The Physics of Protons for Patient Treatment

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Introduction

Presently one of the major health risks mankind faces is cancer. More than one in three people will suffer from this disease or side effects of its treatment at some stage in their lives (1). Because of the deleterious effects that cancer and, oftentimes, treatment modalities have on the human population, better treatment techniques are constantly being sought. Besides surgery, external-beam radiation therapy is a mainstay of cancer treatment and cure. High-energy protons are an important innovation in external-beam radiation therapy, providing highly conformal dose distributions and thus sparing normal tissues through benefits afforded by the Bragg peak. This paper will focus on the physics of protons and facility design in enabling this particle to be used for the clinical benefit of patients.

The Power of the Bragg Peak

In radiation therapy it is desirable to maximize dose delivered to the tumor volume whilst minimizing dose to surrounding normal structures. In the ideal case one would want to deliver the entire radiation dose to the target volume, with no dose delivered to surrounding structures. Protons and other heavy charged particles come close to fulfilling this objective: they deposit most of their energy in a high-dose peak (known as the Bragg peak) at the end of their track (Fig. 1). This peak is created through an exponential increase in stopping power towards the end of the protons' track. Hence, as a heavy charged particle (such as a proton) slows down, the amount of energy it deposits per unit length covered increases exponentially, creating a high-dose peak (2). The depth of this peak in a given material (such as a patient) depends on its initial energy; varying this energy allows the high-dose region to be placed at any depth.

The depth dose profile of protons is in stark contrast to X-rays (considered as a standard external beam radiation modality), which achieve maximum dose either at or just below the surface of the patient. It is only through the superposition of multiple treatment fields from multiple directions that an elevated radiation dose to the target volume is achievable with X-rays. A further disadvantage of X-rays is that they deposit dose beyond the target. Protons stop at the Bragg peak, ensuring that no dose is delivered from the primary radiation field beyond the target. This has great benefit in reducing the dose to structures that lie beyond the target and minimizing the integral dose experienced by the patient (Fig. 2).

Proton Beam Delivery

Proton delivery techniques can be categorized as passive or active in the delivery of a uniform dose to the treatment volume. Passive techniques, which have been most commonly used in the clinical setting (3, 4), spread the beam laterally using a combination of gold (or lead) and Lexan foils (5). The combination of two materials, one of low and the other of high atomic number, produces a flat beam of constant flux and a constant range. Typically a dual scattering foil arrangement (6) is utilized that is optimized to deliver a flat field of the cross sectional area required for treatment. The beam is then modulated in depth using a rotating plastic wheel (7, 8) that effectively allows for the superposition of multiple Bragg peaks of varying energy and intensity to create a region of uniform high dose called the spread-out Bragg peak (SOBP) (6). The beam is then collimated by brass or Cerrobend® apertures and its penetration depth is varied by means of a wax bolus. Such an arrangement creates a uniform dose across the treatment volume, as displayed in Fig. 3.

Active techniques (9-12) employ a magnetically guided proton pencil beam in combination with dynamic changes of beam energy and beam intensity during treatment. One advantage of the active system is that it minimizes interaction between the primary beam and beam modifying devices, in turn minimizing the production of secondary particles. Further, it has the potential to treat complex tumor volumes with greater precision and improved normal tissue sparing. However, the dosimetry and beam

delivery is also more complex and problematic; errors in this regard can lead to high and low dose regions and an incomplete treatment of the tumor volume. Organ motion during treatment is another complicating factor that also needs to be considered for effective and accurate treatment of the tumor volume.

Facility Design

Proton therapy facilities are incredibly complex systems needing to accelerate, transport, and deliver charged protons to a given target volume as specified by the clinician. Unlike X-ray facilities that contain the accelerator, gantry, and beam delivery systems within a single room or bunker, proton therapy departments typically use a single accelerator to provide high-energy protons for a number of treatment rooms (6). Protons are accelerated in the accelerator (cyclotron or synchrotron) and then transported along an evacuated beam pipe to the treatment room. During acceleration and transport, magnets control proton direction and also focus the proton beam overcoming Coulombic repulsion of the like charged particles. Beam is delivered to one treatment room at a time as requested by the treating therapist while the other treatment rooms are setting up and aligning the patient (13).

When the beam arrives at the proton room it must be delivered to the target site. This is typically achieved using a gantry that allows for beam delivery 360 degrees around the patient. Patients meanwhile are aligned using lasers and X-rays images to ensuring accurate alignment relative to the beam delivery system (isocenter). The combination of gantry proton delivery with six-degree-of-freedom robotic patient positioners (Fig. 5) allows clinicians the greatest flexibility in proton beam delivery in treating the target volume while sparing critical structures. Treatment times per beam is of the order of 1-2 minutes, during which time the patient feels nothing and is under constant audio and visual monitoring by the therapy team.

Clinical Advantages of Protons

Protons provide a clinical advantage over other external-beam radiation therapy techniques through the Bragg peak. The Bragg peak (or SOBP, which is used clinically) allows for the delivery of fewer beams to achieve the same target coverage (Fig. 2), in turn limiting the integral dose delivered to other organs. The ability of protons to stop and produce no primary proton exit dose is a distinct advantage over X-rays in limiting dose to the rest of the body and sparing critical structures (Figs. 6 and 7). This is especially critical for pediatric cases (Fig. 7), where additional dose to non-target structures can lead to increased instances of secondary malignancies due to longer life expectancy.

The ability to treat with fewer beams in proton therapy not only limits unwanted dose to the patient but also speeds up treatment time. Faster treatment times limit intra-fraction motion (motion during treatment), allowing for a more accurate delivery to the target, which is essential as treatment become more conformal with tighter margins.

The Out-of-Field Dose Question

It has been demonstrated that protons provide a significant advantage over other external-beam radiation modalities owing to their depth-dose distribution, which allows for maximum dose to be delivered to the tumor volume with no primary particle dose beyond the distal edge. This allows for significantly fewer beams to be utilized, resulting in a much lower integral dose to surrounding critical structures (14). Recently the whole-body dose delivered by protons and other ions was called into question by Eric Hall (15). This dose, which is of particular importance in pediatric patients with long life expectancy and greater susceptibility to radiation-induced cancers, is delivered by secondary neutrons that are produced through primary beam interactions with both the patient and beam-modifying devices. The dose-equivalent values per unit of prescribed proton dose presented in the report of Hall (15) have been questioned (16-18), but the concern remains because of the large uncertainties involved in neutron dose measurements and the RBE of neutrons (19).

Measurements have been completed by a number of groups (20-23) to answer these questions and provide guidelines for physicians in specifying treatment. These are typically of the order of several mSv/Gy close to the edge of the treatment field where the measured result is influenced by

scattered high-energy protons, to sub mSv/Gy at lateral displacements typically larger than 20 cm. Fig. 8 demonstrates the potential of active proton beam delivery systems in reducing the out-of-field dose component to the patient over passive delivery techniques such as those employed at the Paul Scherrer Institute (PSI), Harvard Cyclotron Laboratory (HCL), LLUMC, and the Midwest Proton Research Institute (MPRI).

The characteristics of the proton beam (field size, proton energy, modulation etc.) also impact the dose equivalent delivered out of the field. Figure 9 demonstrates how the external field dose equivalent can vary by more than an order of magnitude based on field characteristics. For a comprehensive summary of the data on this issue, the reader is referred to (20).

A comparison of the studies has shown that the out-of-field doses experienced by passively delivered proton therapy is comparable or less than those delivered in X-ray therapy (24-26), especially close to the field edge. Additionally, the use of fewer treatment beams by passively delivered proton therapy allows for reduced integral doses to surrounding organs, which may be of clinical benefit. Active beam scanning of protons can further reduce the out-of-field dose delivered by proton therapy; however, the method for tumor coverage is more complex and needs careful consideration to ensure that uniform dose to the tumor volume is not compromised. Choice of therapy is an important clinical decision that the physician must make in consultation with the patient, weighing in many factors including the inherent radiation protection issue of out-of-field doses; these may present an important factor, especially for younger patients.

Research Opportunities

Proton therapy provides a unique opportunity to complete research for a number of applications. Firstly, as proton therapy is a growing radiation treatment modality, there is much interest in developing technologies and treatment techniques for clinical applications. Active beam scanning (10, 13), radiosurgery, multi-leaf collimators (27), radiation dosimetry (28-30), immobilization, robotic patient positioners (13) and treatment verification (31, 32) are all being investigated in order to provide tools to the clinicians to improve the efficacy of proton radiation therapy. Protons are also being investigated as a possible imaging modality (33), with the hope that performing proton CT scans will reduce the range uncertainties and patient imaging dose. Meanwhile, clinicians are further developing treatment protocols for a wide range of treatment sites (3, 4, 34-38) in turn improving the efficacy of proton treatment while expanding its application to more patients.

As protons are also the predominant radiation species in space, proton therapy institutions provide an area for Earth-based testing prior to spaceflight. This can include electronics testing to ascertain failure rates and improve design, detector development for radiation protection and spaceflight (39-41) and radiobiology studies in order to achieve a greater understanding of the effects that low-dose radiation will have on astronauts (42-44). LLUMC has a dedicated research room that allows for protons between 20 and 250MeV to be delivered to the experiment along one of three dedicated beam lines. Field sizes of 0.1-50cm diameter can be delivered with passive delivery techniques, while beam scanning allows this to be increased to over 100cm (44). The dedicated research room allows for experiments to be completed separate from patient treatment, ensuring that experiments can remain set up without disturbance for extended periods. Experiments may also be completed in one of the four treatment rooms where clinically commissioned proton fields of 100-250MeV can be delivered to the experimental setup up to 18cm in diameter. The presence of laboratory, engineering and physics support at LLUMC ensures that even the most complex experiments can be supported by a multi-discipline team of proton delivery experts with 20+ years of experience.

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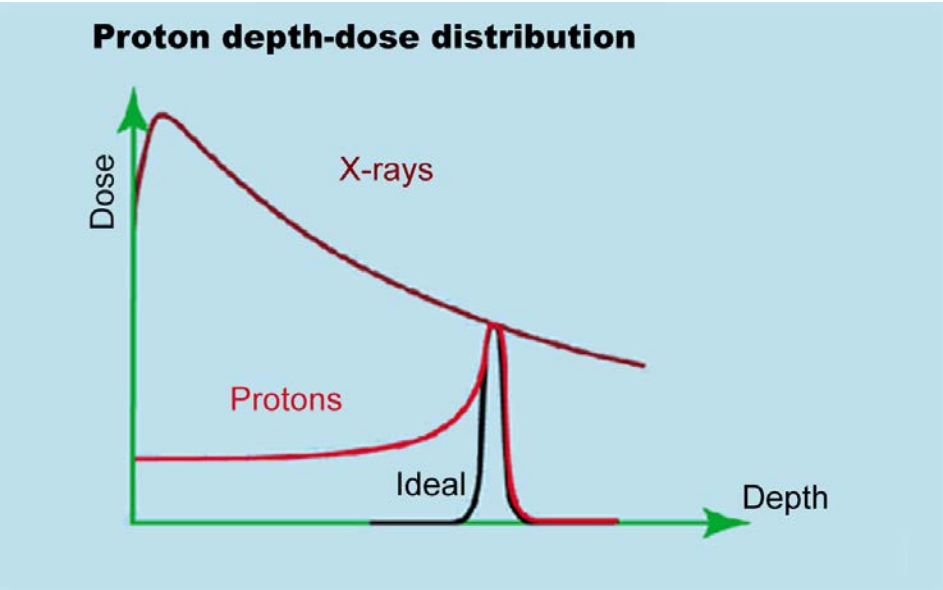

Figure 1: Depth dose distribution for X-rays, protons and the ideal distribution **(2)**

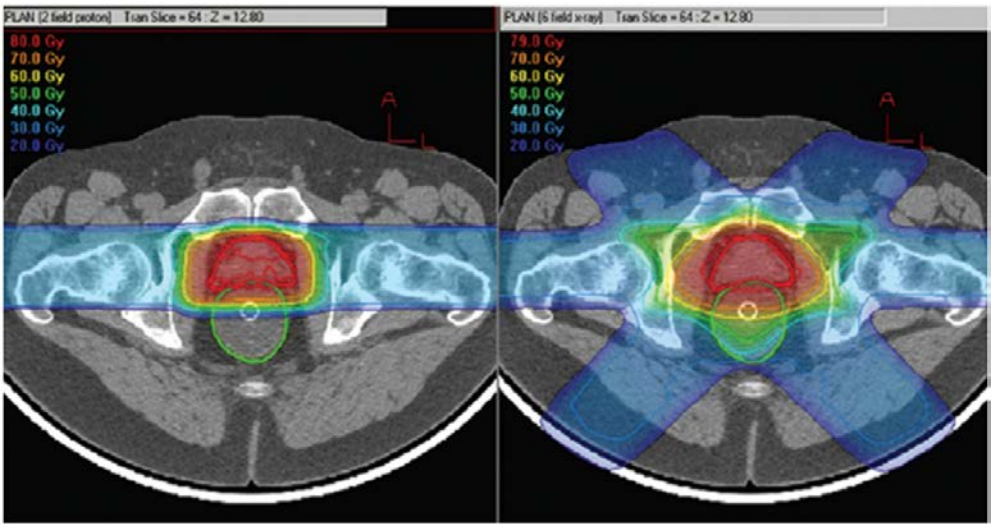

Figure 2: Comparative treatment plans for protons (left) and photons (right). Note the ability of protons to treat the target with only 2 beams hence limiting the integral dose experienced by the patient.

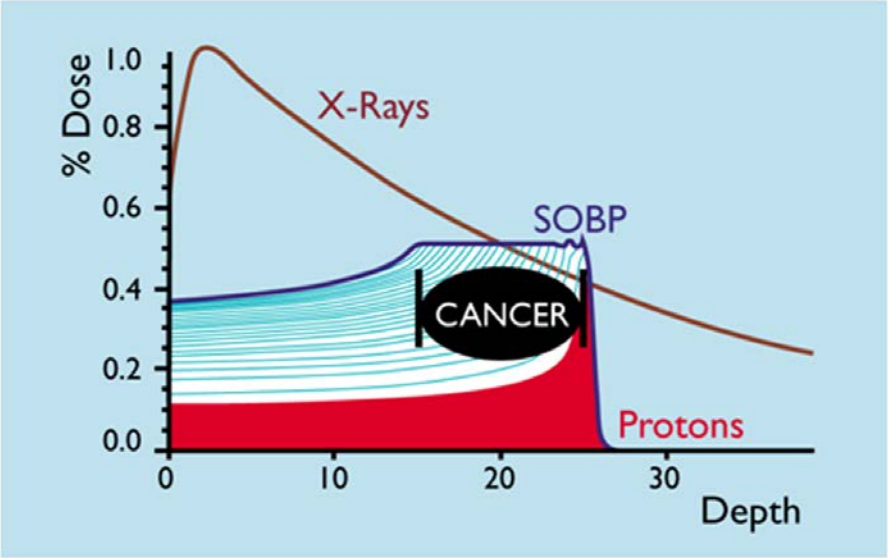

Figure 3: Comparison of the X-ray depth dose curve with the SOBP used in passive proton beam delivery for clinical treatment **(2)**

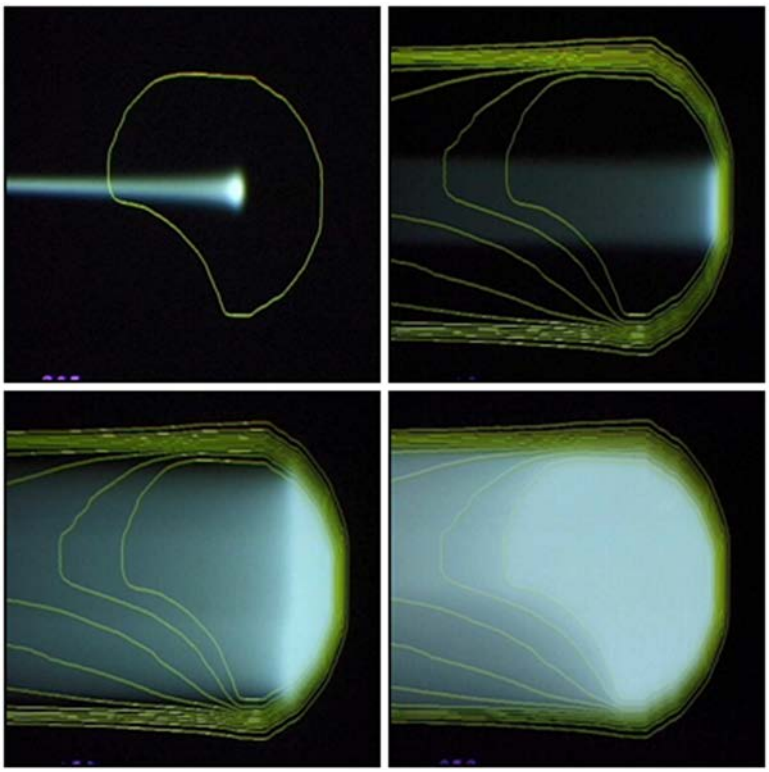

Figure 4: A representation of active scanning, illustrating how the superposition of multiple Bragg peaks or hot spots can be used to create a uniform dose across a desired volume of irregular shape (45)

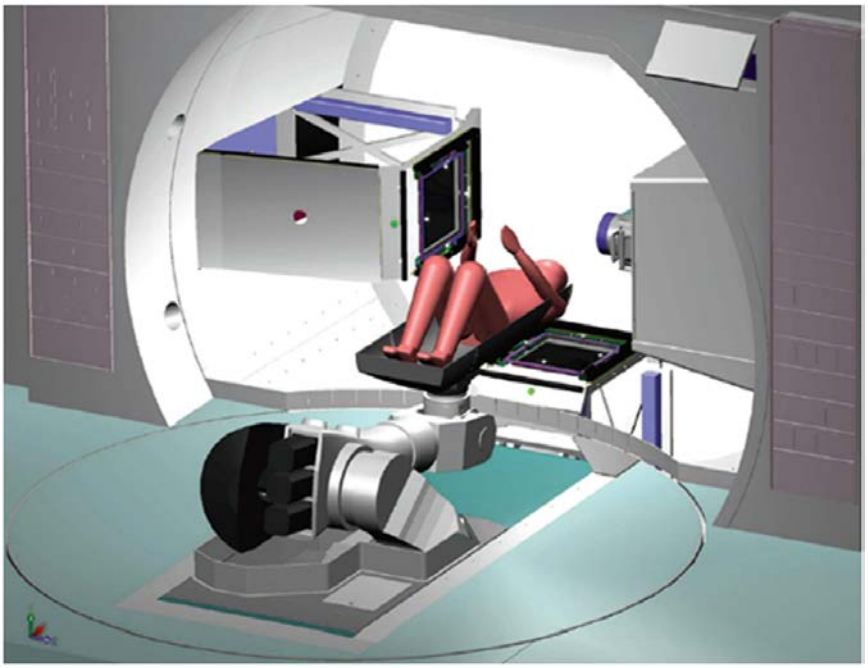

Figure 5: Schematic of the robotic patient positioner and gantry beam delivery system at LLUMC (13)

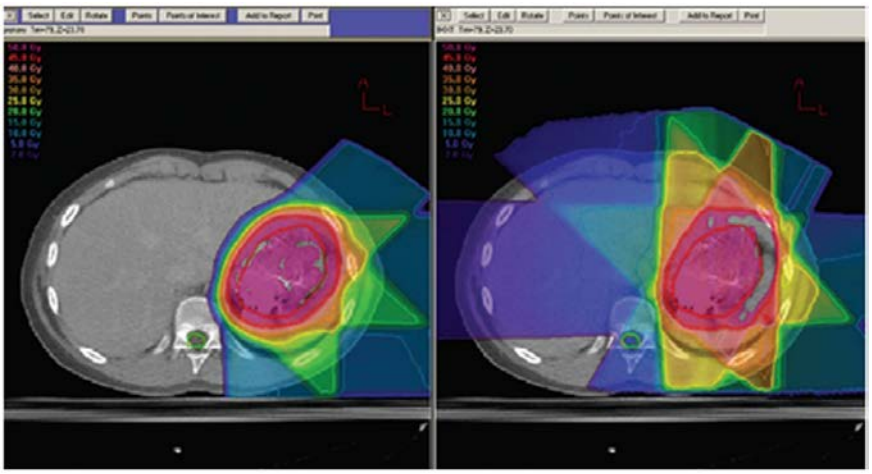

Figure 6: Comparative treatment plans for protons (left) and X-rays (right) in a liver treatment.

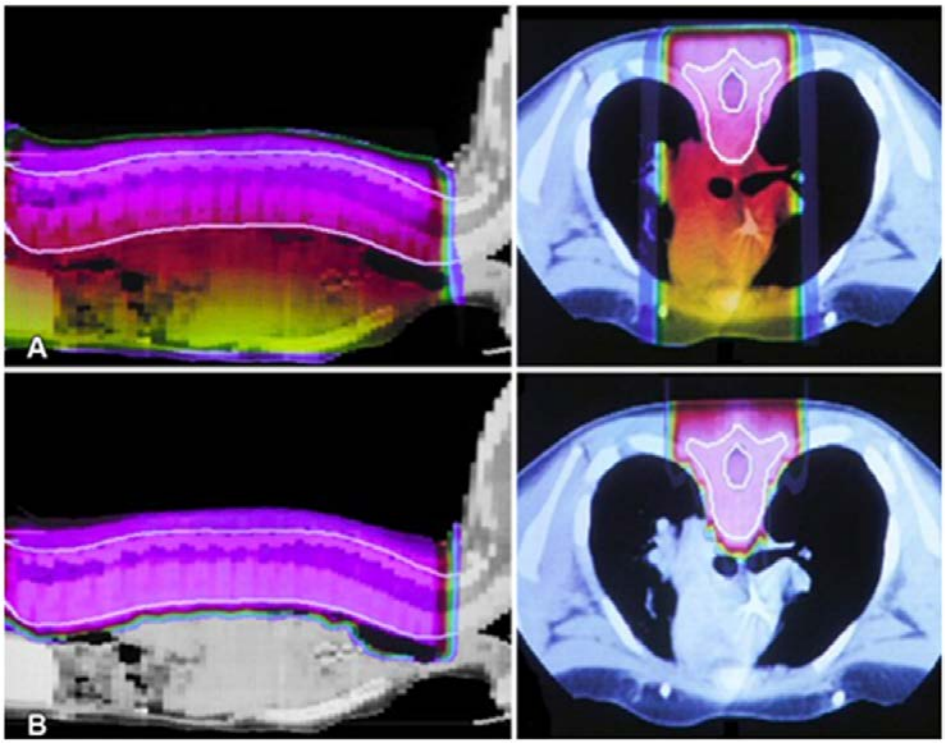

Figure 7: Comparative craniospinal treatment plans for photons (top) and protons (bottom). Note the ability of protons to stop, thus minimizing dose delivery to the thoracic and abdominal cavities.

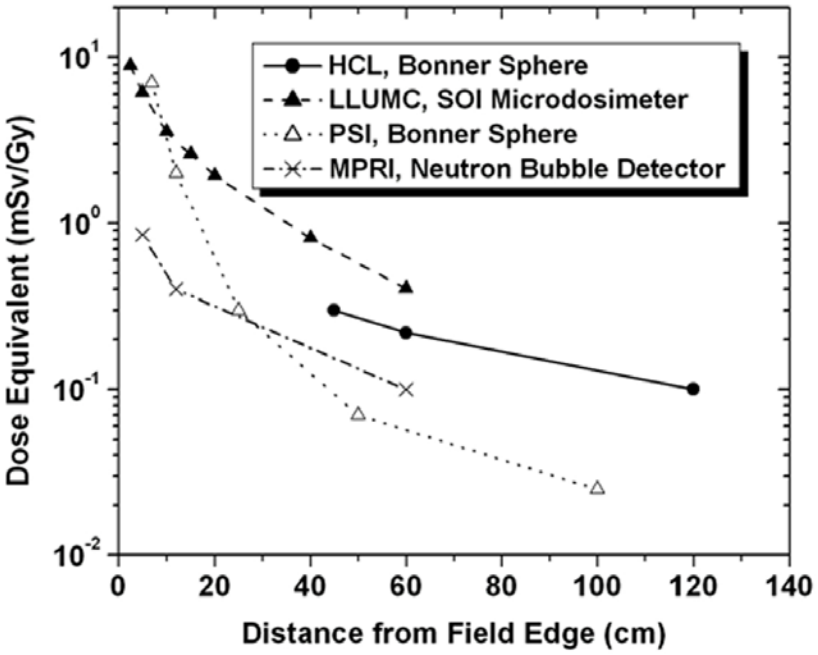

Figure 8: Measured data on out-of-field dose equivalent in proton therapy from a number of centers using a range of measurement techniques and devices. Results are presented from HCL (46), PSI (47), LLUMC (21) and MPRI (22)

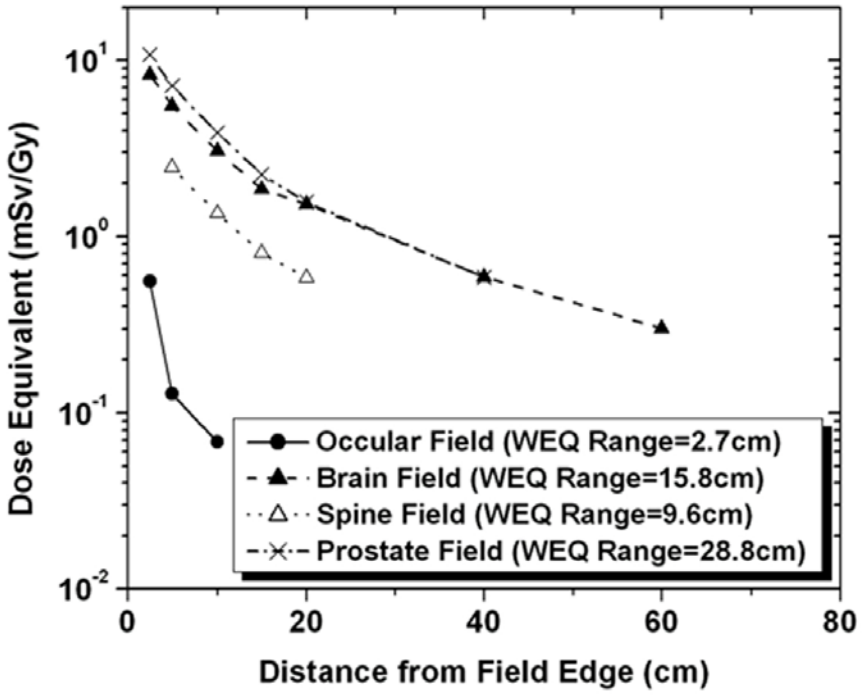

Figure 9: Measured data on out-of-field dose equivalent in proton therapy for a number of different treatment sites and beam configurations (20)