

## The actual Interest in Radiotherapy for the Utilization of Proton Beam, Highlighting Physics Basis, Technology and Common Clinical Indications

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### ABSTRACT

Managing expensive technology is a debated issue in modern radiation oncology. Proton beam therapy (PBT) represents, considering its cost and its foreseen benefits, a typical case of discussion waiting for more robust results demonstrating the presumable clinical gains against the available radiation therapy (XRT) treatment alternatives based on the use of photons. The treatment with particles utilizes many different beams (neutrons, protons, pions, or helium, neon, argon, and carbon ions) that represent a distinct entity respect conventional XRT which uses photons. PBT is the most common form of heavy-particle radiation therapy used so far; it is not a new invention, being its clinical use proposed in a seminal article by R. Wilson in 1946<sup>[1]</sup> and the first patients treated in 1954 at the Lawrence Berkeley National Laboratory in California<sup>[2]</sup>. Since cyclotron or synchrotron, used to accelerate protons to therapeutic energies, were used primarily for research in particle or nuclear physics, the initial clinical activity in proton therapy was carried out in research facilities and the use of protons in clinical practice has grown slowly for several years in non-clinical setting. More than fifty years later, after a long period of seminal work in a limited number of Institutions, PBT has gained public attention in recent years because of the rapidly increasing number of centers around the world, regardless of their high cost. Hospital-based proton beam facilities have been in operation since 1990 after the opening of the first dedicated clinical center at Loma Linda Medical

University Center in California - US. Since that years, commercial entities began to build cyclotrons and synchrotrons for clinical purposes. Over the last 10 years, PBT has gathered more interest in the scientific community and more media and patient attention and is now flourishing in the US and abroad. As of December, 2015, 57 proton therapy centers are in operation worldwide, others are under construction and many more in a planning phase<sup>[3]</sup>. Most patients who have been treated with heavy-particle therapy were treated with protons: PTCOG (Particle Therapy Co-Operative Group) reports that between 1954 and 2014, 137 000 patients globally received part or all of their radiation therapy with particles, and in particular 86% of them with protons<sup>[4]</sup>. The generation of these particles and the building of dedicated centers, however, requires large investments and operational costs and big infrastructure. Only relatively few studies have demonstrated the effectiveness of proton therapy and the effects are surrounded with uncertainty<sup>[5]</sup> being the cost-effectiveness still the core of the controversy around the use of PBT.

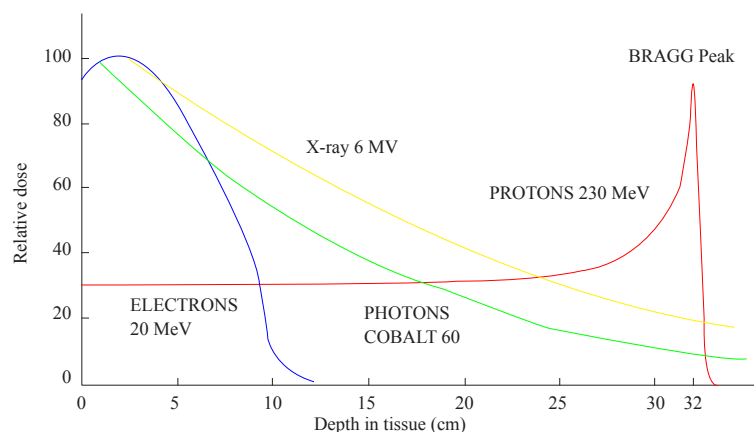
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**Key words:** Proton beam therapy; Particles

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### PHYSICAL PROPERTIES OF PROTON BEAM

Protons have a low linear energy transfer (LET) similar to photons and electrons with similar radiobiologic properties and interactions with tumor and normal tissues facilitating the translation into PBT of dose and fractionation knowledge generated in the field of conventional XRT. The interest in the use of proton beams is due to their unique physical characteristics: protons pass through the



**Figure 1** Comparison of relative depth dose distributions of protons (red) versus other energies used in radiation therapy.

tissues with minimal dose deposition along the path until the end of their paths, where most of the beam energy is deposited as a peak (Bragg peak) (Figure 1) and beyond this point, the dose has a rapid fall-off. This behaviour is very different by that of photons which travel through normal tissues to and beyond the target (tumor) depositing their dose close to their entrance into the body, and thereafter with an exponential decrease with increasing depth. Proton therapy delivers radiation to tumors and their very close vicinity, decreasing integral radiation dose to normal tissues and potentially avoiding collateral damage. Protons also have a sharper beam penumbra<sup>[6]</sup>, which a rapid dose fall-off at the lateral edges at shallow and moderate depths. This form of dose deposition permits a dose distribution easily conformable to targets close to critical structures, preserving the exposition of normal tissues, reducing the integral dose and allowing possible dose escalation. In the end, PBT has the potential for improving tumor control and survival through dose escalation and also for reducing harm to normal organs through dose reduction.

Despite these physical benefits other factors need to be considered to fully evaluate the advantages of protons, in particular the influence by tissue heterogeneity being proton therapy very sensible to the different tissues densities<sup>[7]</sup>. Changes in the composition of tissues (position during daily treatment, organ movements, tumor volume and shape change *etc.*...) can result in a marked effect on target coverage and dose to surrounding organs. In order to reduce the impact of these variations, usually a margin of uncertainty is added to reduce potential tumor underdosing<sup>[8]</sup> so leading to the reduction of the advantage in tissue sparing.

From a radiobiological point of view, at the same level of physical radiation dose, protons are approximately 10% more effective than photons in killing cancer cells. A generic value of proton RBE (relative biological effectiveness) of 1.1 is generally applied for both cancer cells and health tissues cells even though several uncertainties depending on cell lines, dose, fractionation *etc.* could be taken into account<sup>[9]</sup>.

## CLINICAL APPLICATION OF PROTON BEAM

In principle, almost any tumor currently treated with photons can be treated also with protons. The physical characteristics of protons with their lower integral dose and steeper dose gradient in comparison with photons make this beam a desirable tool in many clinical scenarios. This superior dose distribution is well described and represents an incremental improvement in radiation therapy

dose delivery allowing the reduction of the dose of radiation administered to normal tissue uninvolved by tumour.

However, the clinical benefit of protons, either in improved survival or reduced toxicity compared to other treatments, has yet to be fully demonstrated with the exception of a few pediatric or rare adult cancers. Even though many clinical trials in proton therapy are currently ongoing, still lacks strong clinical evidence out of randomized clinical trials, despite its theoretical benefits. The most important controversy in the use of protons regards their cost-effectiveness: whether and when PBT is better than photon-based radiation therapy. Proton therapy is more expensive than conventional XRT and its critics argue that its costs could not be fully justified. Efforts are being made to generate more clinical evidence in support of PBT for other and more common cancers. A recent systematic review of the cost and cost-effectiveness studies of proton radiotherapy by Verma *et al*<sup>[10]</sup> reports that PBT can offer promising cost-effectiveness for pediatric brain tumors, well-selected breast cancers, loco-regionally advanced NSCLC, and high-risk head/neck cancers.

While the debate within radiation oncology community continues regarding the clinical benefits of this low-dose, tissue sparing technique, some ideas on the reported experience in the literature are provided on the following paragraphs.

### Pediatric tumors

PBT for pediatric patients may be particularly beneficial due to potential reduction of late toxicities. The susceptibility to radiation of normal tissues and organ growth and function in children with tumors can cause significant morbidity, functional disability, disturbance of growth, negative cosmetic outcomes and development of secondary malignancies<sup>[11-14]</sup>. The reduction of the volume of irradiated tissue with lower integral dose achieved with protons can improve the rate of late toxicities in patients with an usual long period of survival after irradiation. These considerations make protons of particular interest in the treatment of pediatric cancers and some preliminary reports seem to confirm their capacity to reduce the risk also of the development of second malignancy<sup>[15,16]</sup>.

Dosimetric studies on tumors disseminating throughout the neuroaxis such as medulloblastoma which are treated with cranio-spinal irradiation (CSI) show the substantial reduction in dose to normal tissues with proton CSI when compared with photon CSI<sup>[17,18]</sup>. Moreover, some studies indicate a clearly reduced risk of radioinduced second tumors in patients undergoing proton CSI in comparison with conventional or intensity-modulated radiation therapy (IMRT) CSI<sup>[19]</sup> and reduced dose to several thoracic and abdominal normal tissues<sup>[20]</sup>. This can further have not only a

clinical but also an economic impact saving money<sup>[21]</sup>. Initial clinical experience report favorable local control and rates of acute radiation-induced toxicities equivalent with proton and photon radiation therapy for standard and high risk medulloblastoma<sup>[22,23]</sup>.

Based on the rarity of this disease, the compelling dosimetric data, and the initial clinical results, some have argued that randomized studies with photons are unlikely<sup>[24]</sup> and that PBT is the only ethically appropriate radiation treatment for this tumor<sup>[25]</sup>.

Many other pediatric malignancies are now treated with protons showing interesting results. Performing the comparison between PT treatment plans and the best available photon plans a clear benefit in different pediatric tumors has been evidenced<sup>[26]</sup>. Several reviews are available in the scientific literature on this subject<sup>[27]</sup>. Published reports on ependymoma, craniopharyngioma, retinoblastoma, and low-grade glioma suggest an improved acute and long-term toxicity profile<sup>[18,28-35]</sup>.

#### **Adult malignancies**

Almost every dosimetric study comparing protons with an equivalent photon treatment plan results in a better plan for particles. However, considering the higher cost associated with proton treatment, superior dosimetry alone is not considered sufficient to justify its choice in non-selected cases before having demonstrated measurable clinical advantages. The potential benefits have to be confirmed with more clinical data in an extended follow-up. In adults, the interest in using protons is not only focused in reducing the amount of irradiated normal tissues but also in escalating radiation dose in order to improve tumor control. Proton beam treatment has been most widely used in prostate cancer, particularly in US, and historically recommended for ocular melanoma and chordoma/chondrosarcoma but more recently the field of application has been expanded.

#### **Prostate Cancer**

It is well known that studies of dose-escalation have supported the use of higher radiation dose in order to increase disease control<sup>[36]</sup>. The higher the dose of radiation administered, the lower the risk of recurrence; moreover, lower doses to the rectum and bladder are associated with reduced risk of side effects. The argument in favor of treating prostate cancer with PBT has been partly financial for the generous reimbursement available in US and partly the hypothetical high patient throughput.

However, dosimetric studies don't support clearly the superiority of protons in safer administration of higher dose of radiation; moreover, the uncertainties susceptibility of protons to the organ movement could need larger margins potentially reducing the advantage in toxicity.

In two SEER database analyses comparing protons with photons, no difference in cancer recurrence or complications rates were found<sup>[37,38]</sup>. Even though the SEER data have some limitations possibly confounding these results, there is still little evidence to suggest a clinical benefit for patients with prostate cancer from PBT in comparison to advanced methods of photon radiation.

For these reasons the American Society for Therapeutic Radiology and Oncology (ASTRO) has suggested that proton treatment for prostate cancer would be delivered within the context of clinical trials or registries<sup>[39]</sup>.

#### **Uveal Melanoma**

Uveal melanoma is the most common primary intraocular malignancy in adults and external beam therapy with protons is a very well established and effective treatment option for its treatment being

PBT widely adopted for years in the treatment of this tumor<sup>[40,41]</sup>. Excellent results have been reported with consistently high local control rate (usually > 95% at 5 years) and high eye preservation rate (mostly > 90%). A recent meta-analysis<sup>[42]</sup> compared protons with brachytherapy, the most frequently conservative approach utilized in clinic. PBT is able to reduce the rate of local recurrence and has a number of advantages over radioactive plaques, including easier localization requiring no surgery, no hospital stay, ability to treat larger tumor sizes and tumors surrounding the optic nerve, and lastly avoiding the radiation exposure of medical staff.

#### **Chordoma and Chondrosarcoma**

Schulz-Ertner and Tsujii<sup>[40]</sup> have reviewed the historical results with particle therapy in these tumors. Although excellent local control have been achieved, it must be highlighted that the evidence consists largely in single-institution series and may reflect some case selection bias (even though usually negative). Even though the use of particle therapy in this disease is widely accepted as the gold standard, on a relatively thin evidence base, PBT has established itself as the standard of care for these rare malignancies both in skull base and in the spine<sup>[41-47]</sup>. Also pediatric chordomas can be treated effectively with protons<sup>[48]</sup>.

#### **Breast Cancer**

Several dosimetric studies comparing proton with photon plans revealed substantial reduction in lung, heart, and contralateral breast doses<sup>[49-51]</sup>. Proton therapy has been proposed after mastectomy<sup>[52]</sup>, in patients with bilateral implants<sup>[53]</sup>, and as accelerated partial breast irradiation (PBI)<sup>[54-57]</sup>.

It seems unlikely that PBT could be widely used in breast cancer and it is predictable that it will find selective use in specific clinical scenarios in which the patient's anatomy poses cardiac or pulmonary risks with the use of conventional XRT. PBT can be cost effective in appropriate risk groups of women, i.e., with left-sided breast cancer and high-risk factors for cardiac disease<sup>[58,59]</sup>, and/or in young women with left-sided breast cancer, and in women with long life expectancy.

The use as a form of accelerated PBI is debated with the use of passive scattering technique for the poor resulting cosmesis<sup>[60]</sup> but the use of multiple fields could overcome these results<sup>[61]</sup>.

#### **Lung Cancer**

The use of PBT in patients with non-small-cell lung cancer (NSCLC) has theoretical advantages in terms of sparing thoracic organs at risk and at the same time maintaining adequate target coverage. A recent meta-analysis revealed both statistically and clinically significant decrease in lung and heart dose comparing proton beam plans with photon plans<sup>[62]</sup>. The utility of protons in the treatment of locally advanced as well as early-stage NSCLC has been studied and reviewed<sup>[63,64]</sup>. Protons may offer an opportunity for safe dose escalation also in conjunction with chemotherapy<sup>[65]</sup>. For medically inoperable early-stage NSCLC, a recent meta-analysis compared particle beam therapy with stereotactic body radiation therapy (SBRT) and found no significant differences in survival<sup>[66]</sup> even though the ability of PBT to achieve adequate target coverage with only two to three beams may be advantageous in settings of poor lung function or prior chest irradiation<sup>[67]</sup>. At the moment, realizing the potential benefits of PBT in patients with lung cancer is still a technical challenge, mainly because of problems with delivering protons to moving targets that are surrounded by tissues with large inhomogeneity. PBT for lung cancer is still in its early stages of

clinical testing although offering interesting results<sup>[68-70]</sup>, particularly with regard to the development of appropriate dose algorithms, intensity-modulated proton therapy (IMPT) optimization, motion management, volumetric image guidance, and adaptive planning techniques<sup>[63]</sup>.

### Brain Tumors

The benefits of proton therapy for several brain tumors such as meningioma, low-grade glioma, craniopharyngioma, pituitary adenoma, ependymoma, in adult and pediatric patients, are well documented<sup>[71]</sup>. These cancers are often close to critical structures and surgery is therefore incomplete. Postoperative proton therapy as adjuvant therapy reduces local recurrence and complications compared with photon radiation therapy.

Current investigations are using PBT in the management of low-grade and favorable high-grade gliomas in the hope of reducing radiation-associated adverse effects in patients in a young age and/or achieving at least several years of survival.

In meningiomas the main goal of therapy is also not to dose escalate but to minimize the unwanted cerebral adverse effects of radiation and to minimize decrement of the patient's quality of life. Several series have suggested that proton beam may be a step forward in this regard<sup>[72-75]</sup>. Other benign tumors of the skull base have been treated successfully with protons such as acoustic neuroma or pituitary adenoma<sup>[76-78]</sup>.

### Head and Neck Cancers

Multiple comparative planning studies have shown that the dose distribution attainable with proton therapy appears superior to those possible with photon radiation. The value of protons for the most complex head and neck sites (nasopharynx and paranasal sinuses) resides in the ability to limit the dose to optic structures and brainstem and secondarily the mandible and salivary glands and PBT has been used on a clinical trial basis for the treatment of salivary tumors, nasopharyngeal carcinoma, oropharynx, sinonasal, and paranasal sinus malignancies<sup>[79-83]</sup>.

In these tumors PBT can offer the opportunity of dose escalation for cancers where loco-regional control is currently limited by an inability to adequately deliver therapeutic doses without excessive risk of toxicity or minimizing exposure of normal tissues in order to reduce toxicity for patients with possible long-term control with currently-prescribed doses, but at the cost of potential significant toxicity<sup>[81]</sup>.

However, it is to note that in the head and neck area tissue inhomogeneity is frequent (air cavities more or less filled with fluid, bones...) posing considerable challenge for proton physicists in performing robust treatment planning.

### GI Malignancies

The role of heavy-particle therapy is well established in the treatment of hepatocellular carcinoma<sup>[84,85]</sup>, with promising local control and toxicity profile with the ability to spare more liver with integral dose reduction. This treatment modality should be particularly suitable for patients with Child-Pugh class B<sup>[86]</sup>. The experience is however limited to a few institutional series, usually in Japanese centers, and additional research is greatly needed in this field. Another interesting malignancy treatable with protons is pancreatic cancer since the pancreas is surrounded by exquisitely radiosensitive normal tissues, such as the duodenum, stomach, jejunum, liver, and kidneys. Protons can represent a superior modality for radiation delivery to patients with unresectable

tumors and those with resectable and marginally resectable tumors receiving postoperative radiotherapy<sup>[87]</sup>. Radiation therapy is a critical component of locoregional control in other gastrointestinal tumors and protons can represent a particular challenge with the aim to reduce toxicity concerns<sup>[88]</sup>.

### Hodgkin's lymphoma

Hodgkin lymphoma is a highly curable hematogenous malignancy that affects primarily children and young adults. Consolidation radiotherapy is used after chemotherapy for the treatment of initially involved lymph-nodes. Survivors can have an excessive amount of secondary tumors. Comparative studies of protons beam vs photons show the better distribution of proton in these patients with a reduced integral dose predicting a considerable reduced risk of radiation-induced cancers making of PBT a very attractive option for this patient population<sup>[89,90]</sup>.

### Re-irradiation

The possibility to re-irradiate a recurrent tumour is always limited by the dose of previous radiation, normal tissue tolerance, surrounding critical organs, and time elapsed since the first treatment. The possible adverse effects are related to the involved and surrounding normal tissues and this often heavily restrict the deliverable dose and potential efficacy of re-irradiation. All patients in need of re-irradiation can potentially benefit from proton treatments considering the favourable physical properties of the proton beam. Even though no formal trials have been carried out comparing photons and protons in this field, it is highly recommended to consider protons and possibly compare the best photon plan when a chance of re-irradiation is considered for a patient<sup>[91-94]</sup>.

## FUTURE DIRECTIONS

Although scientific publications confirming the clinical benefits of PBT are relatively scarce, it should be considered the context of technological development in radiation oncology. Historically, any advancement in radiation oncology has been adopted mostly on the basis of physical and dosimetric principles, rather than clinical evidence based on randomized clinical trials. Most of the clinical experience with PBT to date comes from the use of passively scattered beam technology the traditional and widespread delivery technique used in proton therapy. The introduction of pencil-beam scanning technology, which allows for IMPT<sup>[95]</sup>, has demonstrated to be able to further improve dose distribution and is now being increasingly used in clinical activity. The introduction of IMPT might be expected to increase again the gap between photons and protons that the development of recent technical advancements in highly conformal XRT had bridged in the last years. Another possible technical advancement in performing proton therapy is the ability to see the beam track in tissues using a positron emission tomography (PET) scanner immediately after treatment and even quantitate the dose delivered offering an unique opportunity of *in vivo* dosimetry and real-time quality assurance.

Not only delivery techniques should improve but also the theoretical knowledge on biology of particles developing deeper scientific information on the radiobiological effectiveness of protons. Data emerging from recent studies suggest that, for several end points of clinical relevance, the biological response is differentially modulated by protons compared to photons<sup>[96]</sup>. In fact, the exact value of proton's relative biological effectiveness (RBE) *in vitro* and *in vivo*

can vary depending on cell lines, different tissues, endpoint, dose, and fraction sizes<sup>[97]</sup>. The better knowledge and deepening of these data could help to better select tumors to be treated and better predict the behavior of the treatment.

Regarding the application in clinic, even though the advantage of PBT could be intuitive in pediatric tumors where randomized trials could be considered inappropriate or unethical, more prospective clinical studies with collection of clinical data should be performed. Clinical research opportunities are wide in order to determine which patients will gain the most benefit from proton beam considering also the economic implications of using PBT for common sites<sup>[98]</sup>. The expected decrease of side effects and improvement of quality of life should be confirmed in more studies even though some reports are already confirming this hypothesis<sup>[99-101]</sup>. More developments are waited also in the administration of concurrent radiation-sensitizing chemotherapy where improved hematologic tolerance may allow dose intensification<sup>[102]</sup> and of biologically targeted agents.

However, at the moment the high cost of building and running a proton therapy facility remains the most contentious issue in the clinical application of PBT. In order to further spread proton therapy in clinics, the development of smaller and more affordable proton beam units reducing the costs should be the best way to diffuse this innovative radiation treatment.

In conclusion, PBT is a new radiation modality for treating cancer patients that at present is costly and poorly available. It is being increasingly adopted in the oncological community and clinical evidences of efficacy are accumulating. New technical development are awaited in order to make this technology less expensive and more accessible.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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