



Beam range uncertainty and its clinical management in particle therapy

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Abstract – The full theoretical advantages of particle beams in external beam radiotherapy have not been fully exploited, in large part due to uncertainties of the beam range in the patient. For this reason, efforts are underway, either for more precise in-vivo detection of Bragg peak positions or for further reduction of beam range computation errors in treatment planning. Meanwhile, management of the range uncertainty issues with mitigation techniques based on existing technology is critical in providing safe and effective treatments in clinical practice. This paper briefly reviews the definition and causes of particle range uncertainty, the uncertainty estimates currently used in clinical practice, and the corresponding mitigation techniques. It is intended to provide references for clinical practices at new and existing particle therapy centers.

Key words: Range uncertainty, Particle therapy, Clinical management.

Introduction

Nearly two-thirds of cancer patients are treated with radiation therapy (RT) [1]. As the global cancer population continues to grow, new treatment technologies are rapidly evolving with greater scope for implementation. The goal of any RT technique using an external beam is to precisely target the dose distribution to the tumor volume with minimal impact on the surrounding healthy tissues and critical structures [2]. Compared to photon beams widely used in conventional radiotherapy treatments, proton and heavy ion beams have superior physical selectivity in depth because of their lower dose deposition in the entrance region, and the steep increase followed by an immediate decrease at the so-called Bragg peak (Figure 1, under mono-energy scenario). Due to these characteristics, it is possible, at least in principle, to deliver a higher dose to the tumor with better protection of the surrounding normal tissues. As pointed out by Paganetti et al., compared to photon therapy techniques, the total energy deposited in the patient (often referred to as the “integral dose”, displayed as the area under the depth-dose curve) is always lower when using protons or heavy ions for a given target dose prescription, as shown in Figure 1 [3]. These unique dosimetric advantages

provided by proton and/or heavy ion beams have led to improved local control and reduced long/short-term treatment toxicities, as evidenced in multiple clinical trials for various cancer treatments [4–12].

While the sharp distal fall-off of the Bragg peak can theoretically provide a steep dose gradient between the tumor and the adjacent normal tissues, in practice, however, the actual locations of the Bragg peak inside the patient cannot be predicted as precisely as we hope, leading to the possibility of an undershoot (incomplete coverage of the distal portion of the target) or an overshoot (overdosing unexpectedly normal tissues immediately behind the target). This is the so-called range uncertainty problem, a unique challenge in particle therapy that often substantially compromises the theoretical dosimetric advantages of the particle beams. Meanwhile, besides the dose uncertainty addressed above, the relative biological effectiveness (RBE) uncertainty is also noticeable. It was found that the RBE at the distal fall-off of the Bragg peak is remarkably higher than the value universally applied as 1.1 for proton dose calculation [13–15]. As for heavy ions like carbon ions, they have even greater RBE changes compared to protons [16]. In the following sections, we will briefly review the definition of beam range, the sources for the uncertainties, and efforts to manage them with given technologies in the clinical setting.

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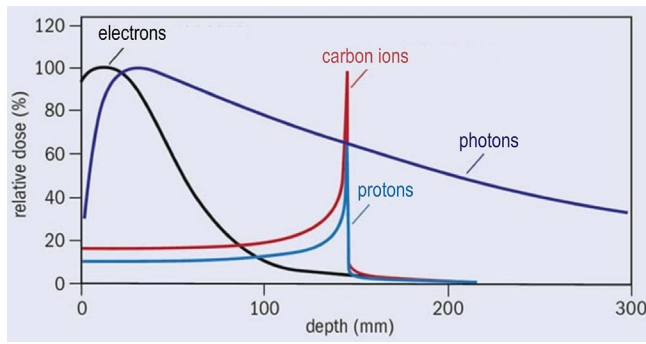


Figure 1. The depth-dose distribution curves of particles commonly used in radiation therapy with the Bragg peaks of protons and carbon ions clearly presented.

Beam range definition for protons and heavy ions

Protons and heavy ions, as charged particles, interact with matter by losing their energy gradually via Coulomb interaction as they travel through the medium and finally stop once all their kinetic energies are exhausted. This process is demonstrated as the Bragg number curve (see the blue line in Figure 2) [17]. The mean range is defined as the distance from entrance to the point where half of the incident particles in the medium stop their trip and the dose takes up 80% dose of the Bragg peak (green line in Figure 2). The range is given by

$$\bar{R} = \int_0^{E_0} \frac{dE}{S(x)} \quad (1)$$

$$S(x) = -dE/dx \quad (2)$$

where $S(x)$ is defined as the stopping power of the medium for that particle at location x , dE stands for the energy loss over the distance dx , and E_0 is the initial particle kinetic energy as it enters the medium.

It should be pointed out that the initial kinetic energy of the particle E_0 can be calibrated highly accurately in modern particle therapy systems with the uncertainty typically less than 0.5 mm across the full range of clinical beam energies. The primary sources of range uncertainty therefore come from the stopping power function $S(x)$, that is, the difference between its values used in computing the beam ranges in the patient during treatment planning and the true values at every point along the beam path during the actual treatment.

Main sources of range uncertainty

The accuracy of the stopping power value $S(x)$ may be affected in two major ways, corresponding to the two main sources of range uncertainty, respectively. The first is the change of stopping power due to variations in beam path during treatment δx , which may be represented by $S(\delta x)$ symbolically. It includes several specific scenarios as follows. For one, patient positioning varies between treatment fractions, with random and systematic errors. Trofimov et al. studied the inter-fractional variations and their implications on the delivery of proton

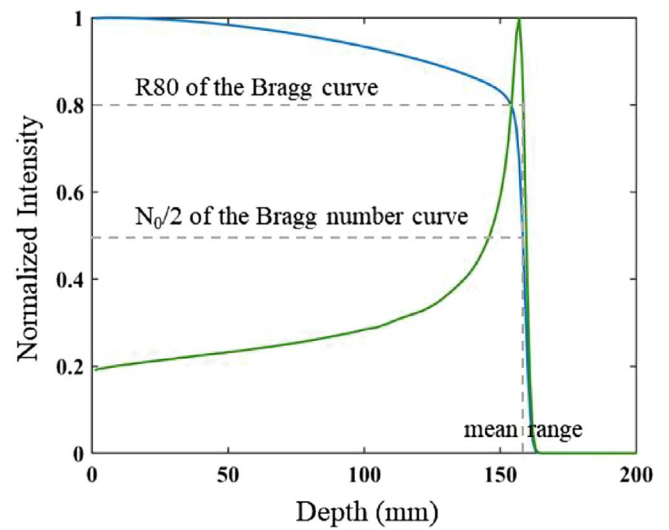


Figure 2. The Bragg number curve of 150 MeV protons (blue line) with its corresponding mean range labeled (dashed line) and the IDD of the same proton energy (green line) with its corresponding R80 range labeled (dashed line).

therapy for localized prostate cancer in 10 patients and found more than a 5 mm difference in the lateral tissue thickness between in-room computerized tomography (CT) scans and the planning CT scan [18]. Patient anatomy changes such as weight loss/gain, shrinkage/progression of the tumor, and/or varying filling of internal cavities could happen during the treatment course. Patient anatomy changes can also be contributed by patient deformation or positional errors in setup, e.g., in H&N setup. Organ motion is another major challenge during lung/liver treatment where respiration could bring substantial motion and deformation of targets and critical organs. All of the above-addressed circumstances lead to variations in the beam path.

The second major source of error in the stopping power calculation is in the function $S(x)$ itself, perhaps expressed as $\delta S(x)$. Specifically, it is in the conversion from the CT Hounsfield Unit (HU) to relative stopping power (RSP) for voxels along the beam path. The most commonly used method for this conversion is stoichiometric calibration first proposed by Schneider et al. [19], using a set of plastic tissue substitutes with known chemical compositions. While the technique has been widely practiced, inevitable uncertainties still exist. Yang et al. found that up to 5% of HU-RSP errors in lung tissues [20]. Consequently, validation of the stoichiometric calibration using fresh animal tissues seems necessary [21–25]. Meijers et al. proposed a range probing method to verify, optimize, and validate CT calibration curves and showed the potential of further reducing uncertainties [26].

Technological advancements in detecting and reducing range uncertainties

A broad range of efforts are continuously made to tackle the range uncertainty problem. The use of dual-energy CT (DECT) data instead of traditional single-energy CT (SECT) data for

treatment planning has been explored with substantial progress in improving the accuracy of RSP estimation [27].

Another direction is the in-vivo measurement of treatment dose/range by taking advantage of some unique properties of particle beams. Patients who receive a proton or heavy ion irradiation have positron-emitting isotopes produced inside their bodies. Positron emission tomography (PET) scan during or immediately after the treatment can produce a 3D distribution of the isotopes which correlates in certain ways with the treatment dose distribution [28]. Prompt gammas (PG) rays are emitted when incident protons or heavier ions interact inelastically with nuclei in the irradiated tissue. Measuring the spatial distribution of PG emission from irradiated tissue can provide real-time verification for the range of a single proton pencil beam with high accuracy [29]. Ion radiography and tomography use the same ion beam source for treatment to generate radiographic or tomographic images by transmission through the patient body to provide direct 2D/3D validation of the relative stopping power ratios for the tissues. Some techniques based on the ionoacoustic effects are under investigation for measuring/monitoring proton beam ranges [30–36]. Meanwhile, for specific sites, post-treatment MR imaging could provide more detailed radiation-induced physiological changes to assist the clinical evaluation of beam range and dose distribution in vivo [37–39].

Clinical management of range uncertainties

Needless to say, the beam range uncertainty problem is real in particle beam therapy. However, the magnitude of the problem and the consequences in actual clinical practices are not to be misunderstood and/or overestimated. Lomax recently summarized a few “myths” that reflect some of the widespread misunderstandings [40]. These include, for example, assuming that Bragg peaks are always as sharp as in water, but without realizing that they could be broadened substantially due to tissue heterogeneity in patients with the dosimetric effect of range uncertainty much reduced. Such myths could go as far as claiming that Bragg peaks are not used in proton therapy and range uncertainty substantially mitigates the advantage of protons. The fact is, however, while beam range uncertainty does present a nonnegligible challenge in the application of particle therapy, its clinical impact could be managed safely and effectively by a variety of approaches and techniques as described briefly below.

Using range margins

This is the technique of adding an extra margin to the beam range to ensure target volume coverage in treatment. The technique has been widely practiced particularly in the early days when passive scattering and forward planning were the dominating technology. The extra margin allows the dose coverage in the treatment plan to go beyond the distal aspect of the target volume to ensure its coverage in case the calculated beam range falls short in the actual treatment. The range margin usually contains two components. One is a percentage of the largest water equivalent path length from the body surface to the distal

surface of the target volume, corresponding to uncertainties in the CT HU-RSP conversion, i.e., the $\delta S(x)$ portion. The percentage is usually in the range of 2.5%–3.5% for most treatment sites except for lung tumors where a much higher percentage may be needed [41]. The other component, usually ranging from one to a few millimeters, reflects factors like accuracy in beam range calibration, and those introduced by potential beam path variations, i.e., the $S(\delta x)$ portion [3]. Specific values of the two components depend on the treatment site and may vary slightly among centers. In addition to the treatment site, it also depends on other factors such as CT scanner, treatment machine, whether IGRT technique is used, etc.

While the extra range margin helps cover the target volume, at the same time it risks delivering prescription doses to normal tissues immediately distal to the target volume. Therefore, the size of the range margin must be selected carefully to avoid unnecessary overshooting. A common mistake is first generating a planning target volume (PTV) with uniform expansion as usually done in photon planning, and then computing the range margin to cover the PTV. As a result, the beam range is increased inexplicitly by the PTV expansion margin unnecessarily. Note that the location of Bragg peak is only determined by the water equivalent path length along the beam path and therefore not affected by geometric target position error in the longitudinal direction of the beam. In consideration of this particular property of the particle beam, the concept of the beam-specific planning target volume (bPTV) has been introduced with the margin of expansion along the beam direction determined only by beam range uncertainties instead of the usual patient setup uncertainties [42].

Patient setup and monitoring of anatomical changes

Patient setup and anatomical changes during the treatment course should be a concern for clinical management of range uncertainty since it could contribute considerably to beam path variations during treatment through the $S(\delta x)$ term as mentioned above.

Imaging guidance plays a critical role in facilitating the patient’s daily setup as close as possible to that of the treatment planning CT, with a preference for 3D-based techniques such as cone beam CT (CBCT) or in-room CT. Note that in photon treatment, patient setup focuses on the reproducibility of the target position. In particle therapy treatment, however, the reproducibility of the beam path is just as important, since any discrepancy in the water equivalent path length along the beam path could affect the location of the Bragg peaks and the associated dose distribution. For treatment sites with potentially large variations in body surface curvature (e.g., breast, extremities), repeatability of the position and the curvature of the body surface is as critical as the alignment of the target volume in deeper tissues, especially in the case of oblique incidence of the beam.

Additional attention should be paid to anatomy changes from the time of CT simulation and throughout the treatment course such as weight loss/gain, shrinkage/progression of the tumor, and/or varying filling of internal cavities, all of which affect particle beam range inside the patient body. Therapists

should promptly identify and report the above-mentioned situations and work with physicians and physicists to determine if CT rescanning and replanning are warranted.

Some centers use a 2 to 4-week interval for acquisitions of the so-called verification CTs to ensure treatment robustness, even if the patient does not show any signs of major anatomy changes [43–50]. By recalculating the treatment plan on the verification CT and performing a robustness evaluation, appropriate measures are taken to ensure treatment quality. Adaptive therapy for particle treatment is also an active research subject aiming at more frequent and active intervention by utilizing the daily setup imaging data (CBCT or in-room CT) [51–56].

Validation of the CT HU-RSP conversion and DECT

To mitigate uncertainties in the stopping power calculation, namely $\delta S(x)$, careful validation of the CT HU-RSP conversion curve is critical. As previously mentioned, the CT HU-RSP conversion curve for treatment planning calculation is typically obtained by the stoichiometric calibration technique using a large number of plastic tissue substitutes for all types of body tissues [19, 57–59]. However, the uncertainties could only be reduced but not eliminated, particularly in regions where materials with the same CT HU can have different RSPs, not to mention uncertainties in CT HU itself due to factors like beam hardening, etc. Consequently, careful validation of the CT HU-RSP curve becomes necessary. It has become popular in recent years to use fresh animal tissues in addition to plastic tissue substitutes for validation measurements, and in certain cases, the CT HU-RSP conversion was adjusted based on the measurements [26].

Animal tissues used for validation usually contain muscle, adipose, bones, viscera, etc. Attention must be given to maintaining their shape and form from CT scanning to subsequent water equivalent thickness (WET) measurements, to ensure the reproducibility and accuracy of the experiment. In general, thicker tissue samples with larger WET values could improve the accuracy of the measurements. If containers were used for the tissue samples, the WETs of the container walls must be measured separately and subtracted from the total measured WETs. Note that animal tissue samples are rarely perfectly homogeneous and this could affect the validation measurements. The particle beam width is limited, and it varies along the beam path and with particle energy. Range mixing effects (the situation where protons with two or more distinctly different ranges are mixed) due to tissue heterogeneity must be considered [60].

Dual-energy CT has been shown to improve the accuracy of RSP estimation for particle beam treatment planning [27, 61]. For each tissue voxel element, DECT generates two HU values corresponding to the two separate X-ray energies used in the scan, instead of only a single HU value obtained from single-energy CT. The additional HU value allows more accurate determination of the tissue composition through more precise radiation physics, and thus more accurate calculations of beam ranges. For example, the use of DECT allowed a reduction of the planning range margin from the traditional 3.5% to 1.7% for brain tumors and 2% for prostate cancer patients,

respectively [62]. The technique has been routinely used in some clinics and will likely be adopted by the broader particle therapy community in the near future.

Robust optimization and robustness evaluation

The range uncertainty problem can affect the robustness of a particle therapy treatment plan in a unique way, particularly in the presence of high degrees of tissue heterogeneity in the target volume and/or along the beam path. In treatment by photon beams, a positioning error will shift the so-called dose “cloud” to a different position, but the dose cloud itself stays relatively undistorted and this will only affect the dose coverage within small margin areas around the edges of the target volume. The problem can be solved by planning the dose coverage for the PTV, an enlarged target volume based on an all-around expansion of the clinical target volume (CTV) with appropriate margins. As a result, the CTV coverage becomes robust against all potential positioning errors during treatment. In particle therapy treatment, however, positioning errors could also cause water equivalent path length changes along the beam path due to tissue heterogeneity and thus changes in Bragg peak locations, resulting in substantial distortions of the dose cloud and consequently target coverage failures. Therefore, treatment planning guided solely by coverage for a fixed volume, e.g., PTV, could not in principle produce robust plans against positioning errors. Instead, the planning process needs to include each and all potential error scenarios into consideration specifically and explicitly, so that the obtained treatment plan is robust against all error conditions in terms of clinical target volume coverage and normal tissue sparing.

This is the so-called robust optimization in the planning of intensity-modulated particle therapy treatment and it is becoming the standard technique in the treatment planning system (TPS) [63–67]. The error scenarios included in the optimization typically contain patient setup uncertainty (± 3 – 5 mm depending on the treatment site) and range uncertainty (usually $\pm 3.5\%$). Some TPSs also provide inter-field uncertainty settings, which enhances the robustness of plans involving non-coplanar fields or multi-isocenters [68]. Fredriksson reviewed a class of robust methods in planning, including expected value optimization, worst-case optimization, conditional value at risk optimization, minimax stochastic programs, etc [69]. Robust optimization for intensity-modulated treatment is strongly recommended if available, especially in highly modulated treatment plans [70, 71]. If robust optimization is not available in the planning system and plan optimization can only be performed for a fixed target volume, whether it is a PTV obtained by the traditional uniform expansion from CTV or a beam-specific PTV, i.e., with consideration of a range margin, then a robustness evaluation must be performed upon the optimized dose distribution.

In fact, the method of robustness evaluation was proposed and applied long before robust optimization became available technically [63, 68, 72]. The method computes the dose distribution for each of the error scenarios and also in their combinations. By evaluating the target coverage and organs at risk (OARs) dose under all worst-case scenarios, the robustness of the plan is demonstrated and evaluated explicitly. Note that excessive robustness for target coverage alone is equally

undesirable since it inevitably means more doses to normal tissues unnecessarily.

Spreading out the effect

A rather common technique for reducing the effect of beam range uncertainty is to use as many beams from different directions as possible. Each beam would then take a smaller share of the prescribed dose and the disturbance to dose distribution due to its range uncertainty would be smaller. The effect of range uncertainty on the overall dose distribution would be spread out to more areas around the target but with a lower magnitude. Fractionated treatment, can be implemented without increasing the daily treatment time due to a unique feature of the particle beam. That is, a single particle beam can in principle deliver a homogeneous dose distribution at the prescription level to cover the entire target volume, unlike the case of photon treatment where the superposition of multiple fields is nearly always needed to achieve the homogeneous dose coverage. As a result, the large number of particle beams can be divided into groups where each of them covers the same target volume but from different beam directions with different normal tissue doses. Each group may contain a single beam or a few beams and can be optimized either by single field optimization (SFO) or multiple field optimization (MFO) within the group. The groups are used in sequence, one for each fraction, with the planned total dose distribution achieved by accumulation throughout the whole treatment course.

Notably, proton arc therapy (PAT) currently under development where proton doses are continuously delivered while the gantry keeps rotating [73], may fully exploit the above-mentioned advantages of multiple beams. Of course, the multiple beam approach and its theoretical extreme, i.e., proton arc, may not be appropriate for all treatment sites. It is certainly more suitable for those where treatment toxicity most likely comes from high doses to critical organs, e.g., in head/neck treatment, and not quite so for sites where low doses to larger organ volume are more concerning, e.g., in liver treatment.

Avoiding ranging out into critical OARs

Given the range uncertainty concern, beam directions must be selected carefully when critical organs overlap with (or very close to) the target. If a beam direction is designed to shoot towards the target and a critical organ is immediately behind it, as shown in Figure 3A, the Bragg peak could easily fall into the OAR during treatment, as shown in Figure 3B, should the beam overshoots due to range uncertainty. Therefore, one should always avoid having the beam range out into critical organs and instead use the lateral beam penumbra for normal tissue sparing. It is true that the distal dose penumbra of the Bragg peak is generally much sharper than the lateral beam penumbra and thus seems better suited for organ sparing theoretically. In reality, however, the associated risk should not be underestimated.

There are of course situations where it is not possible to avoid shooting towards the target with a critical organ immediately behind, as illustrated in Figure 3 and Video 1 (beam 1). In those cases, a special technique may be applied by taking

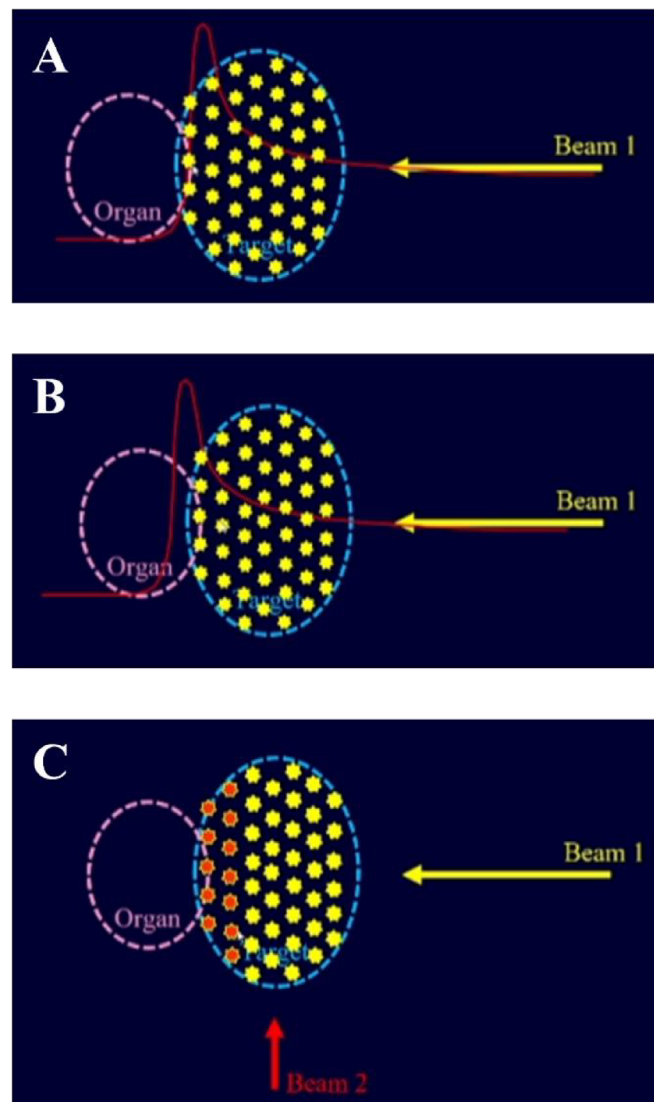
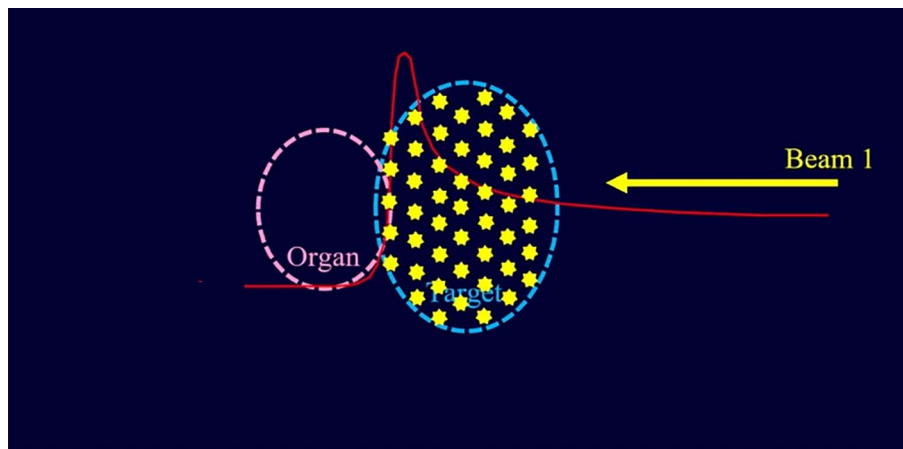


Figure 3. Using MFO to avoid ranging out into critical OARs. (A) Single field setting where beam 1's direction is designed to shoot towards the target. (B) The end of range falling into the OAR when range uncertainty causes beam 1 to overshoot. (C) Multi-fields setting with restricted spot distribution for beam 1 to avoid ranging out into critical organs due to range uncertainty.

advantage of multiple field optimization available for pencil beam scanning. Such optimization is usually performed in two steps, first the distribution of the pencil beam spot positions from each beam over the entire target volume, and then the optimization to determine the number of particles per spot for all the beams simultaneously. As shown in Figure 3C, one can in fact deliberately limit beam 1's spot distribution to only the shallower part of the target (yellow spots). In this way, Bragg peaks from beam 1 will never reach the critical organ even with a potential overshooting caused by range uncertainty. The dose for the remaining part of the target near the critical organ is solely provided by the red spots from beam 2, whose direction allows it to reliably spare the organ using its lateral beam penumbra. Clearly, such techniques may not always be



Video 1. Avoiding ranging out into critical OARs. <https://vcm.edpsciences.org/10.1051/vcm/2024004#V1>.

applicable and sometimes there are simply no alternatives to ranging out in critical organs. In those cases, one must carefully consider the potential risks associated with the overshooting including the effects due to RBE uncertainties near the end of the beam range.

are manually overridden with a uniform value so that the range can be fully covered. However, special attention should be paid considering the beam directions and dosimetric robustness. The beam directions should be “motion-robust”, avoiding large density gradients in the beam path.

Other special clinical conditions

Metallic implants for radiotherapy patients are usually hip, spinal, dental, cochlear, or breast (with magnet) implants [74], which are generally made of high Z materials and are widely heterogeneous in density between patients. Their geometric dimensions as well as imaging artifacts can lead to uncertainty in particle range.

Clinically, it is generally forbidden to have particle beams through metallic implants, but if it does, this situation is worth discussing. Relevant clinical management experience in photon therapy is worthwhile for reference, e.g., AAPM TG-63 [74] and the French Society of Oncological Radiotherapy [75]. First, the HU is more inaccurate due to metallic implants, further increasing the inaccuracy of the HU-RSP curve, and this inaccuracy of the HU needs to be mitigated, e.g., by additional multi-modality imaging or by applying artifact-correction algorithms to obtain more accurate HUs, or by manual assignment of values (HU, density, etc.) with a prerequisite of knowing the actual material composition of the implant. Second, the plan should be designed to keep the beam as far away from the implant as possible. Meanwhile, a thorough interpretation of dose calculation algorithms dealing with voxels with high HU values is recommended.

Moving targets that cause significant WET changes along beam paths is another special clinical concern. Often such situations are referred to the implementation of 4D therapy, and some experiences have been shared in this regard [76]. Internal target volume (ITV) margin approaches are commonly used and if possible, in combination with rescanning (the delivery of dose spots in multiple iterations to smooth out the dose inhomogeneities) technique. The ITV should consider the target positions from all directions. Density override is another approach where the densities of the target and/or some OARs

Summary and outlook

Briefly, range uncertainty in particle therapy originates from errors in the stopping power function that determines the beam range inside the patient. The two main sources for the errors are inaccurate CT HU to RSP conversion for voxels along the beam path during treatment planning and beam path changes/variations from patient positioning, patient anatomy changes, organ motion, etc. during the actual treatment. The problem has been the focus of a broad range of research efforts including the utilization of dual-energy CT for planning, and technologies for in-vivo measurement/correction of beam ranges, for example, post-treatment PET scan, prompt gamma detection, ion beam radiography/tomography, etc. Some of these efforts have made their way to the clinic with substantial improvements in treatments.

While range uncertainty indeed presents a nonnegligible challenge, its effects should not be exaggerated based on purely theoretical perceptions. The clinical context is quite different and there are many techniques to manage the impact of range uncertainty safely and effectively today. As particle therapy expands with broader applications and clinical practices, new approaches are emerging and moving into the clinics with improved outcomes. To name a few, we are transitioning from the use of range margins to robust optimization, from single-energy CT to dual-energy CT for stopping power ratio estimation, from 2D imaging to 3D imaging with possible on-line adaption of beam energies, from limited beam directions in fixed beam treatment rooms to 360-degree gantries allowing many beam directions and possibly arc treatment soon. With these advances and other continued efforts in research and development, the range uncertainty issue will be less and less relevant clinically while we provide the full clinical benefits of particle therapy to our patients.

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Ethics approval

Ethical approval was not required.

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