



Proton Therapy: The Future of Radiation Oncology or an Optimist's Reverie? :

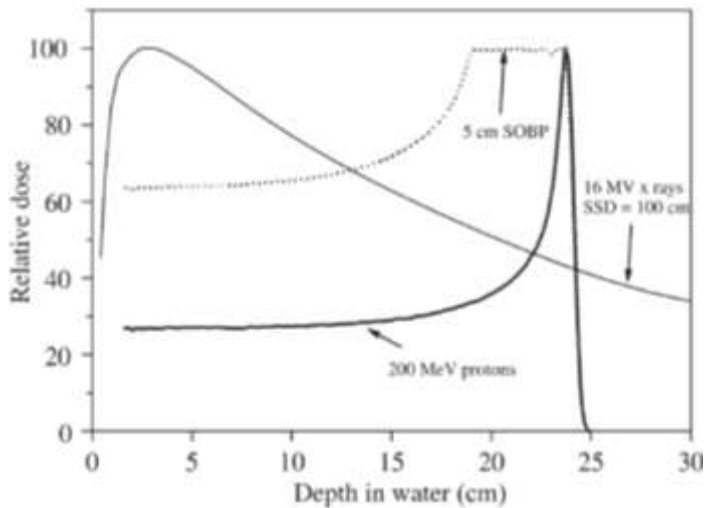
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Introduction:

In 1896, the first ever attempt to cure a human stomach cancer with X-ray therapy by Victor Despeignes lead the foundation stone for modern external beam radiation techniques. After many decades, modern telecobalt and medical linear accelerators were available for clinical application in 1950 s. The initial hope and expectations were great and fulfilled with time as science and technology advanced. Soon it was understood that high exit dose was detrimental, integral dose becomes higher with increased number of fields and surrounding normal tissue toxicity can be limiting factor in delivering curable dose. These factors potentially reduced the therapeutic ratio with increased risk of second malignancy. Chance to overcome these drawbacks came into sight with introduction of particle therapy. The generic term "Hadron therapy" is almost comparable to particle therapy which includes proton, carbon ion and other light ions such as helium, oxygen and neon. Neutron has a limited clinical advantage and role. Of these, proton is the most prominent at present and gaining momentum towards increasing clinical success, though not more than 1% of all patients are being treated with protons worldwide.

Basic Physics for Proton therapy:

Proton is the nucleus of hydrogen atom having unit positive charge. Medical proton facilities produce protons either from cyclotron or synchrotron or synchrocyclotrons. The basic mode of interaction with particle is by Coulomb force either with atomic electrons or nucleus. The beauty and interest of proton lies on a special characteristic known as Bragg peak. As the charged proton travels a path, it experiences a gradual increment in rate of energy loss which becomes maximum just before the proton stops. The deposited energy thus becomes maximum at the end of the path giving rise to a peak in the dose distribution curve, known as Bragg Peak. This entire phenomenon occurs within a very small region. Practically this translates into negligible dose deposition beyond the tumor region. Overall, the integral dose becomes less compared to photons. Whereas the Bragg peak for a monoenergetic proton is very narrow, spread out Bragg peak (SOBP) creates clinically meaningful proton beam thickness. Passive Scatter Proton Beam or Pencil Beam Scanning (PBS) technologies are available for three dimensional or Intensity Modulated proton Therapy (IMPT).



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Radiobiological advantage:

The advantage of proton beam lies not only on its physical property, but also its radiobiological characteristics. With increasing

energy deposition towards the end of the tract, linear energy transfer (LET) and eventually relative biologic effectiveness (RBE) of proton increases. Theoretically this implies a changing RBE for proton. However, conventionally RBE of proton is considered as 1.1 in comparison with photon. This is indeed a common language to ease out difficulties associated with changing RBE with depth.

Clinical implications:

The vast majority of patients and studies using proton are non-randomized, single institutional series and outnumbered by photon series. With increase interest, gradually decreasing cost and increased availability of insurance reimbursements, there is a steady rise in number of patients and clinical studies with proton.

The notable use of proton beam therapy (PBT) has been seen in pediatric malignancies. With increase in survival rate, survivorship and second malignancy are definitely significant issues in these patients. The lower integral dose achieved with proton is beneficial to reduce chance of second malignancies in this group.² Medulloblastoma, ependymoma, craniopharyngioma, and rhabdomyosarcoma are perhaps most common pediatric tumors being managed with PBT. There is reduced chance of cognitive impairment, endocrine abnormality and second malignancy.

If we see adult tumors, most increase with PBT has taken place for tumors in complex locations with sensitive critical surrounding organ at risk (OAR) s. Most important may be base of skull, sinonasal malignancy, head and neck tumors, brain tumors and of course, reirradiation. Initial results are definitely promising in terms of dosimetric advantage and reduced toxicity. Increased interest has also been noticed for abdominal tumors including hepatocellular carcinoma (HCC), lung cancer and breast cancer. In a recent consensus statement by the Particle Therapy Co-Operative Group (PTCOG), indications, suitability and cost effectiveness of different proton therapies (PSPT or IMPT) for lung cancer (NSCLC) have been nicely elaborated. Centrally located Stage I tumor, Stage II or III tumors with or without hilar lymphadenopathy are suitable for PBT, provided stringent QA is maintained.³

In a prospective study from Massachusetts General Hospital (MGH), the feasibility, acceptable toxicity profile and quality of life (QOL) with PBT has been documented for Grade II gliomas as well.⁴

Similar interesting and inspiring results are obtained with other disease sites as mentioned

above. A detailed description though warranted, is beyond the scope of this article.

Notable works with PBT have been done at United States, Japan and Germany.

All glittering about proton?

Definitely no. Like all other technologies proton therapy has its own shortcomings. **The prohibitively high cost of establishing proton therapy facility is perhaps the single most important factor. A single room facility costs approximately 30 million USD and facilities with three to four rooms cost 100 million USD!! For resource limited countries, this may be a luxury.** The cost effectiveness is limited within childhood brain tumors, selected breast cancers, locoregional advanced NSCLC, and high-risk head/neck cancers.⁵

Even with so much interest, only sixty seven centres have current working facilities whereas another forty centres are under construction.⁶

Talking technically, significant uncertainties and limitations can jeopardise outcome if not taken care of properly. The large penumbra due to typical proton scatter can give rise to significant overdosing in normal surrounding tissues and compromise tumor dose. Again, volumetric imaging facility during treatment is rare with proton therapy. This was supposed to be more important and necessary for highly precise treatment with proton. Lack of routine integrated respiratory gating technology is another shortcoming. It may be remembered that both these technologies are widely used with photon beam therapy making the treatment delivery more precise and reproducible.

Coupled with this, there are biological uncertainties. The RBE may be very low at the entrance and very high at the end of the beam compared to the accepted uniform value of 1.1 as used for practical purpose.

Even if we look into studies comparing proton and photon, it is not a win-win situation for proton always. Proton therapy APBI produced significantly more toxicity in patients compared with photon in a series of patients from MGH.⁷

Conclusion:

Time has not yet come where we can conclusively say or expect that proton therapy will ever be able to replace photon therapy. Though the initial studies are promising and path breaking, lack of large randomized trials and long term follow up are two potential caveats. The major achievements are in pediatric tumor and reirradiation as of now. With many ongoing large RCTs and technological advances, it may be possible to have more insight for other diseases and overcome the current technological limitations. That will be a new anticancer weapon in the armamentarium of radiation oncology albeit a costly one.

Further reading:

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