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COMMENTARY

Monte Carlo simulations will change the way we treat patients with proton beams today

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ABSTRACT

Within the past two decades, the evolution of Monte Carlo simulation tools, coupled with our better understanding of physics processes and computer technology has enabled accurate and efficient prediction of particle interactions with tissue. Monte Carlo simulations have now been applied for routine clinical applications. This commentary outlines how simulations have the potential to change clinical practice particularly in proton therapy. Specifically, Monte Carlo simulations will impact treatment outcome analysis, reduce treatment volumes and help understand proton-induced radiation biology.

Proton therapy has been used for decades in radiation oncology. Initially, its application was restricted to only a few centres owing to high-cost and challenging technology. Recently, however, it has become mainstream with many new centres worldwide. The interest in proton therapy is a consequence of its advantageous dose distribution as compared with photon therapy, which is believed to cause fewer side effects and/or allow tumour dose escalation. Proton therapy results in more conformal dose distributions because proton beams stop in the patient and their total energy deposited in the patient (integral dose) is lower than that of photon techniques for the same target volume. Whether these aspects improve treatment outcome significantly depends on the clinical end point and, depending on the site, needs to be assessed in trials.

Monte Carlo simulations take into account the physics of particle interactions on a particle-by-particle basis using theoretical models or experimental cross-section data for electromagnetic and nuclear interactions. Furthermore, they consider tissue inhomogeneities by using specific material properties, for example, elemental composition, electron density, mass density or ionization potential. The appropriate position of inhomogeneities along the beam path and its scattering effects are modelled. Secondary particles can be tracked, which allows appropriate consideration of nuclear fragments. Monte Carlo dose calculation is considered to be the most accurate method to compute doses in radiation therapy. The case for Monte Carlo in proton therapy is even stronger than that in photon/electron therapy. The dose deposition in proton

beams not only depends on electromagnetic but also on nuclear interactions (non-elastic interactions and multiple scattering) that are best calculated with Monte Carlo. Better conformity causes the dose distribution to be more affected by uncertainties in beam delivery, patient set-up/immobilization, tissue heterogeneities and organ motion, thus requiring accurate dose calculation.

Analytical algorithms are computationally efficient, whereas more accurate Monte Carlo-based algorithms are often too slow to be used routinely in treatment plan optimization. A typical calculation time is in the order of minutes to hours on typical computers. Consequently, Monte Carlo dose calculation routines are mainly used in physics research. One of the reasons for the limited efficiency is the desired capability of research codes to study parameters other than dose for research purposes. On the other hand, Monte Carlo codes focusing on calculating dose alone, based on the patient's CT, can be designed with high computational efficiency. The most promising approach is to execute Monte Carlo simulations on graphics processing units, which allow calculation times comparable or even shorter than those using analytical algorithms.¹ It can be expected that these algorithms will be incorporated in treatment planning systems in the near future. Several vendors are working on such solutions or are collaborating with academic researchers to develop them. The future of Monte Carlo simulations in radiation oncology will thus see two types of codes. Some high-efficiency Monte Carlo algorithms will focus entirely on dose calculation for treatment planning. In addition, there will be multipurpose

codes for research and development.² The latter can and will be used more and more to replace difficult or cumbersome experiments. Examples are detector design studies for dosimetry and imaging.

Monte Carlo simulations of dose and biological effects will have a profound impact on patient treatments in proton therapy as described below:

- Monte Carlo simulations will allow improvement in planning and delivery: radiation therapy technology is steadily improving. This holds for conventional therapy as well as for proton therapy. For example, intensity-modulated proton therapy techniques using beam scanning are now being introduced in clinics. This will further decrease the integral dose and allow reduction of the number of fields. In general, most developments in radiation therapy aim at improving clinical outcomes by increasing the accuracy of the planning or delivery process with respect to dose. Often, several developments depend on each other. For example, improving dose conformity to the target in treatment planning might require the ability to deliver complex intensity-modulated fields. At the same time, treatment plan optimization using highly inhomogeneous fields requires accurate prediction of the delivered dose. To ensure that these advances have a clinical benefit, one needs to assess them based on the most realistic dose distribution in the patient instead of the planned dose distribution, which is currently based on analytical dose calculation algorithms using various approximations. The main weakness of analytical algorithms lies in the improper consideration of multiple Coulomb scattering in complex geometries. These shortcomings can be addressed with the use of Monte Carlo simulation methods.
- Monte Carlo simulations will improve treatment outcome analysis: generally, clinical decisions as well as trial design should be made on the most accurate expected dose distribution in a patient. Current attempts to correlate clinical outcome with dosimetric indices is potentially flawed by uncertainties in the predicted vs delivered dose distribution. Thus, routine use of Monte Carlo techniques for treatment planning as well as outcome analysis is highly desired.³ Although Monte Carlo techniques improve dose and outcome predictions in photon therapy,⁴ they can have a much bigger impact in proton therapy owing to the higher dose conformity and generally more inhomogeneous dose distributions in organs at risk.
- Monte Carlo simulations will reduce the volume of irradiated healthy tissues: there are considerable uncertainties in predicting the range of proton beams in patients.⁵ This is caused by many factors such as conversion of Hounsfield unit to relative stopping power, patient set-up, physics approximations in the dose calculation and many others. Clinically, these uncertainties are considered by applying an additional range margin to the prescribed range. Depending on the treatment centre, the margin is typically about 3.5% of the range plus 1 mm, which is added to the prescribed range to ensure tumour coverage.⁵ Although this margin is generally sufficient, it may have to be adjusted on a case-by-case basis because the range uncertainty depends on the complexity of the patient geometry. Consequently, treatment planners do add additional margins for complex head and neck cases or

lung tumours. This requires considerable experience of the planner. On the other hand, for some sites, the margin recipe is too generous leading to unnecessary irradiation of a large portion of healthy tissue.⁶ A large contribution to the range uncertainty is caused by approximations in analytical dose calculation routines implemented in commercial treatment planning systems. Although in most cases, the field-averaged range will be similar or equivalent to the field average range as predicted by Monte Carlo simulations, the minimally required range to ensure tumour coverage is often underestimated by analytical algorithms.⁶ It has been estimated that the use of Monte Carlo techniques justifies a reduction of range margins to approximately 2.4% of the prescribed range plus 1.2 mm,⁵ which would result in a significant reduction of healthy tissue being irradiated and has the potential for reducing treatment-related toxicities. Most importantly, the remaining uncertainties, owing to sources other than dose calculation, are mostly independent of the patient geometry. Thus, the use of Monte Carlo would justify the use of a generic recipe without the necessity for individual adjustments based on the geometrical complexity. Furthermore, a reduction of margins will allow the use of beam angles that are currently avoided because the added range compromises the dose constraint to a critical structure.

- Monte Carlo simulations will be increasingly applied in radiation biology: prescription doses in proton therapy are based on the assumption that protons are 10% more effective than photons (*i.e.* the relative biological effectiveness is 1.1). It is unclear whether variations in the relative biological effectiveness are clinically significant. Most importantly, these variations, as a function of dose, biological end point or proton linear energy transfer (LET), are not yet very well understood. The use of Monte Carlo simulations allows accurate prediction of LET distributions in patients. Elevated proton LET values are associated with an increase in biological effectiveness for most tissues, so that Monte Carlo-generated LET distributions can be the basis for biological treatment plan optimization, as LET distributions can be influenced by intensity-modulated planning techniques.⁷ Furthermore, our general understanding of radiation biology is incomplete, and it will take more research to fully optimize treatments based on fundamental biology. This is particularly important in proton therapy, where mechanisms could be different compared with the photon reference.⁸ Monte Carlo simulations will be fundamental to bridging the gap between radiation physics and biology and between researchers in both domains. Treatment planning optimization is based on dose, a physics parameter, and not, as one would naively expect, on anticipated outcome. Prescription doses and constraints are largely defined empirically. Although experimental studies in cell cultures and animal systems are needed to fill the gaps in our knowledge, Monte Carlo simulation techniques will play a large role in the design and interpretation of such experiments. The Monte Carlo method has already expanded from solving pure physics problems into radiation biology to understand the interaction of particle tracks with subcellular targets, including radiation-induced chemical reactions.⁹

In summary, in the near future, Monte Carlo dose calculations will replace current analytical dose calculation methods in treatment planning for proton therapy. The Monte Carlo

method has a much larger clinical impact in proton therapy than in photon therapy. Its use will improve the predictive power of dosimetric indices in outcome studies and will lead to a reduction of treatment margins. Additionally, Monte Carlo

simulations will play a vital role in radiation biology research and will help to understand and then utilize potential differences between proton and photon radiation biology to increase the therapeutic ratio.

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