the relative biological effectiveness (RBE) of the treatment also increases in parallel with the dose at the Bragg peak region. This translates to a reduction in tissue side effects and complications [3]. It follows that the improved RBE near the Bragg peak caused by the dense ionization reduces cellular repair, which makes the carbon ion beam advantageous in treating radio-resistant tumors near organ-at-risks [4].

1.3 Delivery Method

For the most part, treatment delivery with carbon ion beams are similar to other treatment in particle therapy. Advanced beam delivery systems such as pencil beam scanning, superconducting

rotating gantry, and multi-ion beams are some examples that could enhance CIRT performance. Similarly, motion management is also important in treatment using carbon ion beams. Some practices include beam gating where the beam is turned off after the tumor is moved out of the planned area and repainting layers or treatment volumes, which involves rescanning to capture motion. Finally, for treatment planning, the procedure is similar to other particle therapies with the exception of modeling the biological effectiveness of carbon ion treatment. While it was discussed that the enhanced RBE from using carbon ion beams, there is no clear consensus within the scientific community on how RBE should be modeled. The complexity that arises from this is that carbon ion beams are sensitive to variations in density along the beam path. This causes instability in dose to tumor and OAR. Thus proper treatment planning is needed to alleviate these concerns [2].

2 Challenges

2.1 High Capital Costs

By far the biggest challenge that carbon ion radiotherapy faces is the large initial capital costs. A typical CIRT facility is made up of linear accelerators and a synchrotron which have a large footprint and high price tags. For example, the High Ion Medical Accelerator (HIMAC) in Chiba, Japan, which was commission in the mid 90's, consists of a 2 stage LINAC, and a 42 meter diameter double ring synchrotron, cost an estimated $332M [5] [6] [7]. The Heidelberg Ion-Beam Therapy (HIT) center in Heidelberg, Germany is compromised of a 2 stage linear accelerator built by Siemens and a 65 meter diameter synchrotron [8] [9]. The HIT facility was approved for construction in the early 2000's and cost the Heidelberg Hospital and German government €119M [10]. The last example, National Center for Oncological Hadrontherapy (CNAO) in Pavia, Italy saw its first patient in 2012. This CIRT facility uses an improved version of the LINAC used in the HIT center but has a 78 meter diameter synchrotron [8] [11]. CNAO cost the Italian government an estimated €188M [12]. A study from the Netherlands in 2007 found that the average initial capital costs for a CIRT facility was €159.6M [13].

2.2 Carbon-Ion vs Photon Costs

The comparison between carbon-ion and photon commissioning and operational costs was done to show the large discrepancy between the two technologies [13]. In this study mock designs for a carbon-ion and a photon facility were drawn. Medical data was retrieved from Maastro Clinic in the Netherlands and construction and fabrication costs were averaged prices from the consultant firm Turner & Townsend. Peeters et al. found that for a typical carbon-ion beam facility the majority of the cost, about 2/3 equal to €90M, was used for the construction of all therapy equipment which includes, but not limited to, a linac and synchrotron. Due to the large footprint, the building construction costs came as the second most expensive item at €35M. In total, this mock design of a CIRT facility had a total of €138M. Daily operation and staffing costs were significantly affected due to the larger and more complex nature of CIRT facilities.

In contrast, a photon facility is much cheaper to build and operate. The most expensive capital purchase is for the medical equipment and IT services which compliment the actual therapy equipment. The operation costs were found to be 4 times lower than CIRT due to the abundance of photon facilities around the world. The capital costs and the yearly operation costs were found to be €26m and €8M, respectively.

2.3 Patient Treatment Burden

The burden of the high capital cost ultimately affects the patient and how much they pay for their treatments. Two independent studies found that the average cost per treatment lies between €20,560 and €24,700 and the range for treatments is €15,000 to €40,000. Further, the cost per fraction for carbon-ion therapy is on average 5 times more expensive than traditional photon therapy. Ultimately, the cost per treatment relies upon the number of fractions and cancer being treated. For example, treating prostate cancer with CIRT is comparable in price to other forms of radiotherapy (i.e photons and protons). CIRT treatment is more expensive when treating lung cancer as shown in Figure 2 [13].

3 Potential solutions

Since the accelerator part primarily drives the cost, we will seek solutions other than conventional cyclotrons or synchrotron accelerators to decrease the cost. Fixed Focusing Alternating Gradient (FFAG), Cyclinac, and All Linac are some common choices.

3.1 FFAG

Fixed Focusing Alternating Gradient (FFAG) accelerators [14] can be seen as a combination of both the cyclotron and the synchrotron. These accelerators use a fixed magnetic field that is time-independent, like a cyclotron. Additionally, they maintain strong focus using alternating-gradient, like synchrotrons. There are two types of FFAG: scaling and non-scaling. Scaling FFAG is defined as constant field index k:

$$k = -\frac{\rho}{B_y}\frac{\partial B_y}{\partial x}, \tag{1}$$

$$\left.\frac{\partial k}{\partial p}\right|_{\theta=const.} = 0, \tag{2}$$

and geometrically similar orbits:

$$\frac{\partial}{\partial p}\frac{\rho_0}{\rho} = 0. \tag{3}$$

These two conditions mean the field can be described as

$$B_y = B_0 \left(\frac{r}{r_0} \right)^k \tag{4}$$

The non-scaling FFAG allows violation of this strict scaling law. Studies [15] show FFAG accelerators, non-scaling type especially, can reduce costs due to their compactness (small circumference), less complex magnets with a smaller aperture, and higher repetition rate.

3.2 All Linac

Linac is often used as an injector for cyclotrons or synchrotron accelerators. All linac, which means the accelerator is also linac, is proposed as an alternative solution. One example is the 750 MHz RFQ Linac proposed by Vittorio Bencini et al. [16] This method is developed by European Organization for Nuclear Research (CERN) and will be built as a collaboration between CERN and Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT). This accelerator consists of two radio frequency (RF) cavities, each comprising four distinct modules with their own input power couplers, 12 vacuum pumping ports, and 32 slug tuners. The RF cavities are designed to operate at a frequency of 750 MHz with a subharmonic frequency of 3 MHz. Trapezoidal vanes were utilized and 3GHz Side Coupled Drift Tube Linac (SCDTL) was selected downstream of the RFQ by shown advantages. This design can reduce costs due to its compactness, lower power consumption, and simpler construction.

4 Conclusion

There are currently 13 facilities around Europe and Asia that are using carbon ion radiotherapy to treat patients. From June 1994 to December 2020, 37,548 patients were treated with CIRT using these facilities. Mayo Clinic estimated that about 44,340 people who are diagnosed with cancer each year in the U.S. that would benefit from CIRT treatment [17]. Due to this need, Mayo Clinic is planning to build the first CIRT facility in North America in Jacksonville, Florida. This will allow for expanded options for North American patients for cancer treatment and also allow for patients to be involved in clinical trials that could further show the efficacy of this technology [18].

4.1 Alternatives

Due to the high cost and complexity of CIRT, there are alternative particle therapies, including using light ions, other heavy ions, and boron neutron capture therapy.

4.1.1 Light ions

Light ions are defined as ions with an atomic number less than 10. Light ions are another type of particle therapy. Light ions have beneficial physical properties that have potential clinical applications and advantages over external beam radiotherapy. Proton therapy is currently in use to treat

cancer. In a dose deposition as a function of depth curve, protons have a sharp Bragg peak where most of the ions stop and deposit their dose. This attribute is beneficial in radiotherapy because this high energy loss per path length, or linear stopping power (LET), can be centered within the tumor. Proton therapy clinics are less expensive than CIRT facilities, and there has been limited clinical evidence that carbon ion therapy has an increased benefit as compared to proton therapy.

Additionally, helium ions could be used to treat cancer. Helium has a similar depth dose curve to protons and causes similar radiobiological effects. However, as particles get heavier, they undergo less lateral scattering. Therefore, helium ions have a significant reduction in lateral scattering as compared to proton beams. This means the lateral penumbra is smaller within the patient, which can create a more conformal treatment to the tumor. Additionally, the neutron dose from helium ions may be lower than in proton therapy, and building a helium therapy facility would be cheaper than building a carbon ion facility [19].

4.1.2 Heavy ions

Heavy ions are defined as ions with an atomic number of 10 or greater. Heavy ions include carbon, but there are other ions used in particle therapy. Starting in 1975, Lawrence Berkeley National Laboratory used mostly neon and helium ions, but also carbon, silicon, and argon to provide pituitary treatments to patients.

Neon ions are much heavier than protons and helium, so they have an even smaller penumbra. However, neon and other heavy ions have an increased dose behind the Bragg peak, meaning that additional dose is given to the tissue behind the tumor. Furthermore, nuclear fragmentation in heavy ions causes the high LET region to no longer be limited to the Bragg peak [19].

4.1.3 Boron neutron capture therapy

Boron neutron capture therapy (BNCT) uses ^{10}B and a neutron beam to treat malignant tumors. The principle is that ^{10}B is accumulated in the tumor and then the patient is irradiated with a thermal neutron beam. The reaction of ^{10}B and neutrons produces alpha particles and lithium nuclei, which have a short range of about 10 microns and can cause cellular damage in a localized area [20].

4.2 Future of CIRT

Although there are alternatives to carbon ion therapy due to the high cost, CIRT has benefits. To summarize, carbon ion therapy offers superior tissue sparing since the ratio of the maximum dose to the entrance dose is larger in CIRT than in proton therapy or external beam as shown in Figure 1. Additionally, the larger mass allows for more accurate tumor targeting due to the smaller lateral penumbra. Finally, CIRT offers a higher tumor killing potential per unit dose since carbon ions have a high LET leading to dense ionization that causes clustered DNA damage [21]. Overall, these benefits are applicable to a wide variety of treatments, including head and neck maligancies, prostate caner, breast cancer, and lung cancers, and especially important in pediatric patients where secondary malignancies are of increased concern.

5 Figures and Tables

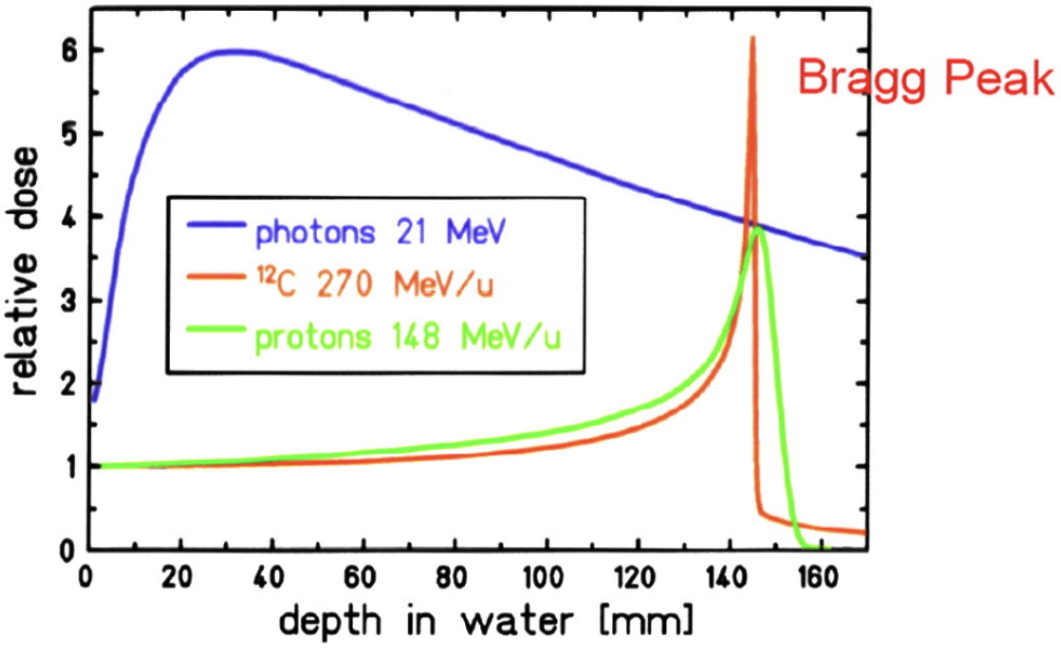

Figure 1: Depth dose curve comparison for photons, carbon ions, and protons [3].

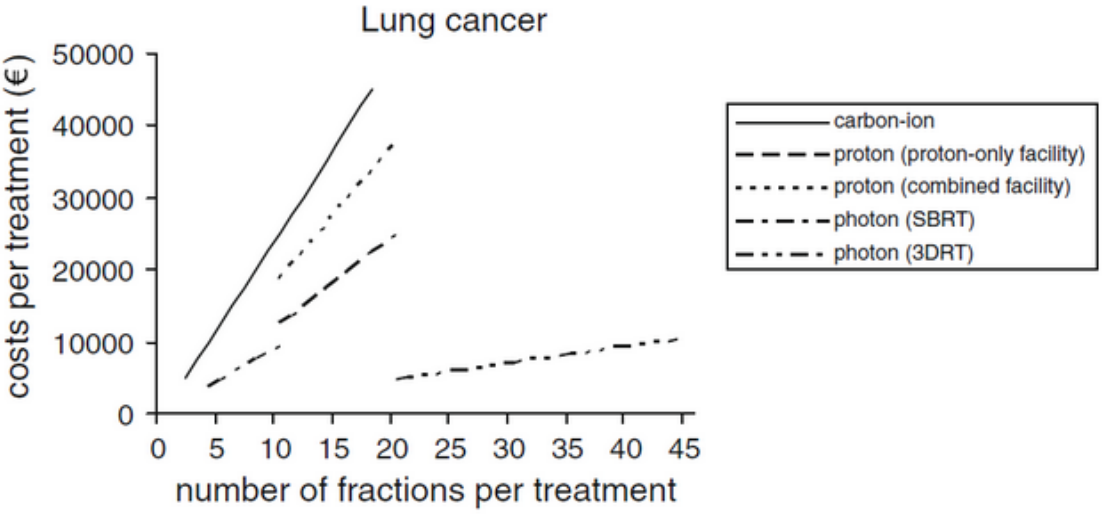

Figure 2: Lung cancer treatment cost for various radiotherapy modes [13].

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