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Exploiting the full potential of proton therapy: an update on the specifics and innovations towards spatial or temporal optimisation of dose delivery

Comment exploiter le potentiel thérapeutique de la protonthérapie : spécificités et innovations (vers l'optimisation spatiale et temporelle de la dose) de cette technique

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Mots clé

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Summary

Prescription and delivery of protons are somewhat different compared to photons and may influence outcomes (tumour control and toxicity). These differences should be taken into account to fully exploit the clinical potential of proton therapy. Innovations in proton therapy treatment are also required to widen the therapeutic window and determine appropriate populations of patients that would benefit from new treatments. Therefore, strategies are now being developed to reduce side effects to critical normal tissues using alternative treatment configurations and new spatial or temporal-driven optimisation approaches. Indeed, spatiotemporal optimisation (based on flash, proton minibeam radiation therapy or hypofractionated delivery methods) has been gaining some attention in proton therapy as a mean of improving (biological and physical) dose distribution. In this short review, the main differences in planning and delivery between protons and photons, as well as some of the latest developments and methodological issues (in silico modelling) related to providing scientific evidence for these new techniques will be discussed.

Résumé

La prescription et la délivrance d' une irradiation par protons ou photons comportent des différences qui peuvent avoir un impact sur le devenir oncologique et la toxicité. Il est important de les connaître pour exploiter au mieux le potentiel de la protonthérapie. Des innovations sont aussi nécessaires dans le domaine de la protonthérapie afin d'élargir la fenêtre thérapeutique et optimiser les populations de patients qui pourraient bénéficier de nouveaux traitements. C'est pourquoi de nouvelles stratégies sont aujourd'hui en cours de développement afin de réduire les éventuels effets secondaires sur les tissus sains, et basées sur de nouvelles approches d'optimisation spatiale ou temporelle de la dose. En effet, l'optimisation spatiotemporelle (par exemple telle que proposée avec le « flash », minifaisceaux de protons ou l'hypofractionnement) suscite un intérêt certain en protonthérapie et permettraient d'améliorer grandement la distribution des doses des protons (biologique et physique). Dans cette courte revue, un point est fait sur les principales différences de planification et de distribution de la dose entre protons et photons avec les techniques récentes, et sont discutés quelques-uns des derniers développements technologiques et en matière de modélisation (par exemple, in silico) pour ces nouvelles techniques.

1 Introduction

Radiation therapy is one of the key components of effective cancer treatment and control, and is used in the treatment of 50 to 60% of cancers. Treatments including radiotherapy now account for 40% of cancer cures, and radiation therapy is by far the most cost-effective modality for cancer treatment with the added advantage of conserving normal tissue function, even when projecting particle therapy on the radiation therapy market. Most of the external radiation therapies are based on irradiation of the tumour using photons. However, proton therapy is an advanced mode of radiation treatment for cancer, which enables tumour cells to be effectively targeted as it allows a very conformational dose deposition (Figure 1). Besides, due to their ballistic properties and precise depth dose distributions, protons can achieve tumoricidal doses while protecting organs at risks and can overcome the limitations of photons. The reduction of the integral dose already makes proton therapy highly attractive for challenging tumours, particularly in paediatrics. The use of protons has been steadily increasing the last 20 years (albeit limited by the high cost of new facilities), and currently about 190,000 patients have been treated worldwide since 1954, with close to 20,000 new patients treated each year.

Currently, proton therapy plans are optimised for each patient's anatomy as far as the spatial configuration of the treatment delivery is concerned, using standard temporal fractionation, such as with photons. Hence there is personalised spatial optimisation for each patient, but not temporal optimisation. Moreover, this temporal distribution of the dose has for now only been crudely optimised, and the latest developments in this regard (such as hypofractionation schedules) are still mostly empirical and limited to a certain class of tumour and sizes. In addition, it would take thousands of clinical trials to find optimal treatment schedules for all cancer types, and this issue is already the subject of extensive research where the roadmap is clear: multicentric shared databases with systematic biological analysis. With rare exceptions and to limit effectively radiation toxicity, current radiation therapy facilities (this is also the case for proton therapy) then deliver dose-rates around 2 $Gy \cdot min^{-1}$, and most clinical protocols involve daily fractions of 1.8Gy.

On the other hand, spatial optimisation of the dose in radiation therapy has reached a plateau by using ever more sophisticated hardware and software (in particular with recent photons intensity-modulated arc therapy and particle therapy which have allowed conformation of three-dimensional spatial dose distributions to the target). Yet, despite such comprehensive therapeutic arsenal, some cancers have limited therapeutic options and respond only partially to current therapies. Prescription and delivery of protons are somewhat different compared to photons and may influence outcomes (tumour control and toxicity). They include differences in dose distribution, radiobiology, and sensitivity to various types of uncertainties. These differences should be taken into account to fully exploit the clinical potential of proton therapy. Hence, innovations in proton therapy treatment are still required to widen the therapeutic window: among others, strategies are now being developed to reduce side effects to critical

normal tissues using alternative treatment configurations and new spatial or temporal-driven optimisation approaches. In this short review, we will begin by recalling the main differences in planning and delivery between protons and photons, then make an update on some of the latest developments and methodological issues (e.g. in silico modelling) related to providing scientific evidence for these new techniques.

2 Differences in planning and delivery

2.1. Difference 1: better dose distributions can naturally be achieved with protons due to their physical properties

At the energies used in proton therapy (60 to 250 MeV), protons lose their energy by interacting with electrons and they slow down until they stop delivering their maximum energy right before this point. The protons depth dose distribution, the so-called Bragg peak showed in Figure 1, shows no dose beyond this point and has a low entrance dose, compared to photons depth dose distribution. The maximum dose deposition at a specific depth can be matched with the tumour localization by adjusting the energy of the incident protons, thereby naturally enhancing the contrast between the doses received by the tumour and healthy tissues. Moreover, by combining different energies, the tumour can be irradiated homogeneously by one unique field (eye tumours for example), unlike with radiotherapy using photons. Figure 2 shows how with the pencil beam scanning delivery technique, now a standard in proton therapy facilities [1].

2.2. Difference 2: protons are more sensitive to physical uncertainties

Nevertheless, radiotherapy with protons faces more uncertainties than with photons, and some reasonable scenario for intensity-modulated/stereotactic body radiation therapy may be contraindications to proton therapy. In addition to classical radiotherapy uncertainties, inaccuracies and non-uniqueness of the calibration from CT Hounsfield units to proton stopping powers ratio necessary for dose computation represent a type of uncertainty that is unique to charged particle therapy. That impacts directly the Bragg peak position, especially in heterogeneous media or with metallic implants involved, and this potential shift of the sharp distal dose fall-off may overdose organs at risk or underdose the tumour. Solutions are summarized in Table 1.

2.3. Difference 3: Protons are more sensitive to radiobiological uncertainties

Protons and photons have different particle's track structures and thus different linear energy transfer patterns, which affect the type of damage and the capacity of the cell to repair it. Relative biological efficiency, defined as the ratio between the doses needed to produce a biological response with protons and with photons, is considered for the dose per fraction and it is traditionally equal to 1.1 for a 2 Gy(relative biological efficiency) dose per fraction. However, relative biological efficiency values can range from approximately 1.1 in the entrance region, to approximately 1.15 in the centre,

approximately 1.35 at the distal edge and approximately 1.7 in the distal fall-off of the spread-out Bragg peak [4]. Consequently, the highest linear energy transfer values can be found beyond the Bragg peak distal region and range uncertainties would impact the biological dose to healthy tissue or organs at risk in that region. Relative biological efficiency variations are more critical in proton therapy.

2.4. Difference 4: planning target volume concept inadequate for proton therapy

Even if reduced, uncertainties remain. In practice, range uncertainty is estimated between 2.5 to 3.5% of the range [5]. In France, we use 3% of the range that could reach 5% for example for tumours located in a heterogeneous media including air cavities or high density material (sinus, oral cavity, etc.). A classical approach is to add margins to the clinical target volume and create a uniform planning target volume as in conventional radiotherapy. Yet range uncertainties are present only in the beam direction distal part. A non-uniform planning target volume could be used, but a more convenient and accurate way to automatically deal with range uncertainties depending on energy and spot position for each proton pencil beam is to use a clinical target volume-based robust optimization. Range uncertainties are mixed with metric uncertainties (patient positioning, delineation, treatment planning system accuracy, etc.) in the robust optimization process. Clinical target volume-based optimization concept is also suitable to include variations of relative biological efficiency and linear energy transfer over the proton beam path in addition to the physical uncertainties [6]. Linear energy transfer-optimized intensity-modulated proton therapy could benefit patients with high risk of radiation-induced toxicity in critical structures close to tumour targets [7]. Usually, clinical target volume-based robust intensity-modulated proton therapy plans leads to better tumour coverage than planning target volume-based volumetric arc therapy but both physical and biological robustness analyses should be considered for proton plans (cf. section 4).

2.5. Difference 5: intensity-modulated radiation therapy versus intensity-modulated proton therapy

Choice of beam orientations is very important in proton therapy. Due to range uncertainties, the distal dose fall-off is paradoxically rarely used to spare serial organs at risk. Instead, tangent beams and their lateral fall-off are used. Moreover, it may be possible to minimize potential impact of range uncertainties by carefully selecting beam angles not to go through regions of day-to-day anatomical variations or region with large anatomical density variations. Due to the possibility to achieve homogenous dose distribution with a few beams, and to limit entrance dose while accounting for range uncertainties, two to four proton fields, that can be coplanar or non coplanar, can be used instead of five to nine with intensity-modulated proton therapy. Once fields' directions are chosen, pencil beam scanning proton therapy plans need inverse optimization to define spots positions (energies in z direction, scanning positions in x and y directions) for each field. A second phase of inverse optimization is necessary to determine the spots intensity. Due to physical properties of protons

described above, with proton therapy it is possible to achieve single field uniform dose through single field optimization, i.e. spots intensity is defined so that each irradiation field individually delivers a uniform dose to the tumour. With single field optimization, it is possible to irradiate homogeneously the whole tumour with one single beam orientation, to reduce integral dose for example, as shown in Figure 3. So called intensity-modulated proton therapy uses spots intensity modulation in a similar way as intensity-modulated radiation therapy is based on photon fluence modulation. With multifield optimization, for both intensity-modulated radiation therapy and proton therapy, each field is highly heterogenous but the sum of all the fields' contribution delivers a homogenous dose to the tumour. Intensity-modulated proton therapy allows better sparing of organs at risk and better clinical target volume coverage for complex tumour localizations [8].

2.6. Difference 6: caution with the small doses per fraction

Relative biological efficiency also depends on the tissue and there is a trend of its increasing as α/β ratio decreases (see section 4). In most cases the relative biological efficiency also increases with decreasing dose, specifically for systems with low α/β ratio. Consequently, for a small dose per fraction, the biological response can be higher than expected and an increase of relative biological efficiency as the dose decreases suggests higher relative biological efficiency values in organs at risk compared with the target. Hence for prophylactic volumes, it is important to make sure that dose per fraction is not too low in case of simulated integrated boost. Moreover, toxicity in proton therapy would be more affected by variations in α/β compared with photon therapy [9]. Assessment of variable relative biological efficiency in proton therapy should be based on tumour control probability/normal tissue complication probability.

2.7. Difference 7: Benefit of proton therapy is not yet fully exploited

Proton therapy developments are still ongoing and benefits are not yet fully exploited. On accelerators, stable beam at lower energies than 60 MeV is not yet available, and range shifters at the end of the beam line are necessary to reach superficial tumours. Lateral penumbra is degraded because of scattering in the range shifter and because of the air gap between the patient and the range shifter. To better shape the lateral penumbra, one can suggest reducing this air gap and use personalized range shifter and collimator. Multileaf collimator could be a solution for pencil beam scanning to optimize the collimator opening per energy layer [10]. However, collimators bring other uncertainties by impacting the protons primary dose [11], and increasing secondary neutron dose close to the patient. Also, accurate dosimetry in small field proton therapy is still challenging because of dosimeter quenching with proton irradiation that can affect dosimeter response. Consequently small volumes are not always an indication for proton therapy. Moreover, new generation proton therapy facilities are based on synchrocyclotrons and flash therapy is an upcoming technology (see section 3.), both using high dose rate per pulse pulsed proton beams. In these beam conditions, absolute dosimetry brings a

lot of uncertainties which need to be assessed, in particular ion recombination and new guidelines need to be defined at very high dose rates or in the Bragg peak region (see also section 4.).

Range uncertainties still don't allow protecting organs at risk with the protons distal fall-off. In-vivo methods exist for range verification that could allow both reduction of safety margins and dose escalation: prompt gammas detection, online positron-emission tomography (PET) and alternative methods such as ionoacoustics [12]. In short term, plans could be adapted during the irradiation in function of the in-beam range monitoring and it is an important step towards the next level of on-line adaptive proton therapy. Knowing and managing these uncertainties will contribute to a better use of proton therapy in standard practice. Additionally, current research suggests that further optimisation of proton therapy will be possible in the next decade.

3 Innovations in the temporal optimisation of the dose

Hypofractionation and ultrahypofractionation (stereotactic body radiation therapy) regimens allow for escalation of the biologically effective dose of radiation therapy and have successfully improved local control and overall survival in various tumours. Yet, photon hypofractionated radiation therapy for different localisation has been a challenge with photons owing to serious and excessive radiation-related toxicities. As well as for photons or heavy ions for some time, advances in proton delivery techniques (in particular intensity-modulated proton therapy) and daily image guidance (in particular cone beam computed tomography) have allowed studying how more ablative doses could be delivered with shortened fractionation schemes. Indeed, hypofractionation could open up opportunities for increased use of proton beams efficiency, capacity and cost-effectiveness savings. Besides, with the move towards moderate to extreme hypofractionation, accurate delivery of every fraction however becomes critical and improved methods for the prediction of the biological efficiency of protons are increasingly important as we push the boundaries of extreme hypofractionation. For instance, proton therapy centres without cone beam computed tomography and relying on orthogonal X-rays for localisation are generally limited to moderate hypofractionated courses.

With regards to clinical data, few series of proton hypofractionated clinical treatments have been reported. Hypofractionated proton therapy appeared effective and associated with low rates of toxicity. For example, the outcome of hypofractionated proton boost (20 Gy given in four daily fractions) for patients with localised prostate cancer has been proven to be as effective as high dose rate brachytherapy boost [13], and several trials now study how well hypofractionated proton beam radiation therapy works in patients with prostate cancer. Other studies also suggest that proton therapy might allow for safer delivery of hypofractionated radiation for locally advanced non-small cell lung cancer with concurrent chemotherapy [14]. The results from these trials are similar to series of standard fractionated proton therapy. Published results are encouraging and support further exploration to evaluate long-term toxicity and understand differences between proton and photon hypofractionated

radiation therapy. Though, an important aspect concerning the radiobiological modelling of high dose per fraction with protons is their relative biological efficiency, and its associated uncertainty is likely to be a limiting factor for more clinical applications. For such protocols, the relative biological efficiency of proton beams is expected to drop below 1.1, eventually leading to an underdosage in the tumour region (relative biological efficiency modelling as a function of the dose and tissue type is illustrated in the section 4.). In addition, the clinical relevance of current relative biological efficiency uncertainties in normal tissues might become more detectable at very high doses per fraction. Some recent reviews have discussed the rationale and evolution of hypofractionated proton therapy in more details [15, 16].

An innovative methodology, named flash radiation therapy, that requires very high dose-rate facilities and consists in delivering over 10 Gy in a limited number of 1 to 2 Gy pulses given in less than 100 ms each, has emerged recently [17-19]. It is delivered with high intensity low electron beams and has shown dramatic normal tissue sparing for superficial tumours. However, few devices are available today to deliver flash radiation therapy and electron and photon machines are now being designed to treat also deep-seated tumours. There is also currently a direction of research about extremely fast irradiations, such as for example the PHASER program, laser-driven accelerators which are considered as the next generation of cost-effective accelerators for radiotherapy, very high energy electrons exceeding 100 MeV, or intraoperative radiation therapy. The beam temporal structure of these accelerators can however be very different, and an important work on dosimetry of flash irradiation is required to support the development of this field and enable the translation of these techniques to clinical practice. As described in Figure 4, a high frequency electromagnetic wave (usually between 50MHz and 3GHz) is generally used for the acceleration, which forms a quasi-continuous particle beam compressed into bunches or pulses (Figure 2a). Depending on the type of accelerator (e.g. to limit the heat in a linear accelerator, to compensate for relativistic effects in a synchrocyclotron, energy modulation), an additional high frequency temporal structure can be added to the first which creates a pulsed beam with a complex structure (Figure 2b and c). As these pulses with dose rates of orders of magnitude higher than in conventional radiotherapy present significant metrological challenges, parameters such as dose per pulse administered, dose-rate within the pulse, and number of pulses delivered have to be carefully controlled, and correction factors for the loss of collected charges need to be applied [20].

The major benefit of flash radiation therapy is expected to be normal tissue sparing. One yet not sufficiently explored effect of flash radiation therapy is its ability to achieve the same tumour control as with best radiation therapy modalities. Flash proton therapy could have additional benefit by allowing dose escalation to the tumour and hypofractionation without increasing the risk of complications to healthy tissues. Flash effects involve radiation chemistry, and more specifically oxygen depletion along the beam track, which leads to tissue sparing in intermediate oxygen tension

tissues. Therefore, it will be critical to determine not only how beam microstructure affects oxygen depletion at the tumour and normal tissue levels but also to better quantify oxygen tension initially and repeatedly for multisession proton therapy.

Several research groups are then investigating the feasibility of flash radiation therapy with proton beams, with respect to the ability of proton accelerators to achieve instantaneous dose rate per pulses and mean dose required to achieve a flash effect [21-23]. The effect of flash dose-rates on cellular response has for example been investigated for a variety of in vitro assays (micronuclei formation, clonogenic survival of cells, DNA double strand breaks detection). One recent study using 4.5 MeV protons at 1000 $Gy \cdot s^{-1}$ as compared to 0.05 $Gy \cdot s^{-1}$ suggested that dose rate could significantly influence the expression of long-term radiation-induced inflammatory responses in normal lung fibroblasts [24]. For laser-accelerated protons (up to 10^9 $Gy \cdot s^{-1}$), the studies for now have not shown any significant dose rate dependent effects other than chromosome aberration, nitroxidative stress and senescence, possibly due to dose per pulse or pulse repetition frequency too low [25-27]. The impact of a pulsed irradiation has also been investigated showing that the bunch repetition rate (variable delay between laser bunches on the order of seconds), could be associated with an oscillation of cell survival [28]. With respect to in vivo work, very promising results with respect to small intestine radioprotection (loss of proliferating cells in intestinal crypts) as an endpoint have been reported in mice exposed to 230 MeV double scattered protons at high dose-rate around 90 $Gy \cdot s^{-1}$ [29]. Zebrafish embryos were also studied with a similar machine (cyclotron), showing a significant reduction of the rate of pericardial oedema for flash dose rates (40 to 100 $Gy \cdot s^{-1}$), but no significant acute radiation effect such as embryonic survival or induction of morphological malformations could be revealed in that study [30].

4. Spatial optimisation of the dose

Despite abundant evidence suggesting that the relative biological efficiency of proton beams varies with many factors (see the review study collected over 70 experimental reports on proton relative biological efficiency [4]) and in particular increases with linear energy transfers, the use of a generic relative biological efficiency of 1.1 at 2Gy in routine clinical practice is still the rule. However, a few recent studies have found significant correlations between image changes after clinical proton irradiation with dose and linear energy transfer: in lung density characterised by Hounsfield units on CT images for chest-wall patients, in brain characterised by contrast enhancement or hyperintensity on post-treatment MRI for glioma patients and paediatric ependymoma patients respectively [31-33]. Despite decades of investigation, these works constitute first clinical evidence of variable proton biological effectiveness (Figure 5). For these reasons, new methods are being developed for the optimisation of proton treatment planning.

Indeed, both physical (range and set-up errors mitigation) and biological (variable RBE modelling) robustness analyses should be considered for proton beam therapy as these can substantially affect the sparing of organs at risk and target coverage. To this end, a next evolution in proton delivery, proton-modulated arc therapy, has been proposed recently, attested by the demonstration of spot-scanning proton arc plan feasibility [35,36]. As a possible alternative to conventional proton therapy, proton-modulated arc therapy has the potential to further improve target robustness and conformality compared to conventional intensity-modulated proton therapy plans, and can reduce concerns of elevated linear energy transfer and relative biological efficiencyat the end of the proton range. The potential of proton-modulated arc therapy has then been explored for different clinical cases (paediatric brain tumours, prostate cancers), showing possibilities for better saving of healthy tissues, albeit at the expense of increased low-dose/low- linear energy transfer volumes [37, 38]. On the other hand, and to mitigate the variability that arises from the linear energy transfer-dependence of relative biological efficiency, some groups have proposed dose optimisation algorithms based on the physical quantities of dose and linear energy transfer, rather than relative biological efficiency models [39]. New physics-based metrics such as a linear energy transfer-weighted dose have been proposed and could be used in treatment optimisation, reducing biological uncertainties to less than 1% in clinical treatment plans [40].

Thanks to their high conformity of the dose, the substantial reduction of the low-dose irradiation of normal tissues, and the possibility of treating complex targets immediately adjacent to critical organs, the treatment of small fields with high proton doses has also often been considered. Stereotactic proton treatments then started with the treatment of intracranial arteriovenous malformations and ophthalmological tumours in the 1960s and 1980s, often using the single scattering technique and by developing dedicated horizontal beamlines. Although it has been also clinical routine for a long time and in analogy to stereotactic body radiation therapy or radiosurgery with photons, proton radiosurgery has been selected to treat brain metastases showing for the first time in a recent report consistent results with respect to photon radiosurgery [41]. The question now arises of determining appropriate populations of patients that would benefit from this treatment (e.g. benign cases, multiple metastases, close proximity to a critical structure, reirradiation, etc.), and designing clinical trials to provide relevant data on neurocognition or late effects and quality of life, in addition to survival outcome [42]. It is important to note however, that there exist additional physical uncertainties in the case of small field proton beam irradiation, such as the limitation of dose calculations engines if a Monte Carlo algorithm is not available [43]. Indeed, pencil beam algorithms generally overestimate the dose delivered to the target volume for small fields (less than 2 to 4 cm) and when thick heterogeneities are present compared to Monte Carlo calculations (increased surface dose measurements by 5%) [44]. These limitations have more impact for individual field calculations, but the discrepancies can generally be mitigated with multiple fields [45]. Volumetric expansions to

account for intrafractional motion and range uncertainties can also have a strong impact on normal tissue irradiation for small fields.

Proton minibeam radiation therapy is another innovative therapeutic strategy that uses small beams and stereotactic proton therapy, based on the use of spatially fractionated very narrow beams. Proton minibeam radiation therapy has the potential to considerably reduces radiation toxicity, while achieving an equivalent or superior tumour control than conventional radiation therapy in preclinical studies [46]. A first theoretical investigation of the clinical potential of this technique has been conducted recently, showing that proton minibeam radiation therapy could provide satisfactory treatment plans for brain tumour patients with only one or two proton minibeam arrays [47].

Moving to new protocols (either flash, stereotactic or proton minibeam radiation therapy) is however complicated and costly, as there is no optimal statistical characterisation of the outcome and clinicians will be reluctant to risk to have worse outcomes than those from conventional approaches. Therefore, in addition to new algorithms and simulation tools specific to previous techniques and enhancing clinical trial design and interpretation, properly conducted in silico studies in the field of proton therapy could also provide faster answers to current uncertainties and allow researchers and industrial to refine their experimental programs. As an example, a model-based approach for selecting patients for proton therapy has been developed in the Netherlands, assuming that patients would be selected for proton therapy if their expected ΔNTCP value with regards to photons was above a threshold of 5% [48]. The uncertainties in the outcome models to predict normal tissue complication probability and to support a model-based trial approach for specific treatment sites were however highlighted [49] based on the current state of the available clinical data, as well as the need for a better validation of normal tissue complication probability models in appropriately composed (enriched) cohorts treated with protons [50]. The adaptation of these generic models to new techniques will then be an important issue in the years to come.

After the clinical implementation of magnetic resonance guidance for photon beams, research on MRI guided proton therapy is also increasing in the last years [51, 52]. Indeed, MRI is a promising candidate for real time image guidance, and could overcome the limitations on the soft-tissues contrast, additional radiation dose to healthy tissues, functional and anatomical imaging inherent in the current cone beam computed tomography techniques. Integrating a MRI into a proton therapy treatment is however a challenge: dose calculations algorithms must be modified to take into account dose distortion effects induced by magnetic fields. To predict these effects which can be significant on charged particles (protons) trajectories, and account for this in treatment planning, Monte Carlo models have recently been benchmarked and validated against experimental measurements, showing very good agreement between measurements and proton trajectories in air or tissues [53]. For X-rays, the influence of magnetic fields on cell survival has been investigated, showing no significant effect.

For protons, early studies have however shown a significantly enhanced cell inactivation efficiency of protons beams within 0.3 to 0.6 T magnetic fields, suggesting potential effects on tumour control or normal tissues toxicity probabilities, therefore requiring further investigation [54].

5. Conclusions

The differences between protons and photons may give some ideas about the patients who could benefit from proton therapy, with outstanding results in tumour coverage, organs at risk sparing and lower secondary cancer risk. However, improvements in proton therapy are still work-on-progress and standardisation through clinical trials is still needed, in particular new guidelines for dose reporting are required in case of robust optimized plans. Recently, spatiotemporal optimisation has also been gaining some attention in proton therapy as a means of improving (biological and physical) dose distribution, and one could speculate that new delivery methods (such as flash or proton minibeam radiation therapy, image-guided proton therapy, hypofractionation) might become the next disruptive innovations in proton therapy. Such paradigm shifts might prove to be a better and faster way to increase cure rate and reduce radiation-induced side effects, thus increasing the number of patients with fewer side effects and thus a better quality of life. Methodological issues related to providing scientific evidence for these new techniques and in general for proton therapy, have however to be addressed, for example developing new (in silico) trials or more accurate physical and biological simulation tools.

Conflict of interests

The authors have no relevant conflicts of interest to disclose.

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Figure legends

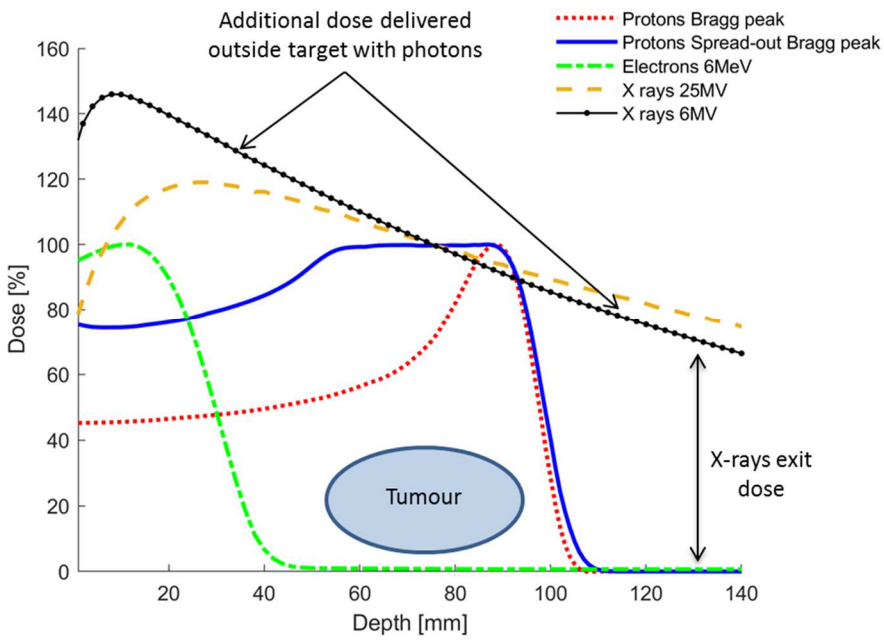
Figure 1. Radiation therapy : comparison of relative depth dose distributions of photons, electrons and protons in case of a single field irradiation.

Figure 2. Pencil beam scanning (PBS) radiation delivery technique: the tumour is irradiated slice by slice. E_i is the energy corresponding to the depth of the irradiated slice, and at this fixed energy the proton pencil beam will be scanned horizontally and vertically thanks to the scanning magnets over the whole slice. Then energy is changed to E_i+1 and the same process occurs again.

Figure 3. Radiation therapy dose distributions obtained with one beam orientation for a craniospinal irradiation case for low risk target volume (in red) irradiated with 36 Gy. For the high risk target volume (in yellow) boosted up to 60 Gy, proton plan used three additional beams, while Tomotherapy® plan used a simulated integrated boost approach. a: protons irradiation; b: photon Tomotherapy®.

Figure 4. Typical beam temporal structure of radiation therapy accelerators.

Figure 5. Radiation therapy: modelling of relative biological efficiency variations (different models are presented) as a function of cell type, dose and linear energy transfer (experimental data from [34]).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X rays 25MV
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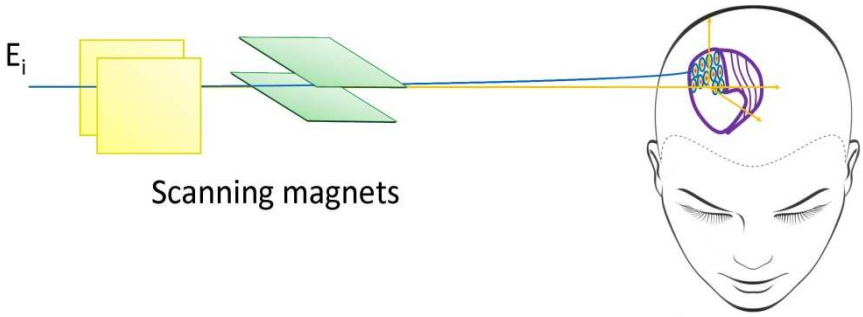
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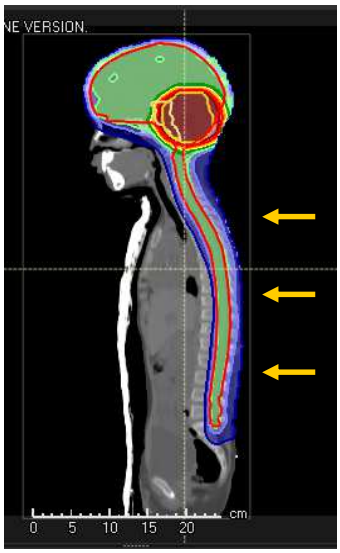
Scanning magnets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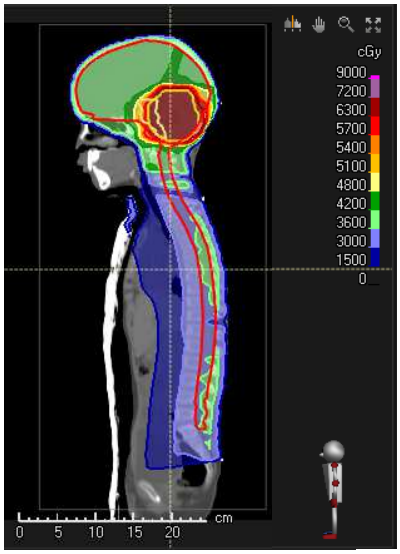
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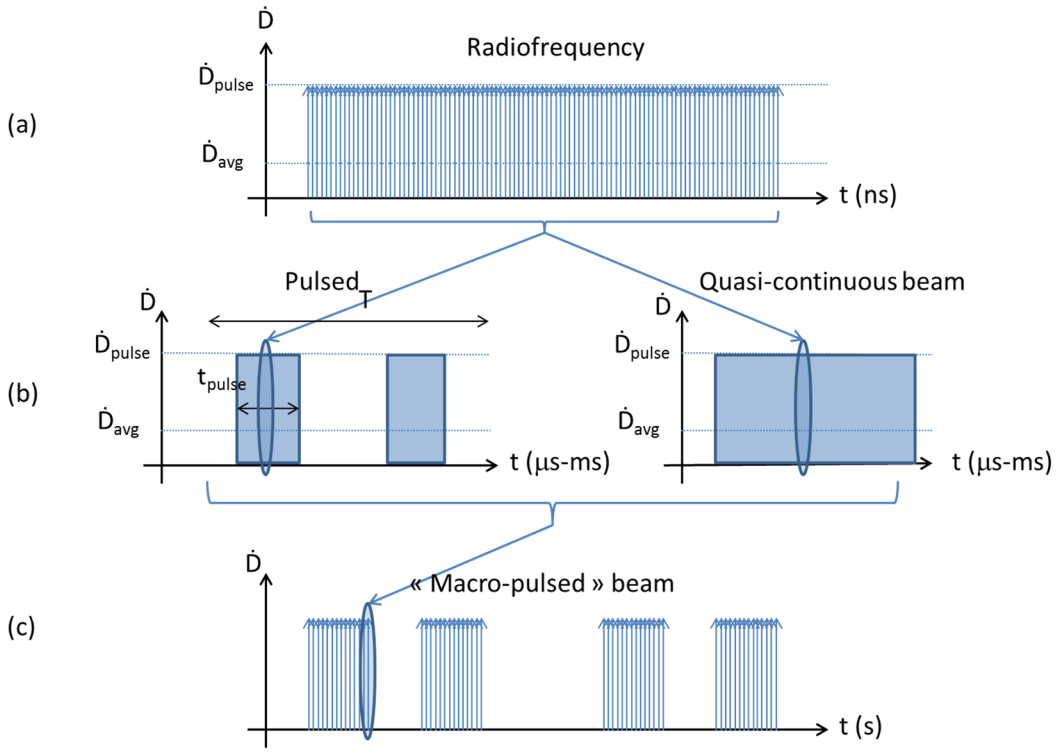
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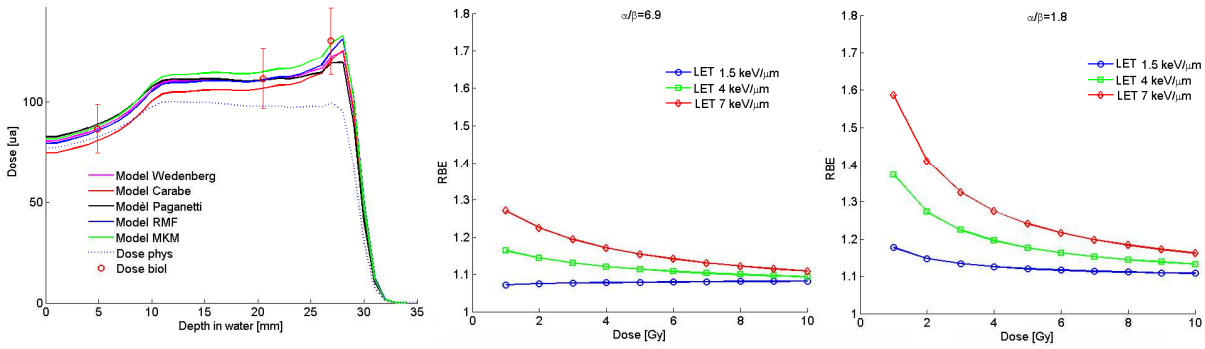
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Table 1. Physical uncertainties involved in proton therapy and some solutions to reduce them and potentially reduce safety margins.

Physical uncertainty	**Solution**	**Accuracy**
Patient positioning	In-room robots (6 degrees of freedom) More demanding immobilization devices (more rigid masks)	Submillimetric positioning accuracy
Contour delineation	Multimodal imaging (MRI, CT, PET, etc.)	
Dose calculation accuracy	Monte-Carlo based dose engine to better take into account heterogeneities, interfaces, large air gap between end of the beam line and the patient GPU allows reasonable dose computation time	Dose distributions are computed within 1 to 2% of the dose, even in extreme conditions
Anatomical changes (tumour shrinkage, weight loss, etc.) from one day to another	Use of three-dimensional in-room imaging such as CT on rails or CBCT Development of online adaptive strategy for proton therapy [2]	
Calibration from CT Hounsfield units to proton SPR and CT artifacts	For metal implants, metal artifact reduction algorithms such as iMAR® (Siemens) or MAR® (General Electrics) using an iterative method for single energy CT can be used To determine the calibration curve, DECT allows acquiring two sets of data at two different energies to directly estimate SPR with less approximation	Safety margins around the treatment volume could be reduced by 35–40% in clinical routine with DECT [3]

CBCT: cone beam computed tomography; CT: computed tomography; DECT: dual energy computed tomography; GPU: graphical processing unit; MRI: magnetic resonance imaging; PET: positron-emission tomography; SPR: stopping power ratio.