RECENT DEVELOPMENTS IN THE USE OF ACCELERATORS FOR RADIATION THERAPY

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1 INTRODUCTION

This is a write-up of a seminar given in the framework of the CERN School for accelerator specialists in Darmstadt (April 2000). The intent of the presentation is to give a brief overview of the use of accelerators for cancer therapy. It focuses mainly on the utilization and the respective merits of different types of accelerators for radiation therapy (RT), but not on the accelerator technology itself. The first half of the work contains a superficial introduction to RT. In the second half the emphasis is put on the most recent developments in this field. For time reasons we do not discuss other medical applications of accelerators, for example isotope production or the use of synchrotron light. For a comprehensive historical review we refer to some excellent textbooks and to the specific literature [1],[2].

A major intention of the presenter's own work (the advanced use of proton therapy) is to show that research in accelerator technology continues to play an important role in the progress of medicine.

2 THE ROLE OF RADIATION THERAPY IN THE MANAGEMENT OF CANCER

Cancer is the second major cause of death (after cardiovascular diseases) in developed countries. The total cure rate is nowadays about 45% (of all cancer patients). This is the result of a slow but steady improvement recent decades.

For about two-thirds of the patients the disease is still well localized within a specific region of the body when the patient is confronted with the diagnosis of cancer. For these patients the chances of cure using a local therapy are reasonably high.

2.1 Cancer therapy modalities

The following therapeutic strategies are presently available:

- **Surgery**

Whenever it is possible a radical surgical excision of the disease is the preferred therapeutic choice. The earlier the diagnosis and the smaller the tumour, the better the chances of a good therapeutic outcome. In this context screening plays an important role in the early detection of the disease. Surgery is the most successful therapy and it accounts for 22% of all cures (this includes early cases, small tumours and skin cancer).

- **Radiation therapy (RT)**

This is the second choice. RT is used with a curative intent when the tumour is inoperable but still well localized. Radiation therapy alone accounts for 12% of all cures, and a further 6% in combination with surgery.

- **Chemotherapy**

When the disease has already spread to the whole body (with distant metastases) the chances of cure are correspondingly lower. Chemotherapy is then used with the intent of eliminating microscopic distant metastasis. This accounts for the remaining 5% of the cure rate.

- **New biological methods**

The largest effort in cancer research today is being made by the big pharmaceutical companies on developments based on new biological sciences, mainly with the aim of controlling the distant spread of the disease. At present, the highest hopes are placed in immuno and genetic therapies. Systemic therapies usually have to cope with the unwanted side effects of the drugs, which are distributed to the whole body. The difficulty of transporting the drug into the core of the tumour and the extremely large number of cancer cells involved in a solid tumour represent major problems for the utilization of systemic therapies for the elimination of advanced solid tumours. For these reasons the new biological methods still aim, in the first place, at the inactivation of isolated cancer cells (the microscopic spread of the disease).

It is likely that, in the foreseeable future, surgery and radiation therapy will continue to play a major role in the control of the primary solid tumour. Whilst waiting for big breakthrough from genetic technologies, it is reasonable to continue to improve traditional established methods, such as surgery and radiotherapy.

2.2 Radiation therapy: a local treatment

It is important to note that the different types of therapy are often complementary and not necessarily exclusive. Many recent successes in cancer management are in fact based on the combined use of different modalities. In addition to the use of radiation with a direct curative intent, radiotherapy is also used for palliation (release of pain, prolongation and maintenance of the quality of life) and for prophylactic purposes (sterilization of localized zones with a suspected microscopic invisible spread of the disease).

Nowadays about two-thirds of all cancer patients receive radiation therapy alone or in combination with other modalities.

Radiation therapy is a local treatment and as such it will continue to play a very important role in the fight against cancer in the future. About 15% of all patients die from failure to control the primary tumour. In Germany alone the cancer registry indicates about 340 000 new cases per year. A total of 210 000 patients still die from their disease [3]. Additional progress in radiation therapy, even by a few per cent, could have a positive impact on the quality of life of a large number of patients. Improvements, as discussed below, could be achieved by using more advanced treatment techniques (for example intensity modulated radiation therapy) and/or by using unusual types of radiation sources (such as external therapy with protons or light ions).

3 RADIATION THERAPY CONCEPTS: AN OVERVIEW

The action of radiation on a biological target is a chain of effects, initiated by the beam. Through ionization (physics) we have the production of radicals (chemistry) causing reparable and irreparable errors in the genetic code (DNA) at the cellular level (biology). For cancer therapy the most important endpoint is to stop the capability of the cancer cells to replicate and thus prevent the tumour from growing further. Unfortunately, not only the cancer cells are damaged by radiation. The dose burden on healthy tissue is the other important effect to consider when planning a radiation treatment. The dose in the tumour is usually chosen as a function of the tolerance of the surrounding healthy tissue. There a delicate balance between the chances of a cure and treatment morbidity due to acute and late reactions.

The following are important concepts in radiation therapy:

- **Therapeutic ratio**

A necessary condition for success of treatment is an inherent higher sensitivity to radiation of the cancer cells compared to the healthy cells. The most important mechanisms are the capability of the healthy cells to repair radiation damage spontaneously and for the healthy tissue to repopulate the irradiated organs with new non-irradiated cells.

- **Fractionation**

Fractionation is the repeated application of the treatment with a fractionated dose at time intervals long enough for repair and repopulation mechanisms to take place (the assumed minimum interval is of the order of 6 h or more). In this way the effects of a positive therapeutic ratio are repeatedly applied and the chances of the outcome are correspondingly improved.

Radiation therapy is typically applied 5 days per week over 5–6 weeks. The fraction dose is typically 2 Gy and the total dose applied is around 50–70 Gy. It is generally believed that the cure is reached by the inactivation over the course of the full treatment of each single cancer cell in the body. Eventually the immune system of the body contributes to the cure at the level of the very last few remaining cancer cells. Usually the dose is chosen as a balance between the chances of eradicating the tumour and the risk of producing complications in the healthy tissue. The desired precision for the prescription of the dose and for the homogeneity of the dose distribution within the target volume is (ideally) of the order of a few per cent (altogether the combined errors should be less than 5%).

- **Physical selectivity (dose localization)**

The success of RT is based on the ability to confine the dose delivery to a small region of the body, which contains the whole tumour. Ideally one would like to deposit only the minimum necessary dose inside the target volume and zero dose outside. In practice this is technically impossible. The most recent strategy is to confine the dose as strictly as possible to the target volume by shaping the dose in all three dimensions to conform to the shape of the target volume (3D dose conformation).

Historically, most of the improvements in RT were achieved by increasing the dose localization using different technologies. This includes computer-based treatment planning, better target delineation using modern diagnostics, advanced beam delivery treatment techniques (conformal therapy), and the use of exotic types of radiation.

- **Radiation quality: the dependence on Linear Energy Transfer (LET)**

The efficacy of only a given type of radiation in destroying the reproductive capability of a cell does not only depend on the applied dose (the energy per mass). The mechanism details of the deposition of the ionization at a microscopic level play an important role as well. The LET describes the density of ionization around the track of the primary ionizing particles measured at the typical size of the cell (of the DNA). The 'dose quality' (expressed by the LET) depends on the type and on the energy of the ionizing particles and has a strong influence on the biological effects. (This is a major subject of radiobiology.)

- **Conventional therapy: low LET radiation as the reference**

The most commonly used sources for external radiation therapy are photon and electron beams delivered by electron linacs. This technology is now substituting cobalt sources almost entirely. Radioactive sources today are often used for interstitial therapy (using afterloading techniques and radioactive implants). All these conventional sources are very similar in their radiobiological effects and represent the standard reference in radiobiology (low LET radiation).

- **High LET radiation: the exotic type of radiation**

The higher cell-killing efficiency of high LET radiation is usually characterized by a radiobiological efficiency (RBE) value higher than 1 (of the order of 2 to 5). The RBE is defined as the ratio of the dose of non-conventional radiation compared to the standard (photons) necessary to obtain the same biological effect. The highest cell-killing efficiency is found at LET values of the order of 100 keV per micron. Above this value the effect drops again (overkill).

Another important radiobiological quantity is the so-called oxygen enhancement ratio (OER). Cells with a deficit of oxygen are usually more resistant to radiation than well-oxygenated cells. The OER expresses this difference. The oxygen-deficient cells are suspected to be the cause of tumour relapse when the tumour is treated with a low LET radiotherapy (an attempt to get rid of this effect is

through the use of special drugs, the so-called radiosensitizers). The negative effect represented by a high OER value at low LET disappears gradually with increasing LET. High LET radiation is therefore potentially more efficient for treating large radio-resistant tumours, when the poor vascularization of the tumour implies the presence of anoxic tumour cells as a potential cause for a treatment failure.

A good classical textbook on radiobiology can be found in Ref. [4].

4 CLASSIFICATION OF ACCELERATOR-BASED RADIATION SOURCES

An excellent introduction to the field of radiotherapy, mainly from the point of view of charged particles therapy, can be found in Refs. [5],[6].

4.1 Low LET beams

The most commonly used low LET radiation sources are:

- **Photons and electrons**

Photons and electrons are classified as low LET radiation beams (the LET distribution is below 20 keV per micron). This radiation type represents the standard used in hospitals. Conventional therapy is discussed in more detail in Section 5.

- **Protons**

Protons are considered to be biologically similar to photons. They are potentially interesting for their superior physical selectivity. The significance of proton therapy in the world is slowly increasing. This is where accelerator technology is expected to contribute most in the future (see Section 6).

4.2 High LET beams

Classified as high LET beam therapies, with a clearly different radiobiological behaviour than conventional therapy, are the following radiation beams:

- **Neutron therapy**

Neutron therapy has been an active field of research over the last two decades. The depth dose curve behaviour for the neutron is exponential with depth (similar to photons). Its physical selectivity is therefore similar to photon therapy. A dozen facilities worldwide are applying neutron therapy (mainly using a dedicated cyclotron). The clinical results were partially encouraging but not enough to justify the installation of new dedicated facilities. The most cited success of neutron therapy has been achieved for the treatment of salivary gland tumours. Owing to its superior physical selectivity, light ion therapy is now slowly replacing neutron therapy.

- **Pion therapy**

Pion therapy is mentioned here only for historical reasons. High LET beams were explored in the 1980s at the so-called pi meson factories at Los Alamos, U.S.A., Triumf, Canada, and at PSI (formerly SIN) in Switzerland. The trials were abandoned mainly due to the difficulty of obtaining beams with a high enough intensity. Another reason was the superiority of the physical selectivity of light ion beams: pions show an excellent behaviour with respect to the dose profile in depth, but multiple Coulomb scattering spoils the quality of the penumbra in the lateral direction of these beams.

- **Light ions (mainly carbon)**

Therapy with high LET radiation is now being proposed again, particularly in the context of light ion therapy. The rationale for the use of ion beams resides in the combination of the high LET with an excellent physical selectivity. The world-wide situation of ion therapy is described in more detail in Section 7.

- **BNCT**

A special role—due to the potential selectivity at a cellular level of the drug (for example antibodies) carrying boron—is played by Boron Neutron Capture Therapy (BNCT) [7]. Accelerator technology could play a role in the production of thermal neutrons with dedicated cyclotrons, instead of nuclear reactors.

5 CONVENTIONAL THERAPY WITH LINACS

5.1 Standard therapy

Today the use of electron linacs represents the state of the art in radiation therapy (low LET radiation with electrons and photons). One should not forget interstitial radiotherapy with radioactive sources and therapy with radioactive isotopes. Linacs can be found in every major hospital and their total number is probably in the order of many thousands worldwide. The electron beam energy can be chosen in the range of 6–25 MeV. The accelerator size is typically less than 1 m long and is mounted on the head of a rotating gantry. The electron beam is bent by a magnetic channel in the direction of the patient. The photon beam is created by bremsstrahlung of the electrons impinging on a metallic target in the head of the gantry. Figure 1 shows a photograph of a modern linac, a Varian machine at the Radiotherapy Department of the Triemli Hospital in Zurich.

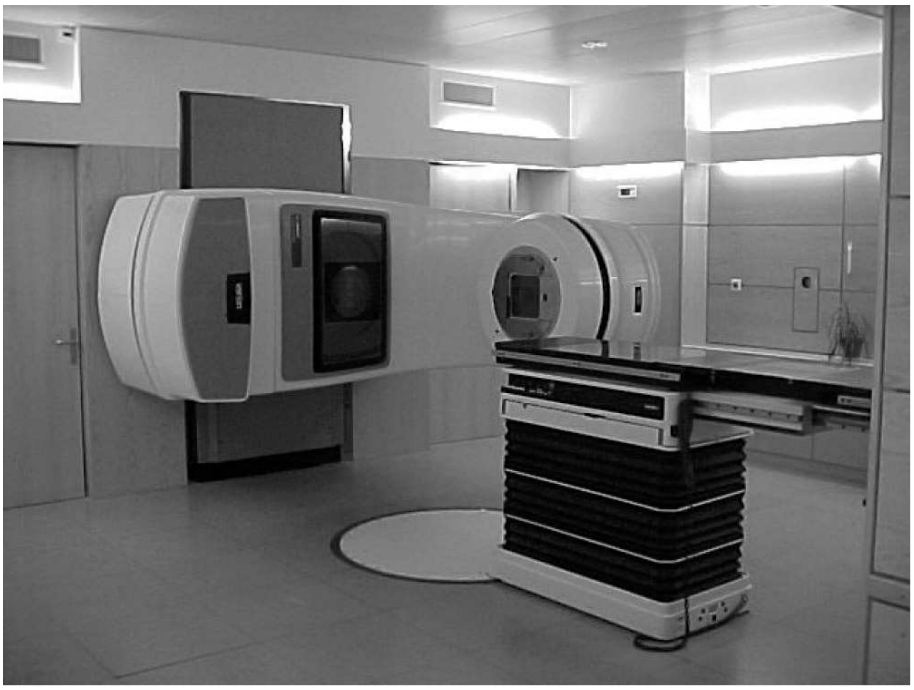

Fig. 1: Photograph of a modern electron linac (courtesy of U. Schneider)

The photons are emitted from the head of the gantry with a homogeneous flux in the solid angle used for the treatment (this covers target sizes of maximally 40 cm at a distance of 1–1.5 m from the source, the so-called source-to-isocent distance). The dose in the patient arises from the secondary electrons created by the photo- and Compton effect. After a build-up region in the first few centimetres below the patient's skin, the dose falls exponentially with depth (see Fig. 2). In order to deposit more dose into the target volume than the surrounding tissue, it is necessary to apply the beam from several directions. For this the gantry is rotated around the patient table. The patient remains immobilized in his treatment position on the treatment couch (preferably in the supine position). An alternative to

the delivery of single static dose fields is the use of a continuous rotation with the beam switched on (arc therapy). The individual dose fields are shaped in the direction transverse to the beam by using individually shaped collimators (designed by the treatment planning programme). So-called Multi-Leaf Collimators (MLC), with a dynamic computer-controlled movement of the leaves, are nowadays slowly replacing fixed collimators. Through the convergent superposition of the dose fields on the target volume and by distributing the entrance and exit doses over several organs, it is possible to apply the necessary (homogeneous) dose to the target volume, whilst maintaining the burden on the healthy tissue below the tolerance limit. The data used for defining the target volume in modern radiotherapy are nowadays obtained directly from computer tomography.

After removal of the bremsstrahlung target from the beam path, the electron beams can be used directly for electron therapy. The depth dose curve of an electron beam entering the patient shows a shallow bump with a limited depth of penetration. The electron range is only several centimetres depending on the initial energy of the beam. Electron therapy is used for treating superficial tumours. Another important application of electron therapy is for intra-operative applications (open body irradiation during surgery, mainly for sterilizing the region where the tumour has been removed).

The accelerators used in hospitals are based on very advanced technology (standing wave electron linacs) and are produced commercially (this has an important impact on cost). The beam is pulsed (with typically 1000 pulses of a few microseconds duration per second). This kind of technology is definitively replacing other, historical types of radiation sources used in the past (X-rays, cobalt sources, and betatrons).

5.2 Most recent developments in conventional therapy: Intensity-Modulated Radiation Therapy (IMRT)

The use of sophisticated beam delivery techniques, support by computer technology, and the information gained with modern diagnostic techniques (Computer Tomography (CT), Magnetic Resonance Imaging (MRI) and Positron Emisson Tomography (PET)) have been at the origin of the progress achieved in RT in the last decade. The dynamic use of multi-leaf collimators and the control of patient positioning using portable imaging devices are the most important technical developments today [8].

The common goal of all developments is to give enough (homogeneous) dose to the target volume whilst reducing as much as possible the dose outside the target volume. Another possibility is to choose where to deposit the unwanted dose (selection of gantry angles). The most promising but also the most challenging approach is to shape the geometrical distribution of the dose such that it conforms as much as possible to the three-dimensional shape of the target volume (3D conformal therapy).

The dynamic use of multi-leaf collimators offers additional possibilities. The most interesting is to apply the dose with a non-uniform distribution of the photon fluence. The flux is varied across the cross section of each dose field. This is IMRT. The superposition of intentionally non-homogeneously shaped dose distributions can result in a homogeneous dose distribution of superior quality (with a higher degree of conformity, especially in the case of target volumes with concavities). This is made possible by the use of advanced optimization algorithms in treatment planning using modern computer technology. The optimization of the delivery of radiation using multiple beam ports is a typical ‘inverse problem’ with a strong analogy to CT. With CT one uses multiple projections (from many angles) to reconstruct complex density images. With IMRT one uses complex dose projections to produce more ideal dose distributions.

Figure 2 shows an IMRT example of the dose distribution for a tumour near the base of the skull. The calculation has been made with the treatment planning package of PSI (courtesy of T. Lomax). The dose is delivered using nine photon fields. Each field is modulated in intensity. One recognizes immediately that the optimization algorithm avoids sending photons towards the brain stem in each of the fields. The dose delivered to this sensitive organ is reduced considerably in this way. The availability of a large amount of degrees of freedom and the strength of the mathematical methods make it possible to

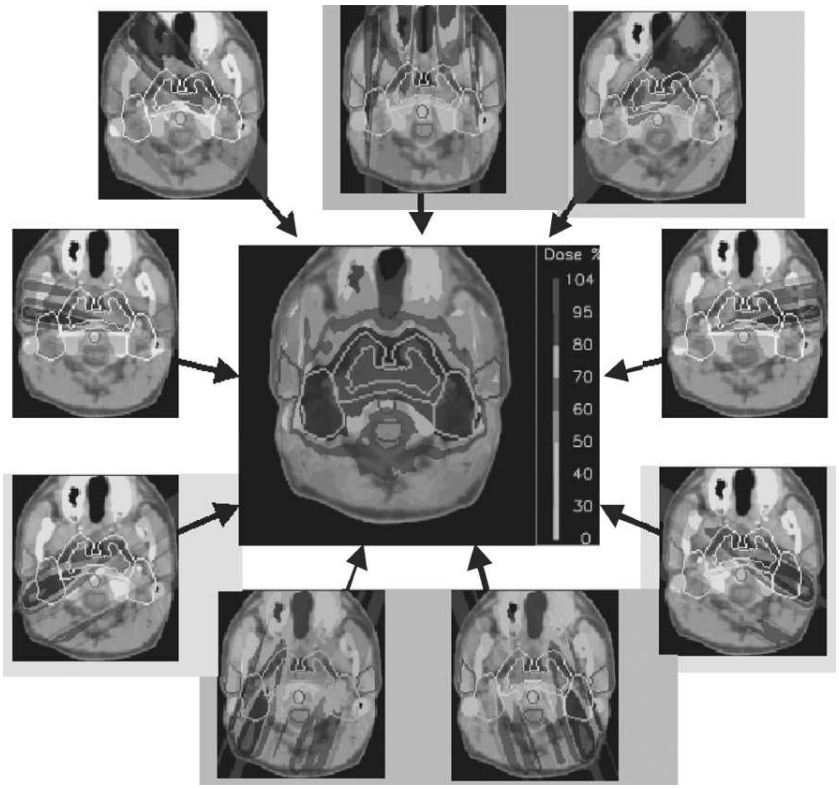

Fig. 2: An example of intensity-modulated radiation treatment planning with photons. Through the addition of nine fields it is possible to construct a highly conformal dose distribution with good dose sparing in the region of the brain stem (courtesy of T. Lomax).

produce a very good dose distribution, shaped in all three dimensions to conform precisely to the target volume with a sufficient homogeneity.

The obvious but most tedious way of applying intensity-modulated photon beam delivery is by using absorbing filters of variable thickness in the path of the beam (individually shaped filters). A more modern approach is to change the position of the leaves of an MLC under computer control as a function of time during beam delivery: this is what is usually meant by IMRT [9]. Another way is to use an array of individual beam shutters in one lateral direction and to work on the dose deposition slice by slice and angle by angle in the other directions. This is called tomotherapy [10]. Tomotherapy is where the analogy with CT is the closest, also from the point of the beam delivery (full rotation and slice by slice beam delivery).

The fashionable keywords in medical physics nowadays are ‘inverse planning’, ‘intensity modulation therapy’, ‘tomotherapy’ and ‘computer-controlled multi-leaf collimators’. These ideas are however not very new. A first example of computer-optimized dynamic beam delivery of conformal radiation goes back as early as 1981 with the pion therapy project of PSI. Pion therapy was delivered to about 500 patients using a dynamic beam delivery technique. The pions were applied simultaneously from 60 concentric pion beams. The patient was moved under computer control along a three-dimensional path inside a cylinder bag filled with water. The degrees of freedom for the optimization algorithm were chosen by changing the velocity of the movement of the hot spot of the dose (fixed at the iso-centre of the machine). From the point of view of the technology this was similar to tomotherapy, but 20 years in advance [11]. Unfortunately, the spot used for pion therapy was rather large (5 cm FWHM). This was because of the large size of the target used for the production of the pions, a problem related to the difficulty in obtaining a sufficiently high number of pions for therapy. Pion and neutron therapy trials

were necessary experiments, which would have to be repeated today if they had not already been done. It is now difficult to prove how these early developments at physics laboratories had an influence on later developments in hospitals. Applied research activities at scientific laboratories are often too far ahead in time to have a direct impact on contemporary life. But the methods are often rediscovered in a slightly modified form at a later time. Wide acceptance is achieved only at the moment of their availability on a large scale through industrial production. Many professionals working in hospitals are now convinced that thanks to this recent technological progress in beam delivery, photons will soon be competitive enough to beat proton therapy. Can IMRT make proton therapy obsolete? This is probably the new crucial question for all centres investigating the potential of proton therapy.

6 PROTON THERAPY

6.1 The Bragg peak

The advantage of proton therapy is given by its superior physical selectivity. Protons have a well-defined penetration range in biological tissue and they deposit the maximum of their energy in the region where they stop. This gives rise to the so-called Bragg peak. Figure 3 shows the dose deposition of a monoenergetic proton beam as a function of the depth. This must be compared with clinical photons, which have a characteristic exponential fall-off of the dose. Protons also offer the possibility to localize the dose as a function of the depth and not only in the lateral direction. Compared to photons and using similar techniques, one can expect to achieve with protons a general reduction of the integral dose outside the target volume by a factor of 2 or 3 (additional dose sparing).

Another potential advantage is given by the electric charge of the particle beams, which creates the possibility to scan the beam by using magnetic scanning techniques (this is probably a more practical alternative to multi-leaf collimators).

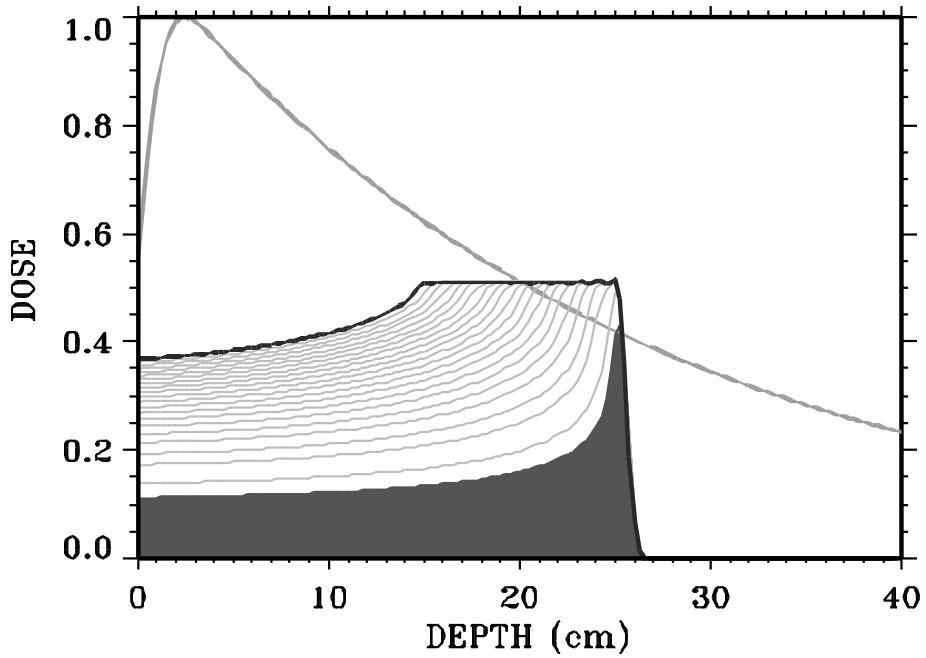

Fig. 3: Comparison of the depth dose profiles of proton and photon beams. The photon dose falls off exponentially with depth. A mono-energetic proton beam is characterized by the presence of the Bragg peak in the region where the protons stop. Through the superposition of many proton beams of different residual range it is possible to deposit a homogeneous dose Spread-Out Bragg Peak (SOBP) in the regions of the tumour (in this case from 15 to 25 cm depth). One can recognize from the picture the potential of dose sparing of the protons in the entrance and exit regions of the beam.

Protons are expected to produce superior results for the treatment of large tumours of complex shape, where a significant reduction of the dose outside of the target volume is clinically desirable. On the other hand, the disadvantage of proton therapy is given by the large size of the accelerator and of the beam lines needed for the transport of the beam. The maximum energy of the beam is chosen at around 230–250 MeV (corresponding to a penetration depth of 33–37 cm in water). Owing to the high magnetic rigidity of the beam the minimal bending radius that can be applied to the beam is around 1.3–1.5 m using conventional magnets close to the saturation limit.

6.2 Beam delivery techniques for protons

For a more detailed discussion on beam delivery we refer to Ref. [12].

The main techniques are:

- **Passive scattering**

Figure 4 shows schematically the principles at the base of the beam delivery with passive scattering.

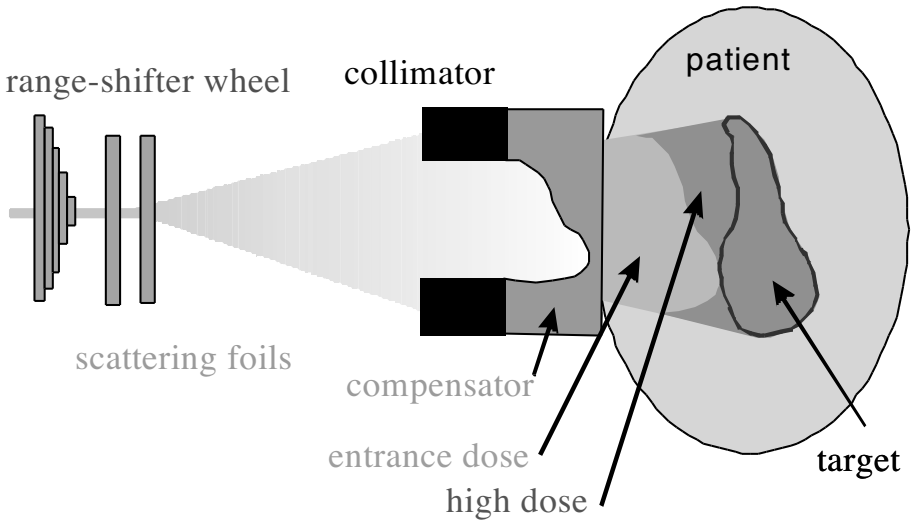

Fig. 4: Elements necessary for beam delivery using passive scattering techniques. Scatter foils are used to produce a homogeneous proton flux. A range shifter wheel is used to produce a SOBP of given dose homogeneity thickness (at a given depth). These hardware elements are selected as a function of the beam energy and target size. Individually shaped collimators are used to shape the dose laterally. A compensator shifts the edge of the dose distribution to conform to the distal side of the target volume. The fixed range of modulation implies an unnecessary deposition of dose at the 100% level outside the target volume.

This technique is the traditional established beam delivery method. The proton beam is scattered by material in the beam ahead of the patient in order to produce a homogeneous flux of protons in the solid angle used for the irradiation (in close analogy with the point source of radiation of conventional therapy). The dose is then shaped in the lateral direction using individual 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 is chosen so as to produce a homogeneous region of the dose in depth (SOBP). The SOBP 'thickness' must be chosen to cover the whole target volume. With protons one can deposit a homogeneous dose distribution from just a single beam direction. This is already an improvement compared to photon therapy, where the dose homogeneity can be achieved only by using several beam directions.

An individual compensator bolus can optionally be added to this set-up. The variable thickness of the bolus is machined to shift the distal edge of the dose field to conform more closely to the deepest side

of the target volume. This improves the degree of conformity of the dose distribution. All the necessary hardware must be adapted and in part created individually for each single field.

This method produces by default a homogeneous dose field of fixed SOBP thickness in depth (fixed range modulation). Without additional devices the passive scattering method is not capable of delivering IMRT methods. One could envisage implementing IMRT with protons by using an additional multi-leaf collimator. In this case one would not make use of the potential to modulate the dose in depth by changing dynamically the proton range (variable range modulation).

The most elegant, flexible, and efficient method for providing inverse planning with protons (IMPT) is by magnetic beam scanning.

- **Beam scanning**

  Figure 5 shows the basic principles of beam scanning technology.

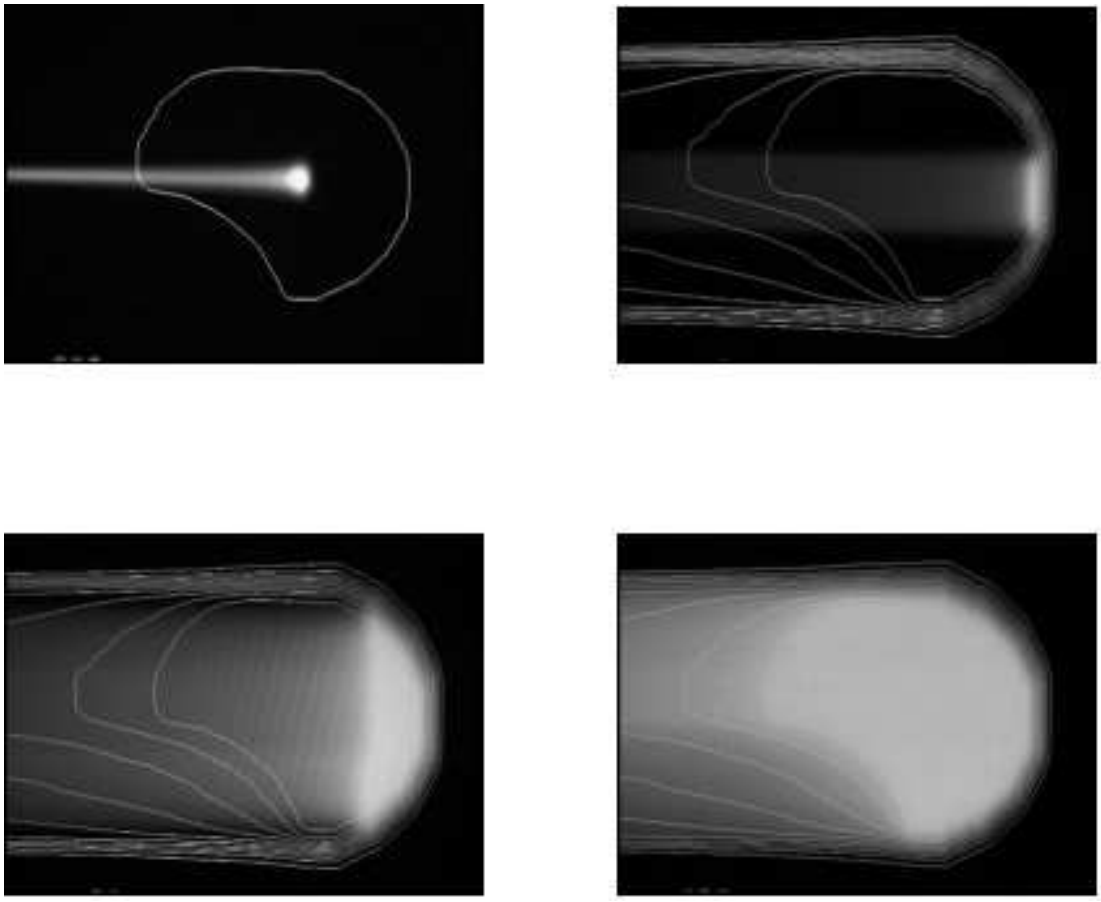

Fig. 5: Basic principles used for beam scanning with protons. Through the delivery of individual proton pencil beams one can shape the distribution of the dose in three dimensions at will, directly under computer control.

In this case the proton pencil beam coming from the accelerator is delivered directly to the patient. Individual pencil beams are added under computer control to provide an individually shaped dose distribution with maximal conformity with the target volume (using variable modulation of the range).

In the lateral direction the beam is usually scanned by magnetic deflection in the beam line ahead of the patient. The modulation in depth is achieved by changing the range of the protons dynamically. A high conformity is achieved by changing the dosage and the position of each pencil beam individually under computer control.

At present the proton facility of the PSI is the only one capable of delivering proton therapy using a dynamic beam scanning technique [13]. The design of the PSI scanning system is based on maximal simplicity without compromising for the flexibility of the dose delivery.

6.3 IMPT: an example

Figure 6 shows, as an example, the potential use of the spot scanning technique for delivering Intensity Modulated Therapy with Protons (IMPT) (courtesy T. Lomax of PSI). With only four 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 simply under computer control, without the need for specific hardware.

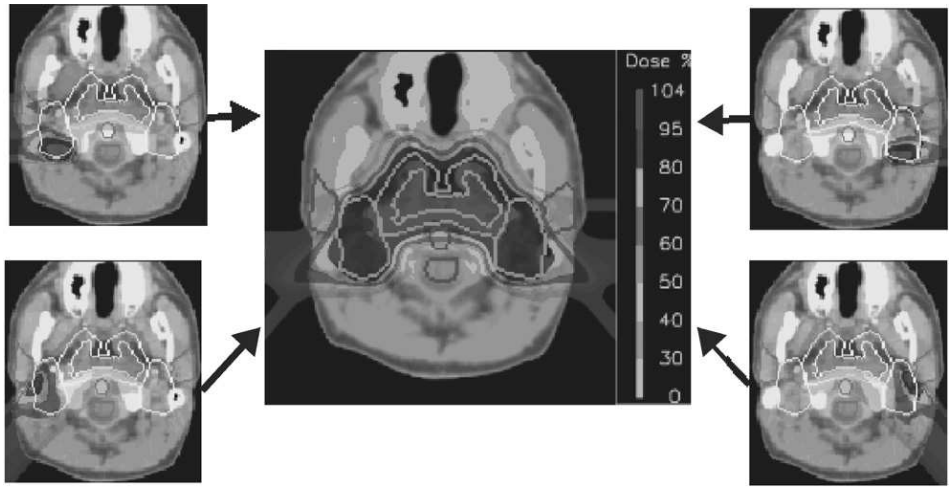

Fig. 6: Example of intensity modulated therapy with protons. A high degree of conformity is achieved using a low number of dose fields. The advantage compared with photons is the general reduction of dose burden outside of the target volume (courtesy of T. Lomax).

6.4 Proton gantries

In order to be able to apply the beam from many directions onto the supine patient, it is desirable to apply the dose using a rotating beam line. This implies the use of a proton gantry. All new dedicated facilities today are designed with gantries.

The proton gantries constructed up to now include that at Loma Linda University, the first place in the world where a proton gantry was developed. The facility started operation in 1991. The second design is the compact gantry at PSI (patient treatments started in 1996). A third type of gantry was recently built at Kashiwa (Japan), where operation started in 1999. A very similar gantry design is ready to go into operation in Boston (USA) and a fourth gantry type is being assembled in Tsukuba (Japan).

Typical gantry designs can be assigned into the following categories:

- **Cork-screw gantry (example: Loma Linda University, USA) [14]**

This gantry is dedicated to beam delivery with passive scattering. The diameter of the rotating structure is 12 m. The double bending of the beam line (first into and then inside a flat rotating structure) with a cork-screw design makes the gantry more compact longitudinally at the expense of a longer beam line.

- **Compact eccentric gantry (PSI, Switzerland) [12],[15]**

This gantry in dedicated to (Cartesian) beam scanning and IMPT. Part of the beam scanning is performed before bending the beam towards the patient. The eccentric mounting of the patient table reduces further the gantry diameter which, at only 4 m, is the most compact of all the known designs. Figure 7 shows the PSI proton gantry.

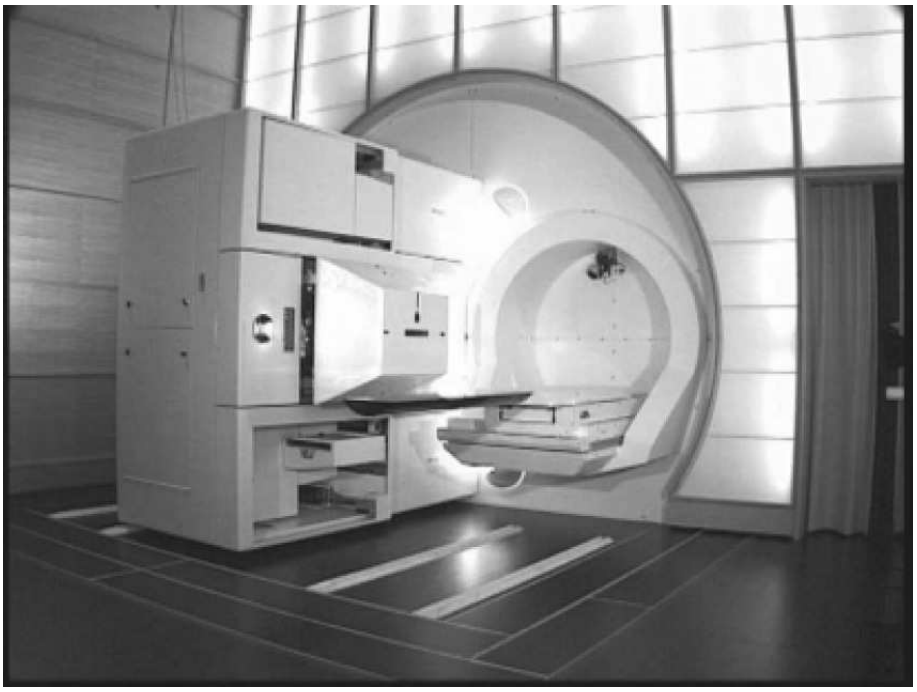

Fig. 7: Photograph of the PSI proton treatment room with the head of the compact gantry dedicated to proton beam scanning

An improved version of this design with the patient table mounted at the isocentre is anticipated for use in hospitals.

- **Barrel gantries (examples: Kashiwa, Japan, and Boston, USA)**

Beam delivery by passive scattering is necessarily performed after bending the beam towards the patient. The space needed for spreading the beam must be added to the gantry radius. The gantry diameter is therefore at least 10 m. A large gantry radius is the price of maintaining the possibility to use the passive scattering technique on the gantry. A large throw gantry can be used for beam scanning. The NPTC crew in Boston is planning to implement beam scanning on their gantry at a later stage.

6.5 Proton facility design

The investments for proton therapy equipment are high. For this reason all dedicated proton facilities are designed with an accelerator serving several treatment rooms simultaneously. The first dedicated proton therapy facility in a hospital was installed at the Loma Linda University Hospital in the USA.

Figure 8 shows, as an example, the layout of the new facility at the Massachusetts General Hospital in Boston, expected to become operational this year.

6.6 Choice of accelerator

The energy of the protons is in principle low enough to allow the use of several types of accelerator. The accelerator types presently used in dedicated facilities are the following:

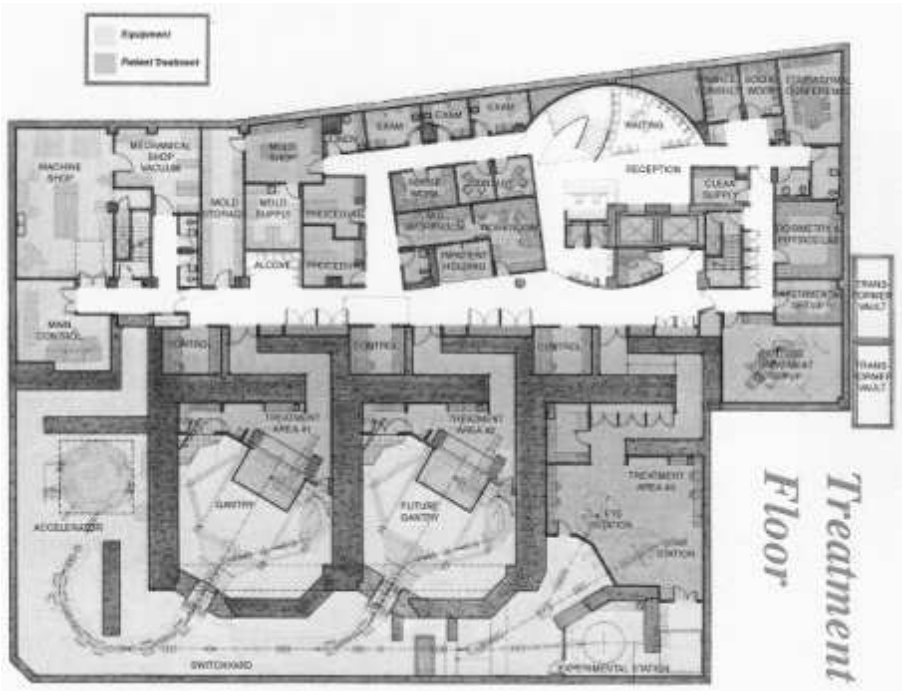

Fig. 8: Layout of the NPTC proton therapy facility at the Massachusetts General Hospital in Boston USA (courtesy of J. Flanz)

- Cyclotrons (examples: Kashiwa and Boston)
- Synchrotrons (examples: Loma Linda University and Tsukuba University)
- Linacs (a proton linac with a sufficiently high repetition rate of the pulse frequency to be used for beam scanning is under development in Rome, Italy) [16]
- Synchrocyclotrons (Orsay, Uppsala)

At present, the major competition concerning the choice of accelerator is between cyclotrons and synchrotrons. The main advantage of a proton synchrotron 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 to beam scanning. One can, however, overcome parts of the problem by providing a stable slow extraction of the beam.

The advantage of the cyclotron is the high duty factor of beam (DC beam)— which is well-suited beam scanning, the high proton current, and the inherent stability of the beam (including a possible easy control of the beam intensity at the ion source). The active modulation of the intensity at the ion source could also be used as an aid for the scanning of the beam. 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 components in the initial region of the facility.

There have been several other propositions:

- **H^- synchrotrons [17],[18]**

The advantage of this approach is the expected easy extraction of the beam from the ring by foil stripping. The idea is to provide a separated extraction for each (short) beam line used for feeding the protons into several treatment rooms, which are ordered radially around the synchrotron ring. The radius of the ring is quite large (the magnetic bending must be maintained low to avoid magnetic stripping of the negative ions).

- **Separated sector cyclotrons [19]**

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 with the advantage of a variable energy machine.

- **Superconducting cyclotrons [20]**

Possible advantages of superconducting cyclotrons are the reduction in the size, the lower power consumption, and possibly the better efficiency of extraction. In the same context there have been propositions to rotate a very compact cyclotron on a gantry. The idea has already been successful implemented, but at a lower beam energy, in the Detroit Facility for Neutron Therapy [21]. Whether this is a good solution for proton therapy is a matter for debate.

- **Variable energy cyclotron using H_2^+ sources?**

The costs for the accelerator are similar to the costs for the beam line switchyard and to the cost of one single treatment room. The accelerator is an important component in the economics of a proton facility. The reliability of the system is a major factor in the specification list of the system.

6.7 List of proton and ion facilities in the world

A regularly updated list of links to the existing charged particle therapy centres of the world can be found at our home page [15].

Table 1 shows the latest update of the statistics of patients treated with charged particle beams (taken from *Particles*, the journal edited at the Harvard cyclotron on behalf of the charged particle therapy community) [22]. This list includes patients treated with light ions and pions. Ion therapy will be discussed in Section 7. Table 2 gives a list of the centres proposing new dedicated facilities for proton or ion therapy.

6.8 Indications for proton therapy

One of the most important indications for proton therapy is the treatment of ocular melanomas. This method was developed at Harvard in Boston. The treatment of ocular melanomas was introduced in Europe for PSI in 1985 (it was actually the great success of this programme and the previous experience with pions that made it possible for PSI to start the construction of a new gantry project for treatment of deep-seated tumours). Up to now, more than 3000 patients have been treated at PSI for ocular melanomas. In Europe the method used for ocular treatment is now also applied at other places: UK (Clatterbridge), Sweden (Uppsala), France (Nice and Orsay), and Germany (Berlin).

The best known example of superior results with protons on deep-seated tumours was demonstrated at the Harvard cyclotron with treatments of tumours close to the base of the skull (chordomas and chondrosarcomas).

Well-documented clinical results were obtained at Tsukuba on liver cancer. Loma Linda is today the only dedicated hospital-based facility that has been operational for many years. LLUMC has recently shown the capability of treating about 1000 patients per year. The majority of these treatments are prostate cancers. This is becoming a true speciality of this centre. Loma Linda has clearly shown that proton therapy is feasible on the basis of commercial and scientific criteria.

There are many other possible therapies waiting to be explored. Proton therapy should be applied in all situations where conventional therapy is encountering difficulties and where a reduction in treatment morbidity is desirable (for example pediatric tumours). PSI is trying to contribute to the field with the development of compact gantries dedicated to beam scanning techniques capable of delivering proton therapy for 'inverse proton planning' in order to compete with the most advanced photon beam delivery methods in the future.

Table 1: World-wide charged particle patient totals January 2000 (from Ref. [22])

Institution	**Country**	**Type**	**Date first Rx**	**Date last Rx**	**Recent patient total**	**Date of total**
Berkeley 184	CA, USA	p	1954	1957	30	
Berkeley	CA, USA	He	1957	1992	2054	June 1991
Uppsala	Sweden	p	1957	1976	73	
Harvard	MA, USA	p	1961		8372	Dec. 1999
Dubna	Russia	p	1967	1974	84	
Moscow	Russia	p	1969		3100	Dec. 1998
Los Alamos	NM, USA	π^-	1974	1982	230	
St. Petersburg	Russia	p	1975		1029	June 1998
Berkeley	CA, USA	Heavy ion	1975	1992	433	June 1991
Chiba	Japan	p	1979		96	Oct. 1996
TRIUMF	Canada	π^-	1979	1994	367	Dec. 1993
PSI (SIN)	Switzerland	π^-	1980	1993	503	
PMRC, Tsukuba	Japan	p	1983		629	July 1999
PSI (72 MeV)	Switzerland	p	1984		3014	Dec. 1999
Dubna	Russia	p	1987		43	Dec. 1999
Uppsala	Sweden	p	1989		215	Oct. 1999
Clatterbridge	UK	p	1989		960	Dec. 1999
Loma Linda	CA, USA	p	1990		4726	Dec. 1999
Louvain-la-Neuve	Belgium	p	1991	1993	21	
Nice	France	p	1991		1350	June 1999
Orsay	France	p	1991		1522	Sept. 1999
N.A.C.	South Africa	p	1993		341	Dec. 1999
MPRI	IN, USA	p	1993		34	Dec. 1999
UCSF CNL	CA, USA	p	1994		246	Dec. 1999
HIMAC, Chiba	Japan	Heavy ion	1994		473	Sept. 1998
TRIUMF	Canada	p	1995		55	Dec. 1999
PSI (200 MeV)	Switzerland	p	1996		41	Dec. 1999
GSI Darmstadt	Germany	Heavy ion	1997		46	Dec. 1999
Berlin	Germany	p	1998		105	Dec. 1999
NCC, Kashiwa	Japan	p	1998		18	Dec. 1999
					1100	pions
					3006	ions
					26104	protons
				TOTAL	30210	All particles

Table 2: Proposed new facilities for proton and ion beam therapy, January 2000 (from Ref. [22])

Institution	**Country**	**Type**	**1st Rx**	**Comments**
INFN-LNS, Catania	Italy	p	2000	70 MeV; 1 room, fixed horiz. beam.
NPTC (Harvard)	MA, USA	p	2000	At MGH; 230 MeV cyclotron; 2 gantries + 2 horiz.
Hyogo	Japan	p, ion	2001	2 gantries; 2 horiz; 1 vert; one 45°; under construction.
NAC, Faure	South Africa	p	2001	New treatment room with beam line 30° off vertical.
Tsukuba	Japan	p	2001	270 MeV; 2 gantries; 2 fixed (research); under construction.
CGMH, Northern Taiwan	Taiwan	p	2001?	250 MeV synchrotron/230 MeV cyclotron; 3 gantries, 1 fixed.
Wakasa Bay	Japan		2002	Multipurpose accelerator; building completed mid. 1998.
Bratislava	Slovakia	p, ion	2003	72 MeV cyclotron; p; ions; +BNCT, isotope prod.
IMP, Lanzhou	China	C-Ar ion	2003	C-ion from 100 MeV/u at HIRFL expand to 900 MeV/u at CSR; clin. treat.; biol. research; no gantry; shifted patients.
Shizuoka Cancer Center	Japan		2002?	Synchrotron 230? MeV; 2 gantries; 1 horiz; funded.
Erlangen	Germany	p	2002?	4 treatment rooms, some with gantries.
CNAO, Milan & Pavia	Italy	p, ion	2004?	Synchrotron; 2 gantries; 1 fixed beam room; 1 exp. room.
Heidelberg	Germany	p, ion	2005?	
AUSTRON	Austria	p, ion	–	2 p gantry; 1 ion gantry; 1 fixed p; 1 fixed ion; 1 exp room.
Beijing	China	p	–	250 MeV synchrotron.
Central Italy	Italy	p	–	Cyclotron; 1 gantry; 1 fixed.
Clatterbridge	UK	p	–	Upgrade using booster linear accelerator to 200 MeV?
TOP project ISS Rome	Italy	p	–	70 MeV linac; expand to 200 MeV?
3 projects in Moscow	Russia	p	–	Including 320 MeV; compact, probably no gantry.
Krakow	Poland	p	–	60 MeV proton beam.
Proton Development NA Inc.	IL, USA	p	–	300 MeV protons; therapy & lithography.
PTCA, Tenet HealthSystem	USA	p	–	Several systems throughout the USA.

Close to 10 hospital-based proton therapy facilities are approved for construction or already available in the USA and Japan. There are several propositions for dedicated facilities in Europe but none seems to be starting at this time.

7 ION THERAPY

7.1 Rationale for light ion therapy

As stated in Section 3, the main advantage of ion therapy is expected from the use of the high LET character of the beam. High LET should have a positive impact on the treatment of very radio-resistant tumours and could be used to eliminate potentially surviving anoxic cells (by virtue of the low OER).

Concerning the physical selectivity, ions have excellent properties, well suited for precision therapy. This is due to the large inertial mass of the ions: multiple Coulomb scattering and range straggling effects are very much reduced compared to protons. A factor adding confusion, however, is the problem of the fractionation of the projectiles. Together with the strong variation of RBE with depth, this makes the dosimetric characterization of ion beams a difficult task.

A major practical disadvantage of this therapy is the higher magnetic rigidity of the beam by a factor of 3 compared to protons (energies up to around 400 MeV per nucleon are necessary for the treatment of deep-seated tumours). This makes the accelerator and the beam lines more bulky and therefore ion therapy more expensive than proton therapy. Owing to the high magnetic rigidity of the beam only synchrotrons are taken into consideration for the acceleration of clinical ion beams.

High LET is, on the other hand, not expected to do better in every clinical situation. What matters in the end are the differential effects between cancer cells and healthy tissue. The cell repair capability of the healthy cells and the amplification of the therapeutic ratio with the fraction number are known to be less pronounced with high LET than with low LET (high LET is for this reason usually applied with a lower number of fractions). Eventually one expects more late reactions. The use of high LET does not automatically imply, as often stated, a generic 'radiobiological advantage'. There could be disadvantages as well. Whether the use of high LET radiation is indicated or not depends on how much the therapeutic ratio improves compared with conventional therapy for a given clinical situation (type of tumour, organs at risk, oxygen content of the tumour). Ion therapy represents new radiobiological ground and the use of high LET is still in a very experimental stage. This is the risk but also the big challenge of this new type of therapy.

The conditions under which high LET radiation is expected to bring superior results under are for the treatment of slowly growing radio-resistant tumours. This concerns a limited but significant number of patients. According to estimates of the German Cancer Research Institute in Heidelberg (DKFZ) about 8000–11000 patients could benefit from proton and ion therapy in Germany alone. According to these figures this would account for the need of typically one or two ion machines and several proton machines in each large country of the Western world.

7.2 Ion beam facilities

Most of the pioneering work on ion therapy was carried out at the Bevalac at Berkeley, USA. Unfortunately, in 1992, for financial reasons, the Department of Energy withdrew its support for the project (mainly because of the high costs of running an old physics accelerator).

In Chiba, Japan, the Institute of Radiological Sciences took over the pioneering role by creating a dedicated facility for ion therapy. This rather expensive facility has two synchrotrons on top of each other. It has been in operation since 1994. The beam is delivered with the passive scattering technique through several fixed horizontal and vertical beam lines.

In Germany ion therapy was started at GSI in 1997. The most important feature of the beam delivery system developed at GSI is the very advanced beam scanning technique [23]. The raster scanning

method of GSI is done on a dedicated fixed horizontal beam line. Transverse scanning is performed by a double magnetic deflection of the beam. The shaping of the dose is achieved by adapting the speed of scanning to the beam intensity delivered by the synchrotron during a slowly extracted beam spill. The energy of the beam is varied on a pulse by pulse basis by changing the settings of the whole synchrotron after completion of the painting of a monoenergetic dose layer. The dose is shaped in all three dimensions through the delivery of many differently shaped iso-energy layers. This is probably the most advanced example of the integration of the accelerator into the beam delivery to the patient. The GSI (with ions) and the PSI (with protons) are the only places in the world where charged particle therapy is applied dynamically using scanning beams. The use of the raster scanning technology on a dedicated ion gantry has been proposed for a dedicated hospital ion facility at the DKFZ in Heidelberg.

In Japan another ion facility (dedicated to both proton and ion therapy) is being assembled near Kobe (the Hyogo facility).

In Europe there are several propositions for ion therapy: the Tera project in Italy, the Austron project in Austria, and the ion-proton facility in Heidelberg. None of these have been approved at the time of writing.

8 CONCLUSIONS

Radiotherapy represents an important instrument in the fight against cancer and is a field of continuous evolution. In the field of conventional therapy we expect to be able to observe, in the near future, significant progress using very advanced beam delivery techniques with photons (IMRT). Similar more advanced developments are also possible with charged particle beams (IMPT). The combination of the new technologies with the physical advantages of charged particles is expected to produce superior results. In this future scenario new technical developments are necessary for both sides to remain competitive. This is why we believe that beam scanning will soon become the generic beam delivery method for proton and ion beam therapy. This strategy must be considered when designing accelerator and beam delivery systems for future planned dedicated facilities.

Radiotherapy with charged particles is the field that can probably profit most from accelerator technology. In the near future the accelerator will no longer be considered a separate entity for the delivery of beam, but 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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