Proton Beam Radiation Therapy – From Physics to Clinical Indications

a report by
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The purpose of radiation therapy (RT) is to maximise the dose delivered to a tumour while minimising the exposure of dose-sensitive critical structures to high radiation doses. During the last decade, technical developments in RT have permitted the production of more conformal radiation dose distributions that better confine the high therapeutic dose to the tumour and respect the radiation tolerance of critical structures in the direct vicinity of the target volume. These techniques should result in an improvement in local tumour control in dose-responsive tumours, with no consequential increase in treatment-induced toxicity.

The use of computerised planning systems in conjunction with modern imaging studies, stereotactic patient positioning, multileaf collimation and, more recently, intensity-modulated beams have achieved highly conformal photon RT. The delivery of more conformal treatment can also be achieved with heavy particle beams, such as protons. Protons have superior dose-distributional qualities compared with photons, as dose deposition occurs in a modulated narrow zone, called the 'Bragg Peak'. The ability of protons to conform dose has been demonstrated in various comparative treatment-planning studies.[1-4] This review highlights some of the specific physical characteristics and describes the radiobiological principles of protons. Current clinical indications are reviewed and future development considered. Non-oncological disease will not, however, be considered in this review (i.e. macular degeneration of the retina and arteriovenous malformation of the brain).

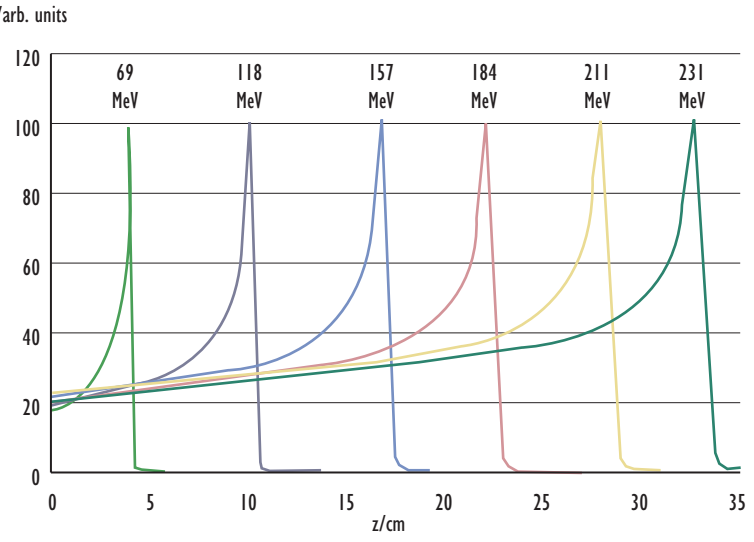
Physical Characteristics of Protons

Unlike photons, which lose their energy exponentially after an initial energy-dependant build-up region, proton-matter interactions produce a superior dose distribution by depositing the maximum dose at a specific depth. This portion of the particle track is known as the 'Bragg Peak'. The Bragg Peak dose deposition is consequential to the inverse relation between the energy transfer and the square of the proton velocity. The dose distal to the Bragg Peak is essentially zero. Consequently, with protons, a significant integral dose reduction outside the target volume is observed when compared with photon dosimetry. The magnitude of this integral-dose reduction is typically by a factor of two to five. Parenthetically, the term 'integral dose', or the total energy absorbed from the beam by the patient, is the product of the mass of tissue and the dose it received. The Bragg Peak is too narrow to be used to treat a clinically relevant volume. As shown in *Figure 1*, the depth of the Bragg Peak can be modified as a function of its incident energy. Several beams of different energies (ranges) can be superimposed to create a uniform-dose region over the depth of a larger (and clinically relevant) target. These extended regions of uniform dose are called 'spread-out Bragg Peaks' (SOBP). When compared to the dose depth for a 15MV photon beam, energy commonly used to treat deeply seated tumours, the SOBP delivers a higher uniform dose to the target area, a lower dose to normal tissues proximal to the target and, more importantly, no dose to tissues distal to the target. *Figure 2* shows the dose distribution for a left temporal low-grade glioma in an axial plane obtained with conventional X-rays and proton treatment plans. As shown in *Figure 3*, the proton plan shows substantial dose sparing to the frontal and temporal lobes. The SOBP results from the passive scattering operating system and is the most mature method for delivering proton beam therapy (PBT). Active (or dynamic) beam delivery necessitates scanning technology. This technology positions the Bragg Peak of a pencil beam and delivers the desired incremental dose at that voxel grid point by a fully automated and computer-controlled process. This process enables these spots of doses to conform to precisely the dose to the target volume. Preliminary clinical results using this delivery system are encouraging.[5-6]

Relative Biological Effectiveness of Protons

Protons have comparable biologic effects in tissue relative to megavoltage (MV) photons used in conventional RT. They are regarded as low linear

Figure 1: Depth in Tissue Curves as a Function of Energy (range, 69– 231 MeV) for Unmodulated Proton Beam (Bragg Peak).



energy transfer (LET) particles, comparable to photon and electron beams.[7] This has the advantage that prescribed doses and fractionation schedules developed for conventional RT are similar for proton therapy. As the beam penetrates the medium and approaches beam range, protons are of lower energy, and thus higher LET. The proton dose-averaged LET of a particular proton beam varies within the Bragg Peak region among other factors. The relative biological effectiveness (RBE) of protons can be defined as the ratio of the dose of a reference beam (usually ^{60}Co or 6MV) required to produce a specific effect in a biological system to the physical dose of proton radiation required to produce the same effect.[8] Its value is not fixed, but for 70–250MeV, protons range typically from 0.9 to 1.9, with an accepted 'generic' value of 1.1 in clinical proton therapy.[9] The equivalent ^{60}Co photon dose is the proton dose multiplied by 1.1. This calculated dose is defined as the Cobalt Gray Equivalent (CGE) dose. Laboratory studies have suggested that the RBE may vary significantly with depth in the Bragg Peak zone.[10] The physical mechanism underlying this RBE increase derives from the stochastic energy deposition events discussed earlier with LET variation in the proton tracks. The RBE for a specified proton beam depends on others factors, such as the energy of the protons, the radiation dose per fraction and the biological model studied.

The dose reported in PBT has no official units. CGE is usually used in publications and Gy-equivalent, (GyE), in carbon-beam therapy. On behalf of the International Commission on Radiation Units and Measurements (ICRU) and the International Atomic Energy Agency (IAEA), a committee, chaired by Professor D T L Jones (iThemba Laboratory for Accelerator Based Sciences, South Africa), submitted a report on "Prescribing, Recording and Reporting Proton Beam Therapy" in early spring 2006. It is proposed that the unit of Gy-isoeffective (Gy(I)) will be chosen. The full report will be published in early 2007.

Clinical Indications

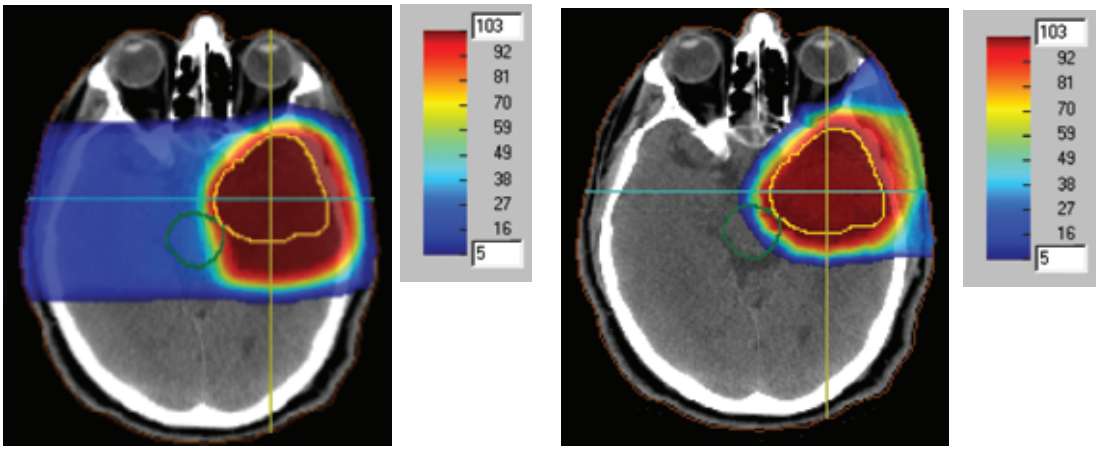
Historically, protons have been used therapeutically in Boston for rare tumours (i.e. chordoma and chondrosarcoma), that are in the direct vicinity of serially organised critical structures. The current indications for PBT encompass ocular and non-ocular tumours. PBT is a conservative alternative to enucleation for the management of uveal melanoma (UM) among various other eye-preserving treatment modalities. No significant difference in overall and metastasis-free survival was observed between enucleation and PBT in a large cohort of UM patients treated in Boston.[11] PBT results in excellent local control and acceptable ocular complication rates. Reported three- and five-year local control rates are superior to 89% and have increased gradually over the years as a result of modifications to the planning process.[12-15] The eye-retention rates after PBT are excellent.[11,16] For large UM, it remains to be demonstrated if transpupillary thermotherapy, administered adjuvantly, will decrease the rate of late complications by decreasing the radiation-induced exudative phenomena and consequential glaucoma, as was suggested in a recent phase III trial.[17] Good dosimetric and clinical results have also been achieved with retinoblastoma,[18] orbital rhabdomyosarcoma and choroidal metastasis.[19,20] Non-ocular tumours treated with protons are benign meningiomas,[6,21-22] sarcomas of the skull base and spine,[5,23,24] head and neck cancers,[25-27] prostate,[28-31] lung and gastro-intestinal/abdominal tumours.[32-38]

As a result of the integral dose reduction with protons and consequential potential reduction of secondary cancers,[39,40] the benefit of PBT will be maximised in young patients. Comparative treatment planning studies have shown that protons spare substantially more non-target structures than does non-proton radiotherapy.[41,42] Various paediatric tumours have been successfully treated with protons.[43-45] On-going clinical trials of PBT are in progress in the US, France and Switzerland for paediatric patients with medulloblastomas, rhabdomyosarcomas and other sarcomas and retinoblastomas.

Costs and Availability of PBT

The delivery of more complex RT will substantially increase the cost of RT. Using newer technologies can occasionally result in decremented costs in some situations, such as treatment time reduction or block replacement afforded by multileaf collimation and a reduced number of treatment portals required for

Figure 2: Dose Distribution in an Axial Plane Through the Center of the Planned Target Volume for X-rays and Protons, Respectively



X-rays plan Proton plan

The colorwash contours are represented by different colors (corresponding values are displayed on the right border of each figure). Colorwash isodoses are in percentage of prescribed dose (54 Gy and CGE for X-rays and protons, respectively).

radiation delivery with particle beam delivery systems.[46] Emerging technologies will ultimately translate in increased total billing as a result of increased time dedicated to treatment planning,[47] longer operating times and the necessity of radiation therapy or planning equipment acquisitions, among other factors.[48]

The additional cost factor for proton therapy over that for intensity-modulated photons is now 2.4 to 3.[49] It is reasonable to assume that the expense of proton therapy per patient will decrease as more facilities are built and greater numbers of patients treated. It must be stressed that these direct costs do not account for other aspects of treatment, such as patient satisfaction or quality of care. Although not formally studied, it is reasonable to hypothesise that delivering PBT for paediatric cancer patients could translate in less late radiation-induced toxicity, thus improving the overall quality of care for these patients.

Decreasing the acute side effects of radiotherapy will also surely promote the physical wellbeing and early return to occupational/social activities during treatment in children and adults alike. The Karolinska Institute group has recently published two cost-effectiveness analyses of proton radiation. This group used a cohort-simulation mathematical model comparing two hypothetical cohorts of children with medulloblastoma receiving either PBT or conventional irradiation.

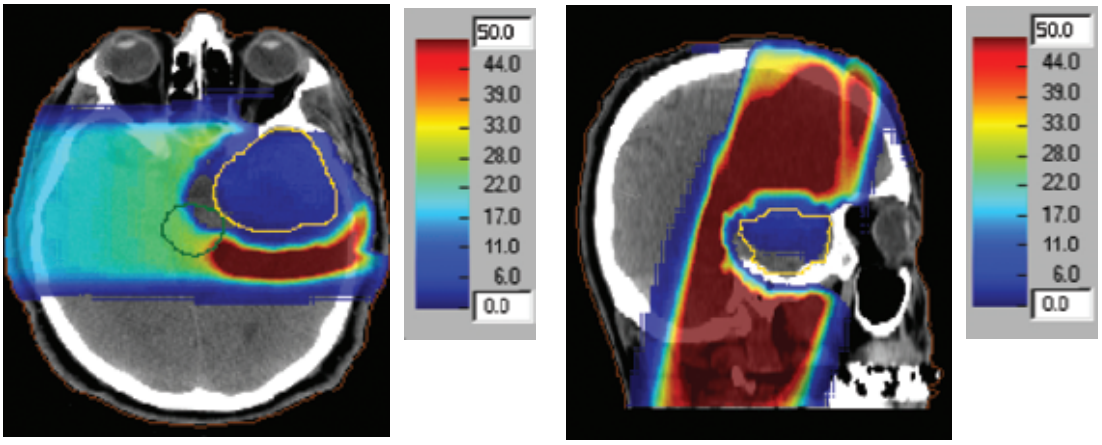
The Markov model simulated the course of events in individual patients from diagnosis until death or age 100 years. Individuals were modelled in differential health states, each associated with a certain cost and utility. Proton therapy seemed to be associated with €23,600 in cost savings and a 0.68 additional quality-adjusted life-year per patient.[50] The same cohort simulation model was used for breast cancer patients.[51] The costs and quality adjusted-life years gained were estimated to be €67,000 for PBT. Base-case simulation suggested that a 2.4% and 13% decrease of fatal cardiac disease and pneumonitis, respectively, should be observed with protons compared with conventional irradiation.

This data suggests that PBT can be cost-effective and cost-saving for various cancers, when compared to conventional radiotherapy. Recent data from Boston has suggested that accelerated partial breast irradiation (APBI) using protons may actually be less expensive than the invasive technique of APBI.[52]

The costs of any therapeutic intervention should be put into a global and wider perspective of the general expenditures of health disorders in a given society. Although cancer is a very frequent disease, occurring in approximately half of the individuals, it only consumes roughly 5% of the global healthcare costs, which is clearly inferior to the amounts of money consumed by chronic welfare illnesses, such as cardiovascular diseases or psycho-mental disorders.[53]

The percentage of radiotherapy billing relative to the cancer-related healthcare costs is marginal. It is estimated that radiotherapy only consumes 5.6% of the overall costs in oncology in Sweden.[54] The 1990 calculations for the European Community reported an average cost per RT of about €3,000, much cheaper that the estimated costs of surgery (€7,000) or chemotherapy (€10,000).[55] If we relate these figures to the demonstrated efficacy of radiotherapy, it can be reasonably concluded that this treatment modality is an inexpensive and cost-effective cancer treatment.

Figure 3: Differential Dose Distribution (X-rays minus protons) in an Axial (A) and Sagital (B) Plane Through the Center of the Planned Target Volume



A B

The colourwash contours are represented by different colours (corresponding values are displayed on the right border of each figure). Colourwash isodoses are in differential (X-rays minus protons) percentage of the dose delivered with X-rays and protons, respectively. Prescribed dose 54 Gy (X-rays) and 54 CGE (protons).

Conclusion

This review has focused on the main advantage of protons over conventional RT, namely, the absence of exit dose, which offers the possibility for highly conformal dose distributions, whilst simultaneously irradiating less normal tissue. When compared with photon RT, protons do not show a major radiobiological benefit, having a RBE of 1.1. The cost of PBT per patient is expected to decrease as more facilities are built and greater numbers of patients are treated. ■

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