Comparison of radio therapy and hadron therapy- with focus on damage of nearby tissues

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1 Introduction

Hadron therapy is an advanced form of radiation therapy that has shown significant potential in the treatment of cancer located near sensitive tissues or resistant to conventional radiotherapy. Unlike traditional radiation therapies that use X-rays, hadron therapy uses protons or carbon ions to deliver highly targeted energy with minimal damage to surrounding healthy tissues.

The precision that hadron therapy has is due to the fact that the heavy charged particles interact with the electrons in the material, in this case the tissue, delivering the highest radiation dose at a peak near the particles range.

The aim of this analysis is to compare the effect of the clinical applications of hadron therapy vs traditional radio therapy such as X-rays for cancer-treatment, highlighting the growing role of hadron therapy as a precise and powerful tool in modern oncology.

2 Radiotherapy

Radiotherapy uses ionizing radiation to selectively destroy cancer cells, especially for solid tumours. It is most commonly used in addition to surgery, but it can be also a definitive treatment avoiding surgery.

2.1 How it works

Radiotherapy typically uses ionizing radiation or high-energy particles. At the atomic level 'ionizing' radiation ionizes atoms by disrupting the electrons out of their orbits within atoms. At a cellular level the most important effect this causes is breaks in the DNA. When such damage occurs in critical parts of the DNA, the cell cannot replicate. Efficient DNA-repair mechanisms in normal cells can repair almost all such DNA damage, but such recovery is more difficult for dysfunctional cancer cells. This difference gives radiotherapy its therapeutic ratio. In addition, ionizing radiation also releases free-radicals and cancer cells are more sensitive to such a toxic rise and succumb, while normal cells can counter this with robust mechanisms.

Different types of cancers react differently to radiotherapy. For example, testicular seminoma and Hodgkin's lymphoma, are highly radio-sensitive. On the other end of the spectrum, sarcomas in adults and melanomas are relatively 'radio-resistant' although radiotherapy is still useful as an adjuvant to surgery, which remains the primary curative modality. The DNA and cellular damage caused by therapeutic radiation can cause acute damage to nearby tissues and long-lasting effects are caused by injury to the vasculature, nerves and by inducing new cancers. The examples of the latter are sarcoma and lung cancer after whole breast irradiation, and breast cancers occurring in those given mantle irradiation for lymphoma in their young adulthood; such cancers are unsurprisingly more common in those with inherited deleterious gene mutations in breast cancer genes.

Character of therapeutic radiation	**Penetration**	**Typical examples**
High-energy photons/x-rays/gamma rays	Deep - can spare superficial structures such as skin	Breast, Prostate, Rectum
Low-energy photons	Short reach — and low dose rate	Intraoperative use — breast, brain, spine, rectum
High-energy electrons	Superficial reach only (1–2 cm)	Skin metastasis, skin cancers, superficial bleeding
Protons	Limits distal dose	Brain, skull base tumours, childhood, spinal tumours

Table 1: Character of therapeutic radiation and typical examples

Modes of delivery of therapeutic radiation	Characteristics	Typical examples
External beam radiotherapy	Requires bulky equipment (LINAC) in underground bunkers. Very versatile. Intensity modulated/3-D planning as well as alteration of breathing can reduce but not avoid harmful scattered radiation (Siemens, Varian, General Electric, etc)	Breast, Rectum, Prostate, Brain, Head and neck, Spine, Oesophagus
Intraoperative radiotherapy	Mobile equipment which is much less expensive than LINAC (Zeiss Intrabeam)	Breast (TARGIT-IORT), colorectal cancer, brain (INTRAGO), spine (Kypho-IORT)
Radioactive molecules	Highly targeted treatment due to tissue affinity. So can only be used for very specific types of cancers	Thyroid cancer with radio-iodine I^{131}
Radioactive wires/seeds	High dose-rate radiation for short distances	Cervix, prostate, sometimes breast

Table 2: Modes of delivery of therapeutic radiation and their typical examples

Generally speaking it's right to assume that higher is the energy of the radiation and deeper would be the penetration.

Traditional radiation employs photons, which have zero mass, at a higher energy and they can be given using linear accelerators (LINACs), or using radioactive materials such as iridium wires.

External beam radiotherapy (EBRT) is typically delivered using LINACs, which are very huge and occupy large rooms. Using large tubes, they create a series of electric potentials, therefore when charged subatomic particles pass through such an oscillating field, they accelerate to a high speed and generate x-rays and high-energy electrons. Typical photons penetrate deep, so superficial layers such as the skin receive a much lower dose, reducing skin toxicity.

High energy electrons transfer their energy to a smaller thickness of tissue (1-2 cm) so can be used for skin cancers or skin metastasis.

The most common form of intraoperative radiotherapy (TARGIT-IORT) uses a miniature linear accelerator in which electrons are accelerated to the gold tip of a 3.5 mm tube generating low-energy x-rays. For breast cancer, various sized spherical applicators (1.5e5 cm diameter) can be inserted in the tumour bed immediately after a lumpectomy to give therapeutic radiation to the tissues at highest risk of local relapse. Smaller LINACs can be made mobile (with some difficulty) and can be used for intraoperative radiotherapy (IOERT) for delivering electrons through an open wound.

2.2 X ray matter interaction

Photons interact with matter via a range of mechanisms, which can be classified according to the type of target, and the effect of the interaction on the photon (absorption or scattering) as it is possible to see in the figure below. At energies beyond the ultraviolet range, the dominant processes are photoelectric absorption, Compton scattering, and pair production. As illustrated in Fig. 2.1, photoabsorption constitutes the largest contribution to the total cross section at low photon energies, pair production is the most frequent interaction at high energies, and Compton scattering dominates in the intermediate energy range.

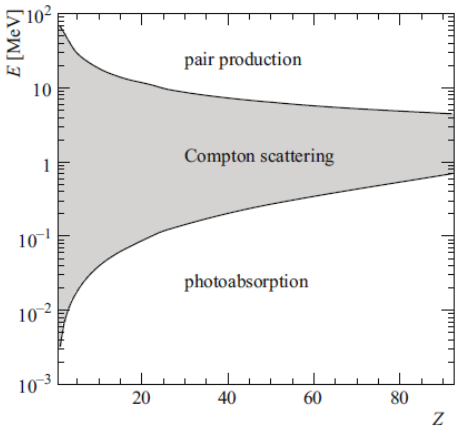

Figure 1: A plot showing regions of pair production, Compton scattering, and photoabsorption as a function of atomic number (Z) and energy (E) in MeV.

2.2.1 Photoabsorption

In a photoelectric absorption interaction, the incident photon disappears and its energy is transferred to the target atom (or group of atoms). The intensity I of a monochromatic beam of photons with energy E thus decreases exponentially as a function of the penetration depth x in a material,

$$I(x) = I_0 e^{-\mu x},$$

where the attenuation coefficient μ is proportional to the atomic density N of the medium and the photoabsorption cross section σ_γ,

$$\mu(E) = N\sigma_\gamma(E).$$

2.2.2 Compton Scattering

Compton effect is an inelastic process in which a photon scatters off a charged particle, typically an electron, resulting in a decrease in energy (increase in wavelength) of the photon.

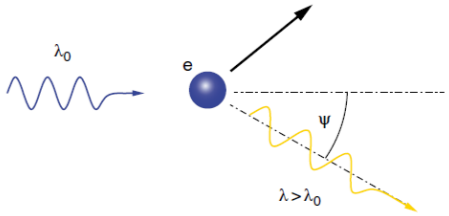

Figure 2: Compton Scattering Diagram

The energy loss in Compton scattering is simple to determine by applying conservation of total energy and momentum, and results in

$$\frac{h\nu_0}{h\nu} = \frac{k_0}{k} = \frac{\lambda}{\lambda_0} = 1 + \frac{\lambda_C}{\lambda_0}(1 - \cos\psi), \tag{1}$$

where the incoming photon has the frequency $\nu_0 = \frac{c}{\lambda_0}$, its wavevector is $k_0 = \frac{2\pi}{\lambda_0}$, ψ is the angle by which the photon is scattered, and λ_C is the Compton scattering length, given by

$$\lambda_C = \frac{h}{m_e c} = 2.43 \times 10^{-2}\,\text{Å}. \tag{2}$$

2.2.3 Pair Production

For photon energies exceeding $2mc^2$, an interaction mechanism becomes possible where the incoming photon disappears and an electron-positron pair, with a total energy equal to the photon energy E, is created. Momentum conservation requires this process, which is closely related to bremsstrahlung (Sect. 2.4.1), to take place in the electric field of a nucleus or of the atomic electrons. In the latter case, kinematic

constraints impose a threshold of $E > 4mc^2$. At high photon energies, the electron-positron pair is emitted preferentially in the forward direction, and the absorption coefficient due to pair production can be approximated by

$$\mu = N\sigma_{\text{pair production}} = \frac{7}{9}\frac{1}{X_0},$$

where X_0 is a material-dependent parameter known as the radiation length.

3 Hadron therapy

Hadron therapy is a form of radiation therapy that uses charged particles like protons or carbon ions instead of the traditional X-rays to treat cancer. Unlike conventional radiation that affects surrounding healthy tissues, hadron therapy is more precise[7]. This makes it possible to target tumors while minimizing damage to healthy tissues.

3.1 Bragg peak and stopping power

During hadron therapy the charged particles, usually protons or carbon ions, penetrate the body with minimal scattering and deposit most of their energy at a specific point called the Bragg peak. The rate of energy loss as a function of the unit distance travelled is called the stopping power, $\frac{dE}{dx}$. The energy loss can be expalined using the Bethe-Bloch formula, which when plotted gives the Bragg curve from where the Bragg peak can be seen.

$$-\frac{dE}{dx} = \frac{4\pi z^2 e^4}{m_e c^2} \cdot \frac{1}{\beta^2} \left[\ln\left(\frac{2m_e c^2 \beta^2 \gamma^2 T_{\max}}{I^2} \right) - \beta^2 \right] \tag{3}$$

In Equation (3) z is the charge of the particle, m_e is the mass of an electron, c is the speed of light and β is $\frac{v}{c}$ where v is the velocity of the particle. γ is the relativistic factor defined as $1/\sqrt{1-\beta^2}$ and W_{max} is the maximum energy transfer possible in a collision.N_a is Avogadro's number and A is the mass number of the material. Lastly, I signifies the mean excitation potential of the medium, which is a property dependent on the material being irradiated [4].
The energy deposition pattern arises because charged particles lose energy gradually by interactions with the material.

$$-\frac{dE}{dx} \propto \frac{1}{\beta^2} \tag{4}$$

As seen in Equation (4), the stopping power increases as v approaches zero by the end of the particles range. When the particle slows down it interacts more with the material, depositing more energy by the end of its range.
The differences between proton and carbon ion therapy are primarily due to their difference in weight and respective stopping powers.

$$-\frac{dE}{dx} \propto z^2 \tag{5}$$

Since carbon ions are heavier and more charged than protons they have a significantly higher stopping power which can be seen in Equation (5).
A proton has a charge of *1+* and a mass of about 938 $\frac{MeV}{c^2}$, which is approximately

1840 times the mass of an electron. On the other hand a fully stripped carbon ion has a charge of $6+$ and a mass approximately 11.9 times that of a proton. This results in a sharper and more intense Bragg peak for carbon ion therapy compared to proton therapy.

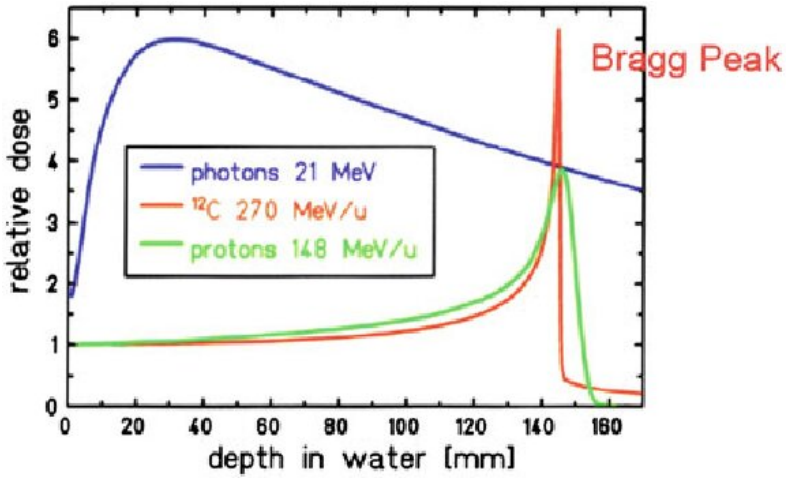

Figure 3: Relative dose deposition at different depth in water of different beams

As seen in Figure (3) carbon ions are capable of delivering higher radiation doses to tumors making them very effective for treating radio resistant cancers while preserving the surrounding healthy tissues[10].Much like with radiotherapy, the damage done to the tumour by hadron therapy is due to the high energy that damage the DNA to such an extent that it is impossile to repair itself[13].

3.2 Uses of hadron therapy

Hadron therapy requires the acceleration of protons or other charged particles, mainly carbon ions in this case. The particles are accelerated by a particle accelerator, such as a synchrotron which they use in Italy, Pavia. There are only six facilities capable of giving proton and carbon ion therapy worldwide, and CNAO is one of the. Located within a large bunker at the CNAO, the synchrotron has a circular design with a diameter of 25m and a circumference of 80m. It is shielded with concrete ranging from 2m to 6m in order protecting against radiation hazards generated during operation[9].
Inside the circle there are two sources which are responsible for generating the necessary particle beams. These sources utilize a mixture composed of gas nuclei allowing for the efficient extraction of charged particles. By using magnetic fields and radio frequencies protons and carbon ions are extracted from the mixture form-

ing beams made up of billions of particles[5].
Inside the synchrotron the particles are accelerated to very high energies with protons reaching up to 250 MeV and carbon ions achieving up to 4800 MeV. To attain these energies the beams are accelerated by a series of magnetic and electric fields that guide and energize them as they travel within the synchrotron. After achieving their target energies the beams are directed out of the synchrotron and delivered to the treatment rooms[9].
There are multiple types of cancers where hadron therapy, and mainly proton therapy since heavy ion therapy is still in the clinical stages, have shown great success. Some examples are:

Tumor Location	**Cancer Type**	**Examples of Treatment**
Brain, Skull Base, and Spinal Cord	Skull base chordomas, Low-grade gliomas, Intracranial meningiomas	Precise delivery to avoid damage to critical structures like nerves and vessels
Head and Neck	Ocular melanomas, Adenoid cystic carcinomas, Salivary gland tumors	Treatment around delicate areas such as eyes, sinuses, and glands
Chest Tumors	Lung cancer, Breast cancer	Focused treatment to spare heart and lungs, minimizing damage to vital organs
Pelvic Tumors	Prostate cancer, Rectal cancer	Precise targeting to minimize collateral damage to pelvic organs
Limbs and Spine	Chordomas, Sarcomas	Highly localized targeting for bones and soft tissues

Table 3: Prominent cancer types treated with hadron therapy at *The National Center for Oncological Hadrontherapy* [9]

As noted from Table (3), the treatments that use hadron therapy are in areas that have sensitive surrounding tissue or delicate tissue, making radio therapy diffucult due to the large amount of energy that gets deposited when the photon travels through the body.

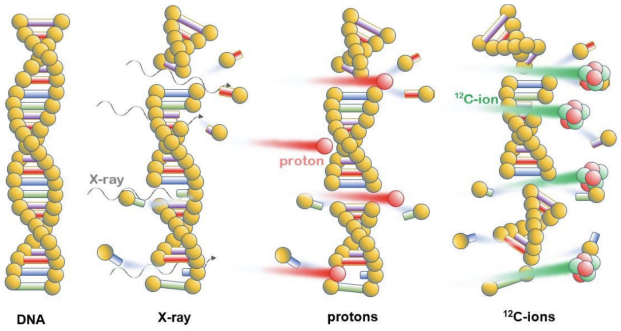

Figure 4: Illustration of the damage to DNA induced by radiation with X-rays, protons and C-12 ions. The damage with protons and even more with C-12 ions provide breakage of the double chain of DNA [3]

4 Comparison and discussion

As discussed in the previous section, proton and light ion beams have very different physical and radiobiological characteristics which diverge markedly from those of conventional radiotherapy beams composed of gamma rays or X-rays. The main issue with X-rays treatments is related to dose deposition properties: a large part of the radiation is delivered to the tissues surrounding the area that has to be treated, causing unwanted damage in the patients. On the contrary, the stopping power of protons and light positively charged particles has a sharp increase near the range giving rise to the 'Bragg peak', resulting in high dose deposition confined to the target area. Fig. 3 shows in a straightforward way the aforementioned difference, using water as example medium.

Furthermore, the Radiation Weighting Factor (W_R), which is a measure of the biological damage to a human for a particular type of radiation, is higher for protons and heavier ions with respect to photons. This means that given physical dose delivered by the hadron beam, the biological damage to irradiated tissues is higher with respect to photons, making it a better option for damaging cancerous cells' DNA (Fig. 4).

However, these advantages can be exploited only if it is made sure that the beam hits the target at any time during irradiation: if it is displaced, the beam would cause severe collateral damage to healthy tissues.

4.1 Photon dose deposition

X-rays have a dose distribution in tissues characterized by an almost exponential attenuation and absorption, delivering large energy near the beam entrance,reaching a maximum at few cm depths, and then continuing to deposit significant amounts

of energy beyond the cancer target. Indeed, when a photon beam interacts with the material electrons will be knocked out from the atoms and influence the way in which the dose is deposited. By looking at Fig. 3 (blue line) some features of the photon beam dose delivery curve in can be identified [11]:

- Surface dose: mostly due to radiation backscattered within the patient, it decreases with increasing photon beam energy;
- Build-up region from surface to the peak δ: in this region the dose builds up as the electrons that have been liberated in the preceding layers deposit their dose, reaching a maximum at a depth δ below the surface;
- Fall-off in dose: the dose falls off due to attenuation of the photon beam.

Hadron beam dose deposition

Protons are light and therefore easier to produce and accelerate with respect to carbon ions. Fig. 5 shows a comparison between the dose delivered distribution as a function of the depth in water by proton and carbon ion beams with different energies.

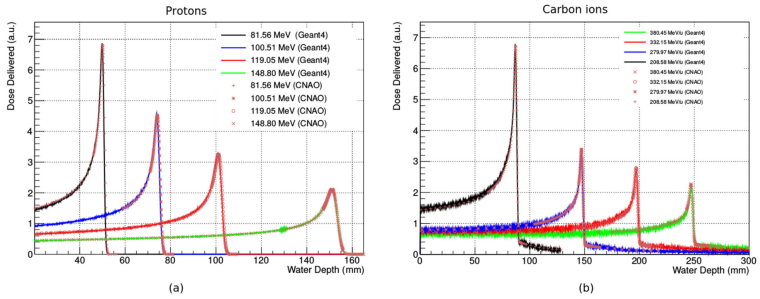

Figure 5: Percentage depth-dose deposited in a water phantom by proton (a) and carbon ion beams (b) with 4 different nominal energies. Curves are normalized at the dose deposited by the beam with lower energy (81.56 MeV for protons and 115 MeV/u for carbon ions). For carbon ions 2 ripple filters (each 2 mm thick) were added. [8]

4.2 Characteristic of ion beam

Differently from the neutral beam of photon, the ion may undergo inelastic collision with atomic electrons, leading to a lateral beam spread mainly caused by Coulomb scattering. Ions may experience this effect in the air between the nozzle and the patient and inside his tissues. The effect of the beam broadening due to the path

travelled in air is relevant at low energies of the beam, while at high energy the most relevant beam-broadening effect occurs in the tissue.

As clearly results from Figure 6, the scattering angle is inversely proportional to the momentum of the projectile, resulting for the carbon ions in higher precision treatment.

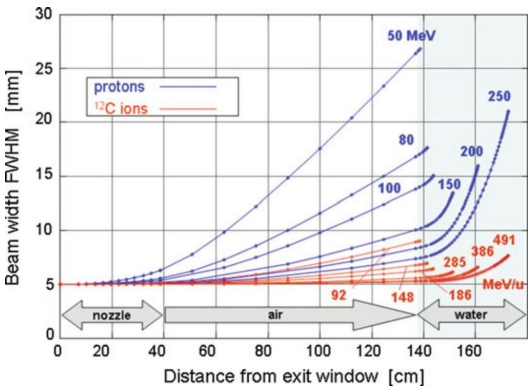

Figure 6: Comparison of the beam width between proton and ^{12}C ion in the air gap and water. [2]

Nevertheless, a drawback of the heavier ions is nuclear fragmentation. ^{12}C atoms may break up into three lighter α-particles that may follow a different path from the original particle. This contribute in increasing range uncertainties. In the distal part of the Bragg curves (beyond the peak), in fact, a "tail" is observed in the dose deposition due to the contribution of the light fragments. Sometimes, to limit the unwanted dose released by the tail of the Bragg peak, is implanted surgically a "sock" in Gore-Tex behind the target, stopping light fragments and avoiding to deposit dose in healthy tissues.

4.3 Biological effectiveness

Different studies have investigated the probability of survival of the cell ad a function of the absorbed dose, identifying cell death as the loss of reproductive capacity. In Figure 7 are represented the survival curves for different beams, radiating Chinese hamster cells. The X-rays dose effect curve has a non-linear trend, meaning that at low doses the radio-sensitivity is small and the cells are able to repair the damage, while at higher dose the curve is more steeper. For the carbon ions there is a strong dependence with the energy. Defining:

- **LET** (Linear Energy Transfer) as the amount of energy that a radiation particle transfers to the material it passes through per unit distance.

- **RBE** (Relative Biological Effectiveness) as the ratio between X-ray dose an ion dose that produces the same biological effect. It measure the effectiveness of different types of radiation in producing biological effects.

At high energy (266.4 MeV), the curve is steeper than the x-ray curve, but still a non-linear behaviour is not negligible. At intermediate energy (11.0 MeV) LET is higher since it means that the beam is closer to the Bragg-peak, as a consequence irreparable damage are much more frequent and RBE is high. However, at lower energy (2.4 MeV), despite the higher energy the curve is less steeper and RBE is lower. This could be explained because the dose deposited by a single ion is much more higher than the one required to kill the cell (overkill). Moreover, the flux required to deposit a these small doses at very high energy is much smaller, thus a fraction of cells may not be hit.

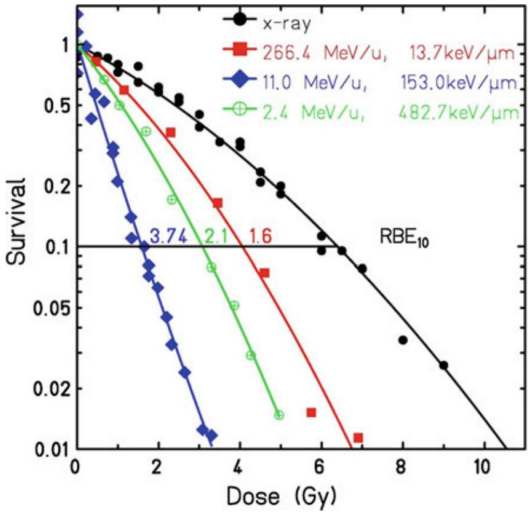

Figure 7: Dose-effect curves of Chinese Hamster for X-rays and ^{12}C ions at different energies. [16]

4.4 Compared result

The higher dose deposited allows to treat more effectively radio-resistant tumors that the weaker conventional radiotherapy is not able to treat. Moreover, the restricted area of deposition of the energy is suitable for cancers surrounded by high-sensitive tissues, minimizing the exposure before and after the target.

Fig. 8 shows the wide range of pathologies treated at CNAO, in Pavia, Italy. This center is one the biggest in Europe for both proton and carbon ions therapy. In their report is declared that for some pathologies such as chordomas, chondrosarcomas and salivary gland tumours, the carbon ions radiation therapy (CIRT) has proven to

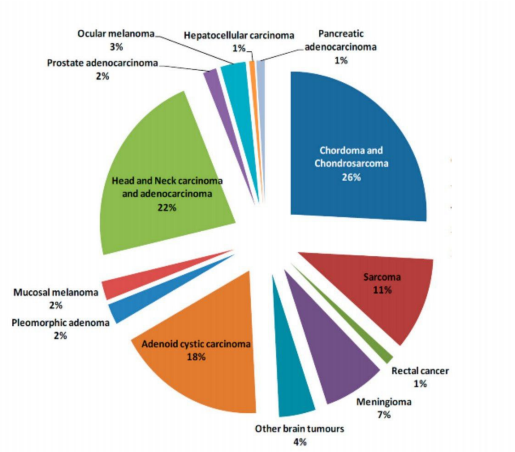

Figure 8: Incidence of tumor pathologies treated at CNAO. [9]

be highly effective. For many other tumour entities such as early-stage lung cancer, oesophageal cancer, hepatocellular carcinoma, pancreatic cancer, gynaecological tumours or prostate cancer, treatment with CIRT is being investigated, mainly through case series and few prospective studies. [9]

Furthermore, other studies of phase I and phase II are focused to prove how the lower integral dose translate in a reduction of acute and long-term toxicity, improving post-therapy quality life. PROTECT is a Phase-II-Trial that evaluate impact of proton therapy for the treatment of cervical cancer. Conventional radio-therapy is a very effective treatment, however the majority of women experience treatment-related toxicity involving the gastrointestinal and urogenital tracts and the immune system. As a result improvement in dose to OAR (Organ At Risk), especially bowel and bone marrow are obtained with the proton-therapy, improving Quality of Life. [6].

A similar study conducted in Pennsylvania on different types of cancer state that, after 90 days, only 12% patients in the proton therapy group experienced serious side effect compared with 28% of radiotherapy group, while the overall outcomes are similar : 56% of people who received proton therapy and 58% of those who received traditional radiation were alive after 5 years. [14]

However, all these studies cannot definitively define an improvement of these new technologies and they agree in the necessity of further analysis. There is no available evidence from randomized phase III studies of the increased efficacy of hadron therapy with respect to convetional radio-therapy. Especially for carbon therapy, further demonstration of the clinical benefit will depend on the ongoing comparative randomized clinical trials. [1]

4.5 Costs

The limited diffusion of hadrontherapy centers is linked to their higher complexity and more expensive than conventional photontherapy. European data for radiotherapy can cost 3'000 to 9'000€, while for hadrontheapy can vary in a range between 10'000 to 20'000€. However, this cost are still lower than other therapy for malignant diseases, such as chemiotherapy (20'000€ to 40'000€). [12]

Furthermore, for some tumors, especially those with long-term adverse effects, ion therapy is more cost-effective to avoid future treatments, such as the previously mentioned cervical tumor, pediatric brain tumors, well-selected breast cancers and others. [15] [6]

5 Conclusion

To conclude, proton and light ion therapies represent significant advancements over traditional X-ray or gamma ray radiotherapy. Their ability to deliver a highly localized dose at the Bragg peak allows for superior targeting of cancerous cells while minimizing collateral damage to surrounding healthy tissues. This is particularly advantageous in cases where tumours are situated near sensitive organs. The higher biological effectiveness (RBE) of protons makes them more effective at damaging cancerous cells, potentially offering improved outcomes in treating radio-resistant tumours. However, challenges such as beam precision, nuclear fragmentation, and the high cost of establishing and maintaining hadron therapy centres limit widespread adoption, and it's important to overcome those limits in order to spread out the great advantages of hadron therapy.

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