Status of Proton Therapy: results and future trends

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Abstract

The number of centres investigating proton therapy in the world is steadily increasing. This review on the present status of proton therapy is addressed to physicists not working in the field. The presentation includes a brief summary of the established medical indications and of the state of the art of the application techniques used. The future trends are seen in the new technological developments, like the use of proton gantries, beam scanning techniques, improved patient handling and in the increasing precision of treatment. The availability of modern diagnostics tools like CT and MRI, accompanied by an extremely fast growth of computer power are expected to help charged particle therapy to become more and more attractive in the future.

1. INTRODUCTION

The general interest in proton therapy is slowly but steadily increasing in the world medical community. In this lecture we attempt to summarise the present situation of proton therapy and try to identify the future trends expected in this field. Section 2 is a general introduction to proton therapy with special emphasis on the medical motivation. In section 3 we describe the present status including the medical achievements and the state of the art of the techniques in use. The future trends are described in section 4.

2. PROTON THERAPY

2.1 The Goal of Proton Therapy

The main purpose of proton therapy is the use of proton beams for the treatment of localised tumours and for radiosurgery with the goal to improve radiation therapy. The expected improvements are of purely technological nature and are represented by the capability of the protons to produce superior dose distributions in the patient's body compared to photons.

As opposed to heavier ions, which by their enhanced high LET (linear energy transfer) produce remarkable differences in the radiation effects at the cellular level, we do not expect with protons any significant radiobiological differences compared to photon treatments.

2.2 The Need to improve Radiation Therapy

Here we want to emphasise the important role which radiotherapy nowadays plays in the fight against cancer. About one person out of three is confronted in his life with cancer and one out of five dies from this disease. The overall cure rate of cancer is currently about 45% [1]. Of these successes about half (22%) are due to surgery. The rest is more or less due to radiotherapy alone (12%) or to radiotherapy in combination with surgery (6%). All other modalities including chemotherapy (1-2%) contribute together only 5% to the cure rate. Radiation therapy is therefore the second efficient weapon available against cancer.

A criticism often advanced by biologists against radiation therapy is that this method is not biologically selective at the cellular level, a "hammer method". They clearly give preference to cell seeking substances like antibodies or new genetic technologies, which are perceived to fight cancer in a more "intelligent" way. This kind of research represents indeed the hope for a future breakthrough in the fight against cancer. The big question then is if these methods will make radiation therapy obsolete. There are justified doubts that a "penicillin-like" drug for cancer will appear in the foreseeable future [2]. A more realistic scenario is to assume that new cell seeking substances will be found in the near future which will be successful against the spread of single distant cancer cells (microscopic metastases). These drugs will however probably not be sufficiently effective to achieve the complete sterilisation of the primary tumour, especially in view of the difficult physiological problem of bringing the drugs to the centre of the tumour by perfusion. The task of stopping the growth of the primary tumour is likely to remain the prerogative of surgery and radiotherapy in the long term future.

About 17% of patients die because of failure in controlling the primary malignancy. These patients are expected to profit from an improved radiation therapy.

The general strategy in oncology today is to consider the different treatment modalities as complements to each other. In the eventuality of a breakthrough for the treatment of distant metastases using immunologic methods, all radiation treatments, which are applied now for palliation, could become curative. Therefore radiotherapy needs to evolve in the immediate future to a higher level of precision.

Technical improvements in radiation therapy are socially desirable and, due to the progress in diagnostics and computer power, are also becoming more feasible.

Among the different technological possibilities for improving radiation therapy the use of protons is one of the most promising.

2.3 Why Protons ?

Protons have the potential to bring significant improvements to radiation therapy by virtue of their excellent physical properties. The dose delivered by a proton beam is well localised in space, not only in the lateral direction, but also very precisely in depth, due to the presence of the characteristic **Bragg peak** (Figure 1).

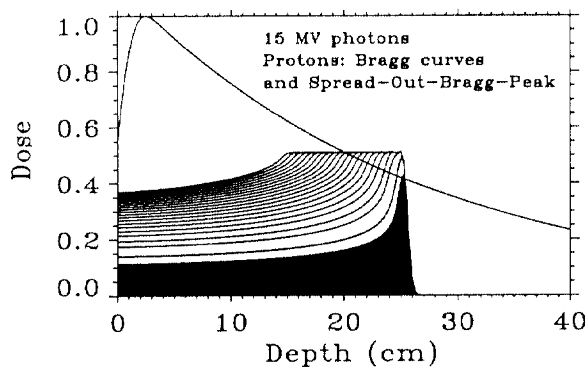

Figure 1. Depth dose comparison of protons and photons.

The presence of the Bragg peak has to be compared with the corresponding dose curve for photons, which exhibits an exponential fall-off and which is therefore not localised in depth.

The advantages of protons compared to photons can be summarised in the following way:

1) The dose beyond the Bragg peak is essentially zero. This is an advantage which can be exploited for the irradiation of tumours surrounded by sensitive structures, where stopping the beam in the tumour before reaching such tissues is of crucial importance.

2) Protons can bring a significant sparing of the integral dose deposited outside the target volume, provided that multiple fields can be applied on the patient using an isocentric gantry, following the strategy used for photons in the hospital. A factor of two to five less dose can be applied outside of the target volume compared to photons [3].

3) Protons are charged particles. As opposed to photons, they can be focused and deflected by the action of magnetic fields under computer control. The dose distribution of a proton pencil beam is well localised in all three dimensions with a dose hot spot at the Bragg peak position. This opens the perspective for a dynamic scanning of the proton pencil beam, with the goal of providing in a routine fashion a three-dimensional conformation of the therapeutic dose to the target volume.

The main disadvantage of proton therapy is given by the high magnetic rigidity of the beams used for therapy. The minimal bending radius which can be applied on a 270 MeV proton beam using conventional magnets operated below saturation limits is of the order of 1.3 m. This makes the size of the accelerator and of the beam transport system correspondingly large and expensive.

2.4 Can we afford Proton Therapy?

The answer is yes, provided that improved clinical results compared to photon treatments can be demonstrated in practice. Conservative estimates show that charged particles will cost about double conventional radiation therapy. This is still much cheaper than many other established modalities, for example chemotherapy. If proton therapy saves medical costs, for example from additional surgery, hospitalisation or drugs, it can be proven to be advantageous also from an economical stand point.

3. STATUS OF PROTON THERAPY

3.1 Proton Therapy world-wide. Medical Indications

About 12'000 patients have already been treated world-wide with protons [4]. The centres which have pioneered charged particle therapy in the past are Berkeley (U.S.A. 1954-1992*), Uppsala (Sweden 1957), Harvard (U.S.A. 1961), Dubna (Russia 1967), Moscow (Russia 1969), St. Petersburg (Russia 1975), Chiba (Japan 1979) and Tsukuba (Japan 1983) [5].

A significant part of these activities was dedicated to radiation neurosurgery. The goal here is to act with localised radiation on small targets in the brain using stereotactic techniques (sequential applications of many small beams converging on a point). The aimed end-point of the dose application is very similar as with surgery, for example the disactivation of the pituitary gland or the occlusion of arteriovenous malformations (AVM). The method is mainly indicated for inoperable lesions and has the advantage of being a non invasive technique.

A large majority of the tumour treatments have been applied to solid tumours in the eye bulb (mainly melanomas) using protons of low energy (around 70 MeV). This technique was developed in Harvard and Berkeley and was then introduced in Europe at PSI (Switzerland, 1984). The success of this application is well documented by its rapid spread to other centres in Europe, in Clatterbridge (Great Britain, 1989), Louvain-la-Neuve (Belgium, 1991), Nice and Orsay (France 1991) and overseas at Indiana University (U.S.A. 1993). The success of the eye treatments has been a big help for the spreading of high energy proton therapy to other sites in the body.

Recently head treatments with a high energy beam (200 MeV) have also been started at Cape Town (South Africa 1993) and at Orsay (France 1991).

The most cited indications for high energy (100-220 MeV) proton therapy are for tumours close to the base of the skull (chordomas and chondrosarcomas), tumours close the spinal chord and tumours in the abdomen (sarcomas and cervix carcinomas) surrounded by sensitive healthy structures. Also worth mentioning are the treatments of lesions in the liver pioneered by the group of Tsukuba using a respiration-gated treatment technique.

* Date of the first treatment and date of the last if treatments have been ceased.

Common to all older facilities was the use of protons delivered by an accelerator originally built for physics experiments and put out of operation at the end of the research period. Also common to the above mentioned facilities is the use of horizontal beam lines (without gantry). Many of them suffer from practical limitations in the available energy of the beam. Others had limited technical resources, like limited access to computer tomography or lack of adequate computer power for the development of modern three-dimensional treatment planning systems.

It is only recently with the completion of the Loma Linda facility in 1991 [6], that protons have become available for the first time in a hospital. Loma Linda is the first and only place in the world offering protons on an isocentric gantry. This progress has been made possible by the initiative of Fermilab in building the first proton accelerator dedicated to therapy (a small compact synchrotron of 250 MeV). Loma Linda has been operational since 1991 and more than 700 patients have been successfully treated there, demonstrating the practical feasibility of proton therapy in a hospital. Protons are also used at Loma Linda for common diseases, like prostatic cancer. The realisation of the Loma Linda facility represents indeed the first important milestone in the history of the promotion of proton therapy.

The realisation in the U.S.A. of the second hospital-based proton therapy facility of the world has been recently approved. The new centre will be realised at the Massachusetts General Hospital in Boston, which has the largest experience in proton therapy. The beam will be delivered by a cyclotron. The contract for the facility in Boston, including beam delivery system and gantry has been assigned to an European company (IBA Belgium). This will certainly have major positive consequences for the future of proton therapy in Europe.

While we are eagerly awaiting the decision to build the first hospital-based proton facility for Europe, which most probably will be realised in Italy using an H^- synchrotron (TERA project), there is an increase in the number of physics research centres proposing proton facilities at dedicated beam lines at their laboratories.

The first dedicated facility with a proton gantry in Europe is now being assembled at PSI [7]. First patient treatments are planned for beginning of 1995.
For the situation of the medical facilities in Europe we refer to the presentation of Prof. F. Farley at this conference.

3.3 Dose Application Techniques

The method used up to now for dose delivery is the so-called scatter foil technique. Figure 2 shows the principle at the base of this dose application method. The beam is spread about four or five meter ahead of the patient, by a system of scatterers (foils or similar devices) in such a way as to obtain a uniform illumination of the spread beam in the solid angle covering the tumour region. The shaping of the dose in the lateral direction is achieved using two-dimensionally shaped collimators in close analogy to photon treatments. The modulation of the proton range is performed using a fast spinning wheel (range shifter wheel). The beam, by traversing a variable amount of material as a function of time, deposits a layer of uniform dose distribution in depth (Spread-Out-Bragg-Peak). The distal edge of the dose is usually adjusted to coincide with the distal side of the target volume using individually shaped compensators. The dose distribution conforms in this way to the distal half of the target volume. By adding together many beam directions one can realise a reasonable conformation of the dose to the target volume.

The dose distribution and the shape of collimators and compensators are calculated in the treatment planning system, using the three-dimensional information (patient body electron density) delivered by computer tomography.

The advantages of this method are its safety, simplicity and reliability. The possible disadvantages are the non-complete three-dimensional conformation of the dose and the large amount of hardware needed for each beam angle on the gantry.

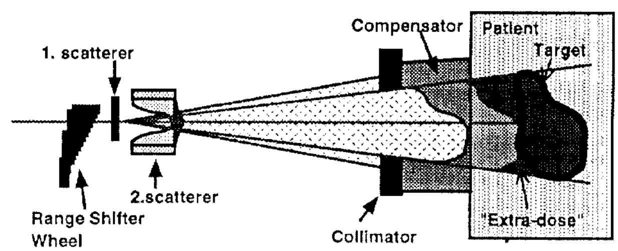

Figure 2. Scatter foil technique.

4. FUTURE TRENDS

4.1 New Technological Developments

The major improvements to be expected in this field are characterised by the following items:

4.1.1 Beam Scanning

Protons are charged particles. This gives the possibility of scanning the focused proton pencil beam in the patient body by magnetic deflection of the beam. The development of the spot scanning technique is the major goal of the proton therapy facility being realised at PSI. A similar approach is under development for ion beam therapy at GSI in Darmstadt.

Figure 3 shows the principle at the base of the spot scanning technique.

The approach chosen for beam scanning at PSI is based on the sequential deposition of a large number of static spot applications, typically 10'000 for a one litre target volume in an overall treatment time of 3-4 minutes. The dose of each spot is controlled by measuring the dose with a monitor system while the spot is being deposited and by switching the beam off with a fast kicker magnet when the required dose has been delivered. The position of the dose spot in the patient is controlled by the action of a sweeper magnet (which shifts the beam in one lateral direction), a range shifter (a stack of polyethylene plates, which are moved into the beam by pneumatic valves and which change the position of the Bragg peak in depth) and by moving the patient in the other lateral direction.

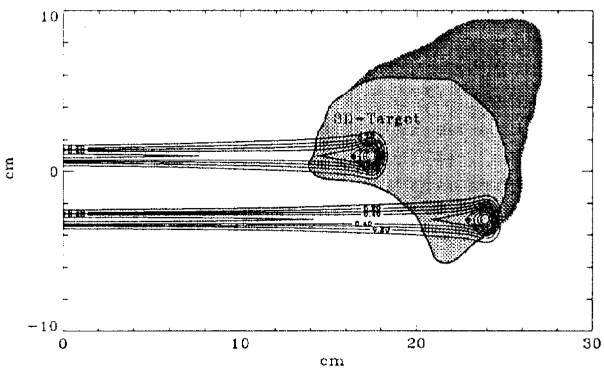

Figure 3a. Principle of the spot scanning technique: through the weighted superposition of individual spots . . .

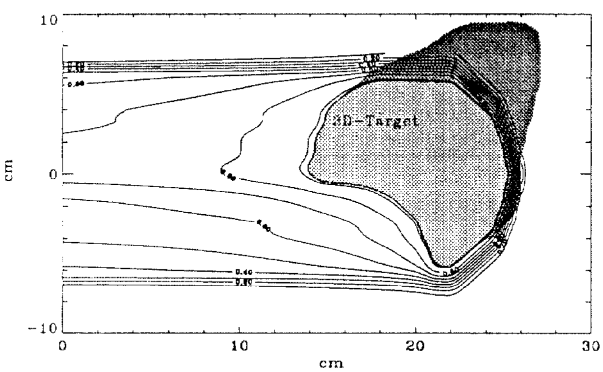

Figure 3b. . . . one can obtain a complete 3D-conformal dose.

The advantages expected using a beam scanning technique are the following. The deposition of the spot dose is completely under computer control without the need to adjust individual hardware in front of the patient. Dynamic treatments can routinely provide an exact 3D-conformation of the dose to the target volume and the full automation is expected to bring more precision and more flexibility. A better utilisation of the proton beam with less activation problems and less neutron background is also anticipated, and as opposed to the scatter foil technique, it is possible to implement this method on a small compact gantry. A possible disadvantage of the method is its increased sensitivity to uncontrolled organ movements during scanning.

Beam scanning is still under development. It should be noted that all future facilities are proposed for the traditional scatter foil technique, but are explicitly required to be upgradable for a beam scanning method ("scanning ready" facilities) at a later stage.

4.1.2 Isocentric Gantry

All new dedicated proton facilities are being proposed with an isocentric gantry.

A gantry system allows one to apply the beam on the patient from many directions and to distribute the entrance dose to different regions of the body, thus increasing the local tolerance to the treatment. The beam line is moved around the patient (and not vice versa) in order to maintain the patient exactly in the same fixed supine position during all phases of the treatment, including the data taking of the CT images used for treatment planning.

The major problem found in the design of a gantry for proton therapy is its size. In a gantry for the scatter foil technique the scattering of the beam is usually performed after bending the beam in the direction of the patient to avoid large aperture magnetic elements. Enough drift space between scatterer and patient has to be provided for the beam to spread out before it reaches the patient. The radius of a gantry for the scatter foil technique is expected to be of the order of 5-6 m. The gantry of Loma Linda spans for example a diameter of 12 m.

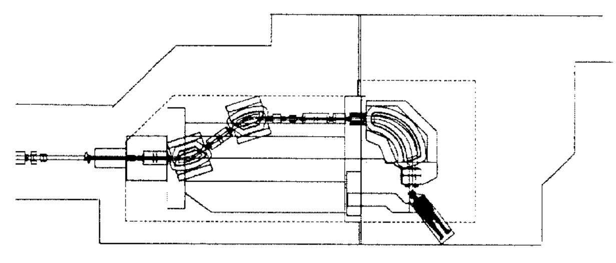

Figure 4. Cross section of the PSI gantry.

PSI is building a compact gantry dedicated specifically to the spot scan technique. By performing the scanning of the beam ahead of the last 90^{o} bending magnet and by mounting the patient table eccentrically on the gantry (using a rotating support which maintains the table horizontal at all times) the diameter of the rotating structure has been reduced to only 4 m. This corresponds to the minimal space needed for magnet and patient table together without any drift space in between. The cross section of the PSI gantry is shown in figure 4. The gantry will be the second proton gantry to be realised in the world and is the smallest proton gantry using conventional magnets proposed so far. It is being commissioned presently. The first beam was successfully transmitted through the beam line in April 1994.

The use of superconductivity and solutions based on the use of pulsed magnets are expected to reduce further the size of future proton gantries. Another proposed idea is to rotate the accelerator around the patient. A small superconducting cyclotron which rotates around the patient has been put in operation at Detroit for neutron therapy. Although running at a lower beam energy than needed for proton therapy this installation shows the feasibility of such ideas.

4.1.3 Increased Flexibility

Future proton treatments will be characterised by an increased flexibility in the choice of the incidence of the beam on the patient. The choice of optimal beam directions is expected to be very important, not only to avoid sensitive structures in the way of the beam but also to select those situations which minimise possible errors arising from density heterogeneities of the patient's body, such as bony structures or air inserts.

In order to increase this flexibility we have decided at PSI to build our gantry to allow for an additional rotation of the patient couch in the horizontal plane. For head treatments we will be able to irradiate the patient from essentially any direction.

4.1.4 Increased Precision

Future proton treatments will be characterised by an increased precision concerning both the positioning of the patient with respect to the beam and the control of the range of the protons in the patient's body.

Better positioning can be achieved using individual mould techniques. Another possible improvement is given by the direct integration of a CT unit into the therapy equipment. The same dedicated CT unit will be used for example at PSI for both acquisition of the CT slices for treatment planning and for the position control (using scout view images) before the delivery of each dose fraction. The patients treated at PSI will be transported from one room to another, ready for treatment, on a special carriage system (lying in their individual couch). This patient transporter has been designed to allow for reproducible mechanical coupling of the patient couch on both the tables of the CT unit and of the proton gantry. This should guarantee a more precise relation between therapy and treatment planning. In addition to the control images taken outside of the treatment room, the control of the position of the patient will also be optionally done directly on the gantry using retractable X-ray tubes and devices for proton radiography.

The control of the proton range in the patient in vivo will be performed by means of in vivo dosimetry and eventually by measuring with a PET camera the beta-plus activation induced in the patient. Proton radiography as a quality assurance tool for proton therapy is presently being developed at PSI. Proton radiography images contain not only data usable for the control of the position of the patient with respect to the beam, but also information on the residual range of the protons. This information can be predicted in the treatment planning programs and can be used as a test of the range of protons in the patient "in vivo".

4.1.5 Computer Power and better Diagnostics Tools

Dose calculations for a conformal three-dimensional spot-scanning technique were unthinkable a decade ago. Today calculations for precise proton treatments in very complex anatomical structures are feasible. At PSI we have developed a fast Monte Carlo code capable of delivering sufficiently high statistics to resolve details of the dose at the CT pixelsize.

Computers able to cope with very large data sizes describing the three-dimensional anatomy of the patient were not available until recently. Another missing prerequisite for the optimal use of proton therapy in the past was the lack of access to modern diagnostic tools like CT and MRI, which can be used to exactly define where to place the beam. With these modern instruments we now "see" better where we want to shoot. For this we also now need a better "gun", the protons.

4.2 New Medical Indications

The availability of improved conformal techniques on proton gantries are expected to extend the list of indications for proton therapy to include large irregular target volumes, paediatric tumours, isolated metastasis, re-treatments, tumours with partial organ infiltration, and also to increase the tolerance for the combination of radiation therapy with other new modalities.

5. CONCLUSIONS

Although the use of protons for therapy was proposed for the first time about 50 years ago, their true potential is starting to be recognised only now. This is documented by the increased number of centres proposing the use of proton therapy in the world and by the practical realisation of the first hospital-based charged particles facilities in Loma Linda, Chiba and Boston. The reason for this delay comes from the dependence of proton therapy on collateral sciences, such as computer and modern diagnostic technology. The fantastic progress observed in these fields in the last years is likely to make the inherent precision of protons more readily available in clinical practice,

6. REFERENCES

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