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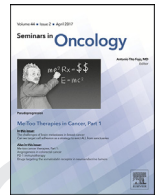
# Charged particle beams to cure cancer: Strengths and challenges

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## ARTICLE INFO

## ABSTRACT

Charged particle therapy is the most advanced radiotherapy method in oncology. The favorable depth-dose distribution and the biological properties of charged particles have potentially a great benefit for reducing toxicity and increasing the local control. While the number of proton centers is exponentially growing worldwide, the therapy remains controversial due to the high cost and lack of level-I evidence of superior effectiveness compared to conventional X-rays. Here we will discuss the advantages and the challenges in both physics and biology to fully exploit the potential of ion therapy in medicine. The challenges include reducing the footprint and costs of accelerators, reducing range uncertainty, exploitation of the biological advantages such as the high effectiveness against hypoxic tumors, and to select patients with biology-driven personalized approaches. International collaboration in the field is likely to bring definite answers to these ongoing problems.

## 1. Introduction

In the 21st century, enormous technological improvements have transformed radiotherapy in cancer care [1]. Image guidance and intensity modulation (IMRT) allowed a tremendous improvement in target conformality with X-rays. Faster and more precise treatments led to treatments of cranial and extracranial treatments (stereotactic body radiation therapy, SBRT) with few fractions and high doses [2]. Biomarkers are also used for personalized treatments of patients with the same macroscopic malignancy [3].

Notwithstanding these outstanding improvements, the physics of X-ray attenuation in matter is unfavorable for radiotherapy, with the dose exponentially decreasing with increasing depth in the tissue (Fig. 1). Conformal radiation treatment requires unavoidable cross-firing of the tumor target from many different angles, exposing a large volume of normal tissue to a "dose bath" of low-to-moderate doses. The irradiation of normal tissue causes toxicity, and limits the total dose that can be safely delivered to the target. Only a different *physics* can solve this problem, and this is indeed the main reason for using accelerated charged particles, that deposit most of their initial energy toward the end of their range in tissue (the Bragg peak) (Fig. 1) [4]. Around the Bragg peak, inside the target, the energy released per unit of track length by the slowed ions become high, producing dense ionization clusters. Densely ionizing radiation has peculiar radiobiological properties that make them more effective than X-rays in killing tumor cells at the same dose, and can elicit unique signaling pathways that further contribute to cancer eradication [5].

Over 200,000 patients have been treated with charged particles worldwide.[1] About 85% were treated with protons, which is the lightest hadron and the easiest to produce and accelerate, and 13% with carbon ions, which has potential physical and biological advantages compared to protons but requires larger and more expensive accelerators [6]. The clinical results supports the rationale of the therapy, demonstrating excellent tumor local control and low toxicity in many tumor sites [7-10], attributes deemed especially valuable in pediatric patients [11-13]. The available results have encouraged many centers to buy or build new particle therapy centers, with expectations that the number of centers will double in the coming 5 years (Fig. 2).

While clinical results to date have been very encouraging, these results have not settled the controversy on the cost effectiveness of particle therapy [14-16]. In fact, level-I evidence from
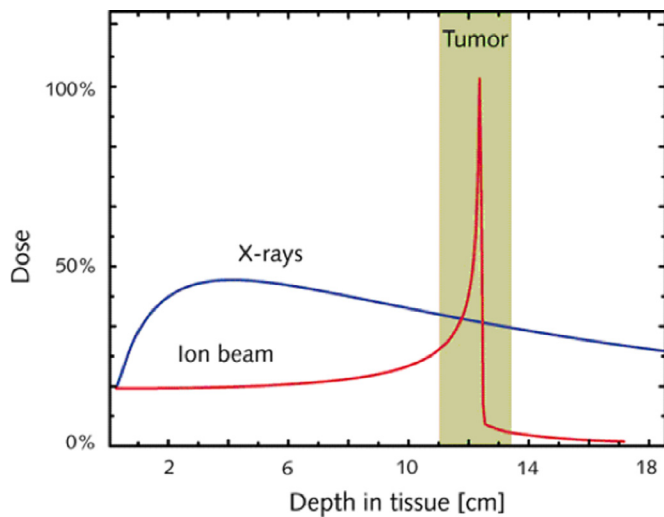
1 Updated patient statistics and centers in operation are available on the Particle Therapy Co-Operative Group (PTCOG) webpage: www.ptcog.ch

**Fig. 1.** Depth dose distribution of different radiation in radiotherapy. Even if both high-energy photons and charged particles are ionizing radiation, their interaction with matter is regulated by different physical processes. As a consequence, the X-ray dose decreases exponentially with depth after the build-up region while charged particles deposit more energy per unit track toward the end of the range (Bragg peak). Image from GSI repository, reproduced with permission. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



**Fig. 2.** Particle therapy centers worldwide. The growth of the particle therapy centers in the 21st century is provided by PTCOG (www.ptcog.ch). Th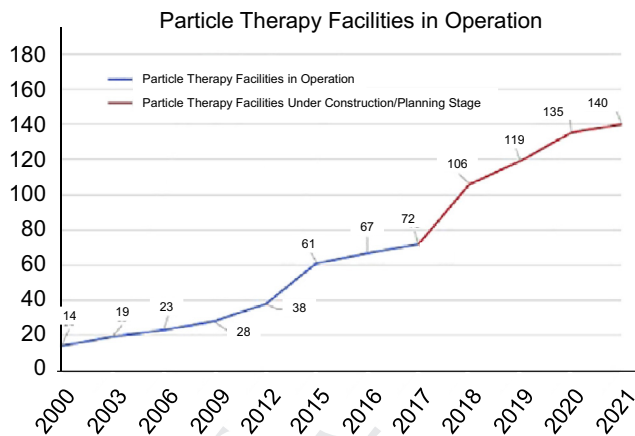e red line represents the expected growth in the coming years, based on the schedule of the facilities under construction. PTCOG = The Particle Therapy Co-Operative Group. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

randomized control trials is still missing. While many phase-III trials are ongoing [6], retrospective analysis of patients with a diagnosis of prostate cancer [17] and prospective randomized trials of nonsmall cell lung cancer (NSCLC) [18] demonstrated similar results for patients treated with IMRT or protons. Given that the cost of particle therapy remains substantially higher than conventional X-ray therapy, in terms of investment, maintenance costs and reimbursements [19] there is continued focus on whether the cost of the treatment can be reduced, or whether the additional cost can be justified by the clinical advantage.

In this manuscript we will describe the potential advantages and the critical problems of particle therapy both in physics and biology. Approaches to reduce the costs and to design biologically-guided clinical trials will also be proposed.



**Fig. 3.** Two field dDepth dose distribution. Example showing a depth dose distribution that more closely emulates that which might be used clinically. The figure shows the dose distribution of two individual beams – one coming from the left and the second from the right with the larger dashes depicting the dose distribution of each individual photon beam and the small dashes the sum of both beams. With two beams from different angles one can see that the ratio of proximal dose to target dose is reduced as the dose administered to the target (gray vertical elliptical structure) is increased but at the expense of additional proximal dose. For the proton beam, one can see an increase in the ratio of the physical dose between the target and the proximal region caused by the Bragg peak.

## Physical advantages

The physical properties of the interactions of charged particles with matter determine, for the most part, the properties of a proton dose distribution. It is the combination of these physical characteristics with the radiobiological sensitivity (discussed below) that will determine the overall biological effect. The key difference between charged and uncharged particles is the mechanism of the interactions with the tissues they traverse. In the case of uncharged particles of energies used for therapeutic irradiation, the main interaction is the Compton Effect, or photons that scatter from atomic electrons. These photons are scattered from the beam and the ionized electrons deposit dose into the medium. The number of photons is reduced exponentially as the beam penetrates further into the patient and the depth dose distribution that is high at the surface and decreases exponentially. In the case of charged particles, the key interaction is also ionization of atoms, but for the most part, the protons maintain their trajectory or scatter only slightly. Thus, the number of protons remains the same as the beam penetrates. However, in this case, the protons lose energy with each interaction, and thus lose energy along their trajectory until they stop at the end of range. Because the amount of energy transferred increases as the particle slows down, the dose deposition increases rapidly when nearing the end of range. The resulting depth dose distribution is the so-called Bragg peak. The classic illustration of the physical dose advantage of the charged particle is these two dose distributions from a single field.

The key differences between these two dose distributions includes the reduced dose in the proximal region – with the exception of the build-up at the very beginning seen with the uncharged particle (photons) – and the lack of dose for the charged particle (proton) beyond its end of range. In practical application we neither use the raw Bragg peak of a single energy derived from a single beam angle, nor do we use a single beam angle with a photon beam. Figure 3 shows the effects of two beam angles for both the proton and photon beam. For the photon distribution one can see a reduction in the proximal dose relative to the target dose, at the expense of additional proximal dose due to the use of a second angle. For the proton beam, one can see an increase in the ratio
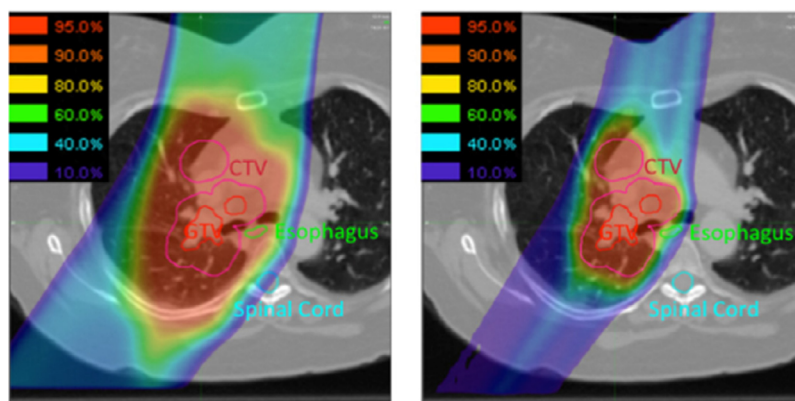
**Fig. 4.** Comparative treatment plans. Proton treatment plan comparisons highlighting the level of conformity that can be achieved given the physical dose properties of charged particles. The treatment plan on the left includes margins added for the various uncertainties sometimes currently estimated v the figure on the right showing a treatment plan without those margins. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

of the physical dose between the target and the proximal region. Beam for beam, the dose to the normal tissue, in ideal circumstances, will be lower for the charged particle (proton) beam.

A number of parameters are needed to describe the physical properties of the proton beam. The specifications are somewhat related to the method used to deliver the beam. Note that a beam from an accelerator is not usually a good match for the geometry of a patient target. Therefore, the beam must be spread to conform to the target volume. One can spread the beam using so-called passive means with scatterers, degraders, apertures, and compensators [20], or one can spread the beam actively using magnetic dipoles [21] to paint the beam across the transverse projection of the target adjusting the beam range by modifying the beam energy. Combining beams is a very powerful tool for achieving conformality. In the transverse direction, the Gaussian-shaped beams can be superimposed achieving an almost arbitrary distribution, within the limitation of the finite beam extent and beam delivery resolution. The summation of Gaussian beams is mathematically very tolerant to the beam size and position. In the depth direction, the Bragg peaks can also be superimposed, with somewhat tighter tolerances compared to a Gaussian shape. Such volumetric distribution flexibility is quite powerful in achieving excellent dose conformality with the target.

### Physics challenges

The use of a proton beam clinically must factor in the practical aspects of beam delivery. There are several aspects to be considered. Perhaps the most obvious issue is that if the depth or transverse position of the target is displaced relative to a very conformal dose distribution, then neither the target nor the surrounding tissue will receive the desired dose. This is true for both proton and photon conformal fields. The difference is the sensitivity of the putative target position. For example, as regards a proton beam, a shift in the *depth of a target* changes the location of the "end of range", while as regards a photon beam a similar change in depth will change the dose by an amount that depends on the conformality of the planned distribution. Changes in the depth of a target can be a consequence of a physical shift of the target within the anatomy or changes in the beam's path. Additionally, a "shift in target location" can result from imperfect knowledge of the anatomical densities as derived from scans, including errors in the conversion of X-ray scan densities to charged particle stopping power. Shifts of the target in the *transverse direction* can result from changes in the target location, possibly due to organ motion, and is a practical possibility that can be compensated by

the inclusion of appropriate margins in treatment planning. Organ motion deserves special considerations, especially when the beam treatment has a time-dependence, such as the case with proton beams.

These challenges and sensitivities essentially result from the lack of perfect, real-time imaging so that an accurate proton beam stopping power is determined at the time of treatment and the target position is well identified. Improved imaging techniques with greater accuracy in defining both the depth and transverse positions are being studied to help guide beam delivery. Scanning techniques well suited to adaptation with the appropriate input information are available. Improved imaging techniques to more accurately describe depth using PET images, prompt gamma detection and proton radiography [22-24] are under development. Improved conventional imaging techniques such as cone-beam CT are being implemented in proton therapy facilities along with CT on rails. Consideration is also being given to MRI-guided systems.

Currently the dose distributions that are created with proton therapy, while quite conformal, are not as conformal as they could be from the physics point of view. Fig. 4 shows a comparison between a currently practical treatment plan and one that could be realized with improved positioning information.

Perhaps another challenge, which could be addressed with physics, is that the beam energy required for the therapeutic application of proton beams is about 230 MeV. The equipment required to accelerate and deliver such a beam to a patient is larger and more expensive than photon treatment machines. There has been considerable effort to reduce the size and cost of proton accelerators for particle therapy. However, reducing the size and cost of gantries is also an important goal, if in fact a gantry is necessary. One interesting consideration is the realization that proton beams, and in particular scanned protons beams, require fewer beam angles to achieve a desired dose distribution than photon beams. Carrying this to the extreme one may ask if it is possible to deliver acceptable treatment fields without a gantry. This has been explored [25] and the results seem promising. If one is to compare costs, one must attempt to compare similar functions. One should not, for example, compare the cost of one LINAC to the cost of a multiple room proton beam facility including building and clinical infrastructure.

### Radiobiological advantages

Charged particles possess radiobiological properties that make them significantly different from X-rays. The main physical property responsible for the different biological effects is the linear

**Table 1**

Radiobiological advantages of charged particles compared to X-rays. In the Bragg curve (Fig. 1) particle LET is lower in the entrance channel (plateau) where the normal tissue is exposed (ie, Low LET), than in the Bragg peak region, where the tumor is irradiated (High LET).

| | Low-LET | High-LET | Potential clinical advantages |
|---|---|---|---|
| Relative biological effectiveness (RBE) | ~1 | >1. Up to 3 in most clinical situations, close to fast neutrons | High effectiveness in radioresistant tumors |
| Oxygen enhancement ratio (OER) | ~3 | <3. Can be as low as 1 | High effectiveness for hypoxic tumors |
| Fractionation | Large sparing effect | Small dependence on fractionation | Fractionation spares normal tissue more than the tumor |
| Cell-cycle dependence | S-phase cells are more resistant | Little difference in sensitivity of the different phases | Effective against rapidly dividing tumors |
| Inter-individual variability | High | Low | More uniform response to the same dose |
| Cell migration | Increased | Decreased | Reduction of metastatic potential |
| Angiogenesis | Increased | Decreased | Favorable microenvironment for tumor death |
| Immune response | Low (?) | High (?) | Potential improvement in combination with immunotherapy |
| Enabling technologies | | | |
| | X-rays | Charged particles | |
| FLASH (dose rates >40 Gy/s) | Very high dose rates cannot be achieved | Very high dose rates possible with electrons and ions | Sparing of the normal tissue, enhanced therapeutic window |
| Spatially fractionated therapy | Requires coherent focused X-rays and high dose rates that can only be reached at synchrotron radiation facilities | Demonstrated with protons, possible with heavier ions. | Sparing of the normal tissue, enhanced therapeutic window |

LET = linear energy density.

energy transfer (LET, also linear energy density), but even particles with the same LET have different biological effectiveness (track structure effects) [26]. LET is proportional to $z^2/\beta^2$, and therefore it is especially high for slow, heavy ions. A high ionization density induces clustered DNA lesions that are difficult to repair [27] and may elicit distinct signaling pathways [5,28-30]. The properties of high-LET, densely ionizing radiation can be extremely beneficial for particle therapy (Table 1). The relative biological effectiveness (RBE) further increases the physical peak/plateau ratio in the spread-out-Bragg-peak (SOBP), and makes it possible to increase the dose to the tumor without causing further toxicity. The RBE is only a scaling factor, but can contribute to the success of the therapy against radioresistant tumors, where dose escalation with X-rays is prevented by the limited tolerance of normal tissues to higher doses. High-LET radiation is felt to be particularly effective against radioresistant cancer stem cells [31,32]. Beyond RBE, there are many other biological factors that can be exploited using particles (Table 1). High-LET ions have a reduced oxygen enhancement ratio, and are therefore particularly effective against hypoxic tumors [33,34]. Very important is also the reduced interindividual radiosensitivity of tumors to particles [35], that makes the response of different patients more predictable; and results in reduced angiogenesis of tumors after exposure to particles [36,37].

A field of study with high enthusiasm at the present time in cancer therapy is the combination of radiotherapy with immunotherapy, which has been applied in several clinical trials with encouraging results in stage IV patients [38,39]. Preliminary results suggest that charged particles can be more effective than X-rays in eliciting immune response [40] and, if confirmed, this property could decisively boost particle therapy in the clinics.

Finally, charged particles enable technologies that may further widen the therapeutic window in radiotherapy. These include FLASH radiotherapy [41], where very high dose rates (>40 Gy/s) are needed and lead to sparing of the normal tissue without modifying the tumor response [42]; and spatially fractionated minibeam therapy [43], which uses a grid structure that strongly increase normal tissue tolerance. FLASH was originally discovered using electrons [44], and while it is very difficult to achieve these high dose rates with X-rays, studies with protons are ongoing [45]. Spatially fractionated therapy has been tested with coherent soft
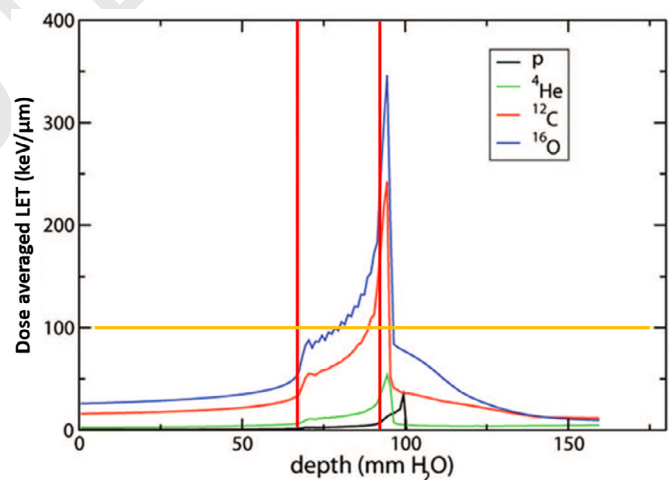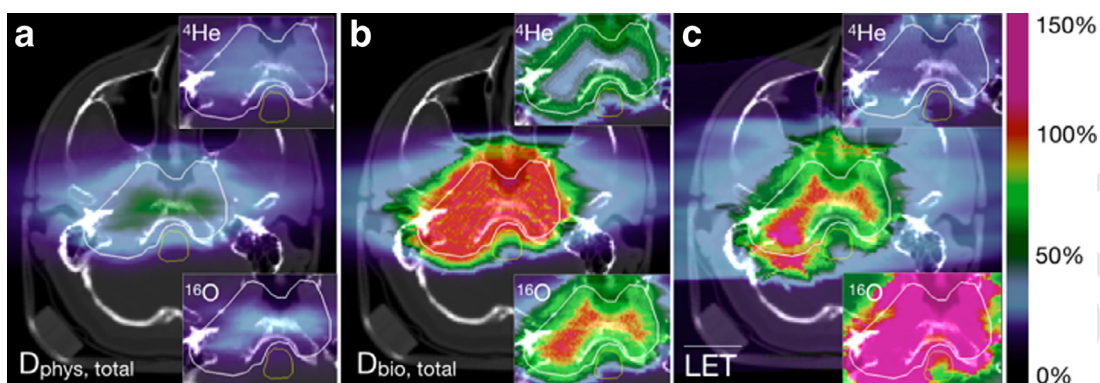


**Fig. 5.** LET distribution in a treatment. Dose-averaged linear energy transfer (LET, also linear energy density), as a function of the depth in tissue for a single spread-out-Bragg-peak (SOBP) of different ions. The vertical red bars between tumor depth of 50–100 mm H$_2$O) indicate the tumor target volume. The vertical yellow line highlights a dose averaged LET of 100 keV/μm, which is around the peak of radiobiological effectiveness of charged particles. It can be seen that, even for heavy ions, most of the tumor is exposed to a low, suboptimal LET. Simulation by TRiP98, courtesy of Dr. Emanuele Scifoni. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

X-rays from synchrotron radiation [46], but has been already demonstrated with protons [47] and in principle can be used also with very heavy ions [48].

## Radiobiological challenges

Even if the radiobiological properties of particles appear extremely favorable for radiotherapy, in reality it should be said that most of the characteristics in Table 1 apply to densely ionizing heavy ions. The energy deposition of fast protons is much more similar to X-rays, and their LET generally low, with the exception of the distal edge of the SOBP, where notoriously protons can have a high RBE [22]. In fact, a constant RBE = 1.1 is applied in proton

**Fig. 6.** Multi-ion treatment planning. Biologically optimized four-field $^{16}O + ^{4}He$ plan for a partially hypoxic skull base chordoma (a) Total physical dose (b) Total biological (RBE-OER-weighted) dose (c) Dose-averaged LET distribution. Insets correspond to the partial contributions from $^{16}O$ and $^{4}He$ fields. For (a) and (b) the color scale represents the relative dose compared to the dose of 2 Gy, for (c) the relative LET compared to the LET of 60 keV/µm. Image obtained with TRiP98, details in ref. [56], reproduced with permission. LET = linear energy density; OER = oxygen enhancement ratio; RBE = relative biological effectiveness. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



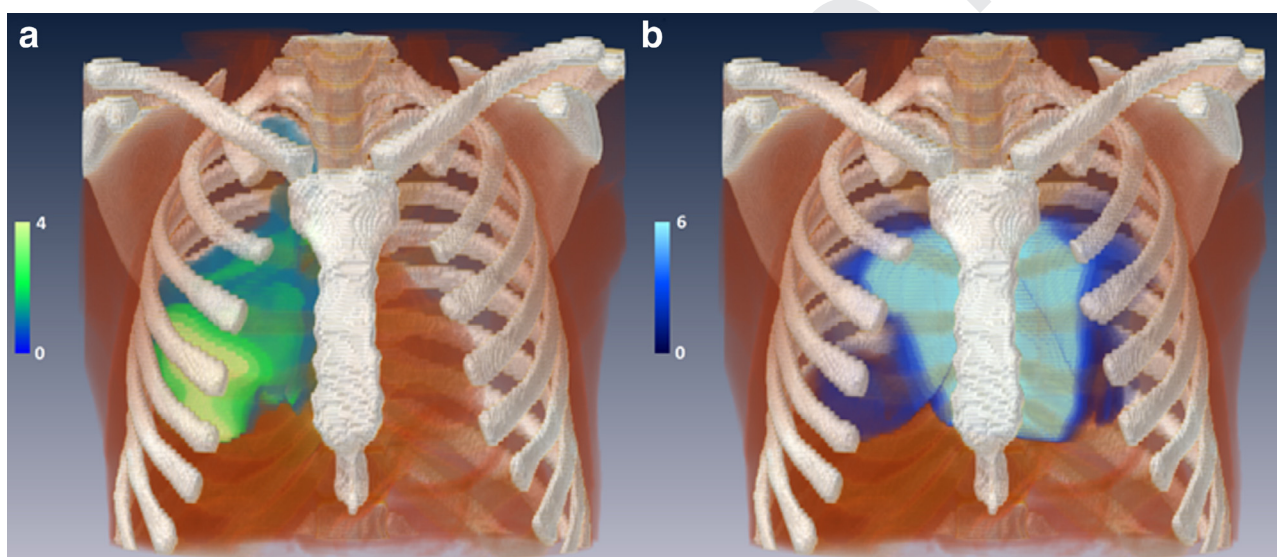**Fig. 7.** Voxel-based analysis of the NSCLC patients from the MD Anderson randomized trial [18]. 3D volume rendering of significant clusters of differences in biologically effective dose (BED) between (a) patients who developed symptomatic radiation pneumonitis and those who did not; and (b) patients treated with IMRT v. proton therapy. The color bars represent the significance level, expressed as -log$p$. Details in ref. [61], reproduced with permission. NSCLC = nonsmall cell lung cancer. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

therapy practice [49]. Even if it is recognized that this is a rough approximation and that the proton RBE is variable [50-52], it remains to be elucidated whether this relatively low LET has any impact on clinical response.

The RBE has been introduced above as an advantage of charged particle therapy, but it can become a harm if it is underestimated in the normal tissue. Radiographic evidence of high-proton RBE in the brain [53] and in the lung [54] is a cause of concern for possible unexpected toxicities such as brain necrosis in pediatric patients [55]. Measurements of normal tissues tolerance doses to particles in animal models is a high priority research topic in particle radiobiology [56].

A variable RBE is instead always used in carbon-ion therapy to optimize the treatment, but even for this heavy ion the LET may be too low to overcome hypoxia [57]. Using heavier ions, such as $^{16}O$, can be beneficial to reduce the oxygen enhancement ratio [58], but the experience of the pilot trial at the Lawrence Berkeley Laboratory in the 70s-80s demonstrated that very heavy ions can produce severe toxicity in normal tissue [59], being the LET already so high in the entrance channel that RBE for normal tissue toxicity

increases. In addition, even with heavy ions, the LET distribution within the tumor is highly heterogeneous, with only small volumes in the distal part of the SOBP, exposed to high-LET, and large tumor volumes where the LET is only moderate or low (Fig. 5).

With current treatment planning, clearly the radiobiological advantages of densely ionizing radiation have not yet been fully exploited. One simple strategy would be to expose the tumor not to a uniform dose, but to a uniform LET. The constraint of a uniform tumor dose has been relaxed in modern radiotherapy, where SBRT normally delivers overdosages in the central tumor volume [60]. It would be then possible to deliver a uniform high-LET, to make sure that all tumor cells, including cancer stem cells and cells residing in microscopic hypoxic volumes, are exposed to densely ionizing particles. This LET painting [61] can, however, substantially increase the dose to the normal tissue. An interesting strategy is multi-ion LET painting, where a combination of light and heavy ions is used to achieve conformality in dose and LET. Multi-ion painting is currently limited to in silico studies [62], but can be a breakthrough strategy to fully exploit the biological advantages of particle therapy (Fig. 6).

The biological advantages of particle therapy are not considered in patient selection and clinical trials. By definition, randomized clinical trials include patients that can highly benefit from particle therapy, and those whose benefit is small and undetectable. It would be more rational to select patients on the basis of radiobiological considerations – for example hypoxic tumors should be treated with heavy ions. The approach currently under evaluation in the Netherlands is to select patients for proton therapy based on the assessment of the normal tissue complication probability (NTCP). The approach calculates the patient's treatment plans with protons and IMRT and the expect toxicity with the two treatment modalities [63,64]. Only patients with an estimated % reduction of the NTCP-value beyond a threshold are selected for proton therapy.

The problem of the Dutch system is that it is based on a NTCP model, and radiobiological models are affected by high uncertainty. For example, the $\alpha/\beta$ ratio is affected by large interindividual variations, but is used to calculate biological effective doses in clinical practice [65]. Moreover, ignoring biological properties can bias the results of the clinical trials. An example is the recent NSCLC phase-III clinical trial comparing IMRT and proton therapy [18]. The trial had been carefully designed to detect a significant decrease in toxicity, specifically pneumonitis. The same target dose was prescribed, and therefore no differences were expected in local control, but the reduced dose to the normal lung was expected to result in lower toxicity. Surprisingly, the clinical data showed no statistically significant differences in both survival and rate of pneumonitis in patients treated with X-rays or protons [66]. The results apparently do not support the view that the reduced "dose bath" with protons translates into a clinical benefit. However, using a voxel-based comparison of the treatment plans, it has been shown that in the upper region of the lung patients exposed to protons had a reduced dose compared to those treated with X-rays. On the other hand, patients experiencing radiation pneumonitis were exposed to higher doses in the lower part of the lung and the heart (Fig. 7). Therefore, the normal tissue sparing that protons indeed provided actually occurred in a region that was not involved in the development of radiation pneumonitis [67]. The analysis of this trial shows how difficult is to perform randomized trials in radiotherapy, and that radiobiological considerations are essential to address the right medical question and to provide the maximum benefit to the patients.

## Conclusions

Charged particle therapy is rapidly growing worldwide (see Fig. 2), yet it remains controversial. International research efforts are challenging the main issues such as reducing the footprint and cost of the accelerators, improving precision by reducing range uncertainty, and fully exploiting the biological properties of the particles. Radiobiology of densely ionizing radiation is indeed so markedly different than X-rays that charged particles should be regarded in radiotherapy in much the same way as a "different drug" is treated in medical oncology. Research and development in this field is a major international effort, and the coordination of this effort is necessary. The Particle Therapy Co-Operative Group (PTCOG; www.ptcog.ch) was born to help specify the parameters of the first hospital-based proton therapy system and has now grown to include 72 centers from 21 countries, and counting. PTCOG has structured subcommittees that address specific clinical and research problems and allow exchange of information among groups working in different continents. The mission of PTCOG has also evolved to identify the current challenges of particle therapy and to help find ways to overcome these so that this modality may eventually be available to all those who could benefit from it. The collaboration in the PTCOG may provide decisive help in supporting the expansion of particle therapy and full exploitation of its potential in medicine. Q3

## Declaration of Competing Interest

The authors declare no conflict of interest

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.seminoncol.2019.07.007.

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## Glossary of Terms

**Hadron:** Most of the mass of ordinary matter comes from two hadrons, the proton and the neutron. In particle physics it is a composite particle made of two or more quarks held together by strong forces in much the same way molecules are held together by electromagnetic forces.

**Bragg peak:** When a fast charged particle moves through matter, it ionizes atoms of the material it encounters depositing a dose along its path and losing energy. A *Bragg curve* describes (plots) this energy loss of ionizing radiation as it travels through matter. The Bragg peak is a pronounced peak on the Bragg curve that for protons alpha-rays and ion rays occurs immediately before the particles come to rest. The Bragg peak occurs because as the charged particle's energy decreases and it begins to slow, the interaction cross section increases. That the peak occurs just before the particle comes to a complete stop is explained by the fact that the energy lost by charged particles is inversely proportional to the square of their velocity. The Bragg peak is named after William Henry Bragg who discovered it in 1903.

**Spread-out-Bragg-peak (SOBP):** A major attribute of proton beams for cancer treatment is due to the Bragg peak that results in a sharp rise in dose at the end of the penetration range, and quickly falls to zero beyond the range. However, when using a single proton-beam energy the sharpness of the Bragg peak means that very high doses can only be delivered to a very narrow depth range. To "widen" the treatment range, the energy of the incident proton beam can be varied, and various energies with appropriate weighting are deployed thus creating a "spread-out Bragg peak" (SOBP).

**Compton effect:** An increase that in the wavelength of X-rays or gamma rays that occurs when they are scattered. The Compton effect is an unusual result observed when X-rays are scattered on some materials. Unlike predictions of classical physics that the wavelength of radiation scattered off atoms should be the same as the wavelength of the incident radiation, X-rays scattered off some materials have wavelengths that are different from the wavelength of the incident X-rays. To explain the increase in wavelengths Compton used Einstein's idea of light as a particle arguing that electromagnetic radiation cannot be explained as a purely wave phenomenon but that electromagnetic waves can behave like a stream of photons. Thus if (a) in the target material valence electrons are loosely bound in the atoms and behave like free electrons and (b) if the incident X-ray radiation is a stream of photons, an incoming photon colliding with a valence electron transfers (looses) some part of its energy and momentum to the target electron and leaves as a scattered photon with a longer wavelength than the incident radiation.

**Proton radiography:** Use of protons for image capture. In practice, high-energy protons used as the radiographic probe illuminate an object. The protons are absorbed and scattered by the object, and these are then brought to a focused image by a magnetic lens system. In turn this can be recorded by an imaging detector. The advantages include (1) the need for fewer protons than X rays for comparable quality images; (2) improved signal-to-noise ratio as a result of the greater penetrating ability of protons; and (3) enhanced discrimination between two similar materials with protons.

**Linear energy density (LET):** High LET means high energy density, resulting in double strand DNA breaks, and short-range radiation, sparing adjacent normal tissues.

**Multi-ion painting:** Biological optimization of treatment plans for tumors using multiple ion species simultaneously. Cell killing of biologically heterogeneous targets is optimized with the use of different ion beams simultaneously.

**FLASH radiotherapy:** The delivery of ultrahigh doses of radiation in fractions of a second, The need to use highly specialized equipment has limited research and pre-clinical studies. The ability to deliver an ultrahigh radiation dose in milliseconds could in theory lead to greater efficacy. Because it would reduce the impact of patient motion the need for target margins would be reduced and also reduce the volume of healthy tissue irradiated. Fewer treatments, could also minimize or eliminate the problem of inter-fraction motion, and increase efficacy by accommodating more patients in any given period of time.