LATEST DEVELOPMENTS IN PROTON THERAPY

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Abstract

The intent of this review is to give insight in the present status and on the prospective future of proton therapy. The major point of reference is conventional therapy with photons. Traditional radiotherapy is showing nowadays a very rapid progress using advanced dynamic beam delivery techniques and sophisticated computer algorithms for treatment planning. The new fashionable concepts in medical physics are "Inverse planning" and "Intensity modulated therapy". Proton therapy compared to photon therapy has the advantage of the localisation of dose in depth, but implies higher costs for the accelerator and beam lines. Within the field of proton therapy the competition is between the established traditional beam delivery techniques using passive scattering and the new methods based on magnetic beam scanning. The innovative developments are compact gantries dedicated to beam scanning capable of delivering "intensity modulated proton therapy". Despite many uncertainties, proton therapy is steadily gaining in socio-economical importance. About 10 hospital-based proton or heavy ion therapy facilities are now under construction or already available in the U.S.A. and Japan. Europe is waiting.

1 INTRODUCTION

For about 2/3 of cancer patients the disease is still well localized within a specific region of the body at the time of diagnosis. For these patients the chances of cure using a traditional local therapy are reasonably good. Based on the experience of the last decades one can anticipate that surgery and radiation therapy will continue to play a major role in the control of primary solid tumours also in the future. Although a breakthrough from genetic technologies (mainly against the systemic spread of the disease) is possible, it is equally important to continue to improve the established local treatments. Any additional progress in radiation therapy can improve the number and the quality of life of cancer survivors. Improvements are expected from advanced treatment techniques (intensity modulated radiation therapy) and/or by using unusual types of radiation sources (protons and ions). The use of protons is presently the most promising alternative to conventional therapy with photons.

2 PROTON THERAPY: MOTIVATION

Protons have a well-defined penetration range in biological tissue and they deposit the maximum of their energy deep in the body in the region where they stop. This gives rise to the so-called *Bragg peak.* This feature has to be compared with the exponential fall-off of the dose with depth of clinical photons. We refer to figure 1 of reference 1 for the graphical comparison of the depth dose distributions of proton and photon beams [1].

With a single proton beam it is possible to localise the dose not only in the lateral direction but also as a function of the depth in the patient. Compared to photons one can achieve with protons a general reduction of the integral dose outside of the target volume by a factor of 2 or 3 (this is a clinically significant dose sparing for the surrounding healthy tissues). Protons are expected to produce superior results mainly for the treatment of large tumours with complex shape.

The disadvantage of proton therapy is on the other hand the large size and costs of the accelerator and of the beam lines needed for the transport of the beam.

3 PHOTON THERAPY: THE REFERENCE

The use of sophisticated beam delivery techniques, the support from computer technology and the information gained with modern diagnostic techniques (CT, MRI and PET) have been at the origin of the progress achieved in general radiotherapy (RT) in the last decades. The obvious goal of RT is to shape the geometrical distribution of the dose such that it conforms exactly to the three-dimensional shape of the target volume. The therapy is then named *3d-conformal therapy*. The dynamic use of multi-leaf collimators offers here new technical possibilities for achieving this goal. The most interesting is to apply the dose with a non-uniform distribution of the photon fluence for each of several converging dose fields. The superposition of intentionally non-homogeneously shaped dose distributions can then result in a homogeneous dose distribution of superior quality (with better conformity, especially for target volumes with concavities). This method is called *intensity-modulated therapy (IMRT)*[2]. A similar approach is known as *tomotherapy* [3].

Fig. 1 shows an IMRT example for the dose distribution of a tumour close to the base of the skull. The calculation has been done with the treatment-planning package of PSI (courtesy of T. Lomax). The dose results from the superposition of 9 inhomogeneous photon fields. The availability of a large amount of degrees of freedom and the strength of the mathematical methods make it possible to produce excellent dose distributions.

Many professionals working in the hospitals are convinced that thanks to the recent technological progresses in beam delivery, photons will be soon competitive enough to beat proton therapy in practice.

Will IMRT really make proton therapy obsolete? This is probably the most crucial question for all centres now investigating the use of proton therapy.

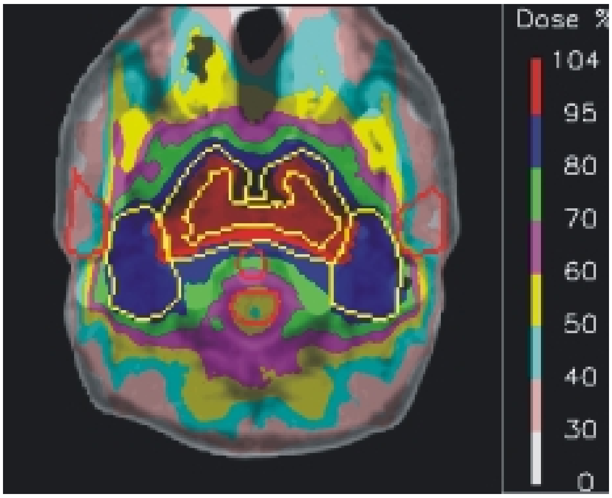

Figure 1. Example of intensity modulated therapy with photons. The dose distribution (shown with color shading in percentage of the dose) is obtained through the superposition of 9 convergent photon fields (courtesy of T.Lomax PSI). The yellow contours represent the targets (the visible tumor, the treatment volume with involved linph nodes). The red lines represent organs at risk to spare (salivary glands, brain stem).

4 PROTON THERAPY: BEAM DELIVERY

The major competition within the field of proton therapy regards the choice of the beam delivery technique [1][4].

4.1 The passive scattering technique

This technique is the traditional beam delivery method. The proton beam is scattered by material in the beam ahead of the patient in such a way as to produce a homogeneous flux of protons in the solid angle used for the irradiation. The dose is then shaped in the lateral direction using collimators. A fast spinning wheel of variable thickness (range shifter wheel) introduces a variable amount of absorbing material in the beam as a function of time. The resulting modulation of the proton range can be chosen such as to produce a homogeneous region of the dose in depth (the spread-out Bragg peak, SOBP). An individual compensator bolus can be optionally added to this set-up to shift the distal edge of the dose field to conform more closely to the deepest side of the target volume. All the necessary hardware must be adapted and in part created individually for each single field. This makes the beam delivery with multiple dose fields on a scattering gantry rather laborious. This method produces by default a homogeneous dose field with a fixed SOBP thickness in depth (*fixed range modulation*). The implementation of IMRT on a beam delivery system with passive scattering is a rather difficult and unpractical issue.

4.2 Beam scanning

In this case the proton pencil beam coming from the accelerator is delivered directly into the patient. Individual pencil beams are sequentially deposited under computer control. A high conformity is achieved by changing the dosage and the position of each pencil beam individually under computer control. In the lateral direction the beam is usually scanned through magnetic deflection of the beam ahead of the patient. The modulation in depth is achieved by changing dynamically the energy of the protons. The range can be adjusted as a function of the beam position in both transverse directions *(variable range modulation*).

The major advantages of the spot scanning technique compared to passive scattering are the additional dose sparing due to the variable modulation of the range, the dose delivery without patient specific hardware and the capability to deliver *intensity modulated therapy* (without additional modifications). The major disadvantage is the higher sensitivity of this method to *organ motion during scanning*. For this reason the treatments at PSI are confined up to now only to tumours in the head and in the low pelvis.

At present the proton facility of PSI is the only one capable of delivering proton therapy using a dynamic beam scanning technique [5]. 45 patients have been treated with this new beam delivery method. The prototype is starting now to work satisfactorily.

4.3 IMRT with protons: an example

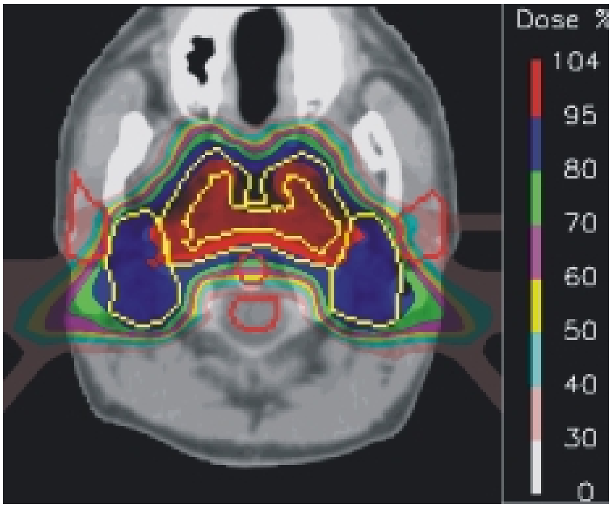

Figure 2. . Example of intensity modulated therapy with protons. The dose distribution is obtained this time with only 4 fields (courtesy of T.Lomax PSI). The advantage compared to photons is the reduction of the dose outside the target volume.

Fig. 2 shows as an example the potential use of the spot scanning technique for delivering *intensity-modulated therapy with protons (IMPT)* (courtesy of T. Lomax of PSI) [6]. With only 4 modulated fields one can deliver a highly conformal dose to the primary target and a reduced dose to the affected lymph nodes (the secondary target) with a maximal sparing of the organs at risk (brain stem and parotid glands). All this can be designed and delivered just under computer control without the need of patient specific hardware. With protons we can avoid the "dose bath" outside the target volume typical of photon-IMRT.

We now believe at PSI that in order to remain competitive with the most advanced photon techniques, beam delivery by active beam scanning will be a necessity for any future proton therapy facility. This is confirmed by the fact that the existing hospital based facilities (Loma Linda, Boston and Tsukuba) are now planning to implement beam scanning in addition to passive scattering in the near future.

5 PROTON GANTRIES

Another term of characterisation of proton therapy facilities regards the design of the proton gantries.

Loma Linda University is the place in the world where the first hospital-based facility with proton gantries was realised [7]. The facility started operation in 1991. The second gantry of the world is the compact gantry of PSI. Patient treatments started there in 1997. A third gantry was realised recently at Kashiwa (Japan) (the start of patient treatments was last year). An almost identical gantry design has been realised and is now ready to go into operation in Boston (U.S.A) this year. Another new gantry type is presently being assembled in Tsukuba (Japan).

The gantries dedicated to passive scattering (either of the "Cork-screw" type like the gantry of Loma Linda University or of the "barrel" type like at the Massachusetts Hospital in Boston) are necessarily characterised by a very large diameter of the rotating structure of the order of 11-12 m. This is the consequence of the need of a long throw to spread the beam after bending the beam towards the patient.

The compact eccentric gantry of PSI (fig. 3) is the only example of a gantry dedicated to beam scanning. The beam is scanned along orthogonal axes (Cartesian scanning). Part of the beam scanning is performed within the beam optics of the beam before bending the beam towards the patient. In this way no space is lost between bending magnet and patient. The eccentric mounting of the patient table reduces further the gantry diameter down to 4m, which is the most compact of all known designs. A more practical version of this design with the patient table mounted at the isocenter is now under study at PSI for future use in the hospitals (see section 8).

Figure 3. Picture of the treatment room of the PSI gantry.

6 PROTON ACCELERATORS

Another competition within the field of proton regards the choice of the type of accelerator used. The major rivalry is between cyclotrons and synchrotrons [8].

- Synchrotrons (example: LLUMC at Loma Linda)

The main advantage of the synchrotron solution is the variable choice of the beam energy extracted from the machine. The main disadvantage is the pulsed nature of the beam, which is not well suited for beam scanning. One can however overcome parts of the problem by providing a stable slow extraction of the beam.

- Cyclotrons (example: MGH Boston)

The advantage of the cyclotron is the high duty factor of the beam (DC beam), which is well suited for beam scanning, the high proton current and the inherent stability of the beam (including a possible precise control of the beam intensity at the ion source for active beam scanning). The main disadvantage is the fixed energy, which requires the use of a degrader followed by an analysing beam line. This implies a higher activation of the components in the initial region of the facility.

- Synchrocyclotrons (examples: Orsay, Uppsala)

Such machines are used only at old physic facilities. They have not been re-proposed for new facilities since they combine the disadvantages of cyclotron and synchrotron (fixed beam energy and pulsed beam).

- Linacs (Rome)

A proton Linac with a high pulse repetition rate of 400 Hz suitable for beam scanning (with adjustment of the beam intensity pulse by pulse) is under construction in Rome, Italy [9]. At the moment the stages for energies up to 7 MeV for isotope production and 65 MeV for eye treatments are being realised.

There have been also several other propositions:

- H-minus synchrotrons [10,11]

The advantage of this approach is expected from the easy extraction of the beam from the accelerator ring by foil stripping. The idea is to provide separate extraction on short beam lines feeding the protons into several treatment rooms arranged radially around the synchrotron ring. The accelerator is rather large (the magnetic field must be maintained low to avoid magnetic stripping of the negative ions).

- Separated sector cyclotrons [12]

By having a large separation between the sectors using superconducting magnets, one could provide variable beam energy extracted from different orbits. This would combine the advantages of a cyclotron (the duty factor) with the advantage of a variable energy machine.

- Super-conducting cyclotrons [13]

Possible advantages of superconducting cyclotrons are the reduction of the size, the lower power consumption and the better efficiency of extraction. High temperature superconducting cyclotrons have been also proposed [14].

- Fast cycling synchrotron [15]

The most recent proposition is coming from Brookhaven. They propose a fast cycling synchrotron with strong focusing and with 15 Hz repetition rate capable of beam delivery by scanning. The shaping of the dose in scanning mode should be achieved by controlling the intensity of the beam pulse by pulse (in addition to the usual beam delivery by scattering).

7 THE STATUS OF PROTON THERAPY

Loma Linda has now shown the capability of treating close to 1000 patients per year. Loma Linda has therefore shown for the first time the feasibility of proton therapy on a commercial ground.

A list of links to some of the charged particle therapy centers of the world can be found at our home page location [16]. For the latest update on the statistics of patients treated with charged particle beams we refer to “Particles”, the journal edited at the Harvard cyclotron on behalf of the charged particle therapy community [17]. At the same web address one can find the most recent list of the centers proposing new dedicated facilities for proton or ion therapy.

Close to 10 hospital-based proton or ion therapy facilities are approved for construction or already available in the U.S.A. and Japan. There are several propositions for dedicated facilities also in Europe but none seems to be able to start up at this time.

8 THE NEW PLANS AT PSI

The PSI gantry system is the only one in the world at present capable of delivering proton therapy with *range intensity modulated proton therapy* (RIMPT).

The PSI gantry system is still a prototype. Based on the practical experience of using the PSI gantry for actual patient treatments, we are now proposing some basic modifications. The goal is the design of a second-generation compact gantry dedicated to beam scanning for a commercial realisation in hospital-based facilities.

The planned improvements for the new PSI gantry are:

- A new gantry layout

We propose to build the next gantry with the patient table at the isocenter (fig.4). The gantry diameter will be somewhat larger than for the first PSI gantry (6 meter instead of 4 m), but still significantly smaller than with any other existing design. We will limit the gantry rotation to +,-90° from the vertical on one side (eventually 270°) and we will install the patient table in the gantry pit on the opposite side. This leaves enough space for a large fixed floor (with the only exception for the opening for the nozzle underneath the table when the beam is coming from below). The table shall be able to perform a continuous 180° rotation in the horizontal plane. The major goal here is to provide an easy access to the patient table at any time on the basis of a *fixed permanent floor*.

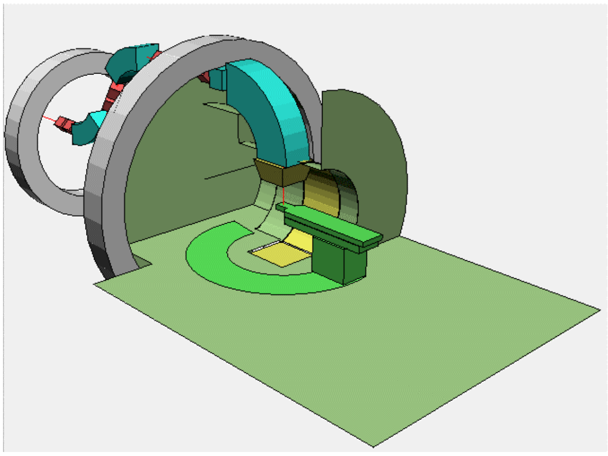

Figure 4: proposed layout for a new compact gantry dedicated to scanning. See text.

- A moving nozzle enclosure

For the next gantry we propose to move mechanically the nozzle shield during scanning, by exactly the same amount as undergone by the patient on the patient table. In this way the nozzle will not have any apparent motion with respect to the patient (this is the point of our present design which is often criticised). This will also provide a supporting frame for mounting individually shaped *collimators and compensators* in front of the patient (as possible *optional devices*). For very superficial tumours the use of collimators could improve the precision of the treatment (by providing a sharper lateral fall-off of the dose distribution). For deep-seated tumours scanning alone is expected to be more precise.

Another goal is to be able to simulate scattering on a small compact gantry by scanning a broad pencil beam on a very coarse grid. Through the reduction of the "granularity" of the scanned picture, one can afford to apply *multiple repainting* of the target, when this is needed for the treatment of moving targets in the thorax.

The aim of these developments is to provide more *compatibility* with the old established passive scattering method on a system dedicated solely to scanning, in order to make the total replacement of the old scattering technique easier to accept.

- Improved scanning methods

We plan also to include in the design other options for future developments. We shall first investigate the possibility for a *fast dynamic energy variation* in the beam line ahead of the gantry, by placing the range shifter ahead of the gantry (to be used as a fast degrader). A dynamic energy variation ahead of the gantry could make the quality of the spot scanning method less dependent of the patient distance from the nozzle. The effect to avoid is the blowing-up of the pencil beam due to multiple Coulomb scattering in the range shifter plates (propagating in the air gap before the patient).

For the new PSI project PROSCAN (the planned extension of the present facility) we plan to use a dedicated cyclotron. We shall study the utilisation of beam *intensity modulati*on from the accelerator (as a replacement for the kicker-magnet and eventually for a continuous magnetic scan motion).

Another possibility to be investigated is to use *a second faster lateral magnetic scanning* (scan transverse to the gap of the last 90° bending magnet of the gantry) in order to be able to perform multiply repeated repainting of the target volume.

All these ideas clearly underline our preference for the use of a cyclotron followed by a degrader. In our opinion a very *stable DC beam* with a *fast reliable intensity control* is one of the most important requirements for future improved scanning methods.

All the mentioned developments aim at the replacement of the scattering technique with a system dedicated solely to scanning. This in order to be able to use small compact gantries. We believe that in the long range, solutions offering both scanning and scattering on a large throw gantry are probably too expensive for competing with advanced IMRT photon techniques.

9 CONCLUSIONS

Radiotherapy represents an important instrument in the fight against cancer in a field in continuous evolution. In the field of conventional therapy we expect to be able to observe in the near future a significant progress using very advanced beam delivery techniques with photons (IMRT). Proton therapy has to follow with similar more advanced developments. The combination of the new technologies with the physical advantages of charged particles is expected to produce superior results compared to photons. This is why we expect that beam scanning will become soon a widely accepted beam delivery method for proton and ion beam therapy. This new strategy must be considered when designing accelerator and beam delivery systems for future planned dedicated facilities. In the near future the accelerator will not be considered any more a separated entity for the delivery of beam but it will be more and more directly involved with the task of delivering the dose safely, reliably and precisely to the patient.

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