Potential Benefits of Proton Therapy in Clinic

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Proton therapy offers great potential in cancer treatment compared with the conventional photon therapy. The advantages of the unique physical properties of protons are a reduction of integral dose to critical structures proximal to the target area and less radiation related side effects. There are many cancer related indications that may benefit from the advantages. The challenges in proton therapy are dealing with physical uncertainties that affect the dose distribution, improving the technology to make proton therapy more efficient and proofing the clinical- and cost-effectiveness.
This critical review discusses the physical properties, beam production and delivery, cost-effectiveness and the clinical facet of protons including CNS tumours, prostate cancer, left-sided breast cancer, head and neck tumours and Hodgkin's disease.

Proton therapy uses beams of charged particles instead of photons to irradiate tumours. In 1946, the physicist dr. Robert R. Wilson proposed the medical use of protons for cancer treatment. Approximately 10 years later the first patients were treated with protons. In the following 35 years research experiments were done and the first clinical data was obtained. In 1990 the first hospital based proton facility was opened.[1]
Nowadays, there has been an agile increase in the worldwide availability of proton therapy. Because of the unique physical properties of protons, proton therapy has potential advantages in cancer treatment compared with the conventional photon therapy. Conventional radiotherapy often results in damage of normal tissue and limited prescription dose due to the tolerance dose of critical structures. Proton therapy offers a reduction of dose to normal tissue and might be a better alternative treatment for a number of cancer related indications. However, there are many discussions going on about the clinical- and cost-effectiveness of proton therapy.

Physical properties

Protons have a lot of advantages compared with photons. When protons pass through tissue they slow down losing energy by collisions with atomic electrons. As a result there is a higher probability of interaction with electrons. At the end of the particle track the loss of energy is the greatest resulting in a maximum dose deposition to the tissue. This very steep increase in deposited energy is called the Bragg peak. Behind the Bragg peak, there is a very sharp dose falloff. These properties can result in a reduction of integral dose to critical structures proximate to the tumour, called target area, and no dose a few centimetres distal to the target area compared to conventional photon therapy. This might lead to less radiation related side effects including secondary malignancies.
The Relative Biological Effectiveness (RBE) is the ratio of absorbed dose of a reference type of radiation to the absorbed dose of another type of radiation, to achieve the same radiobiological effect.[2] The RBE of protons is 1.1 versus 1.0 of photons hence protons are biologically more effective than photons. As a result, less dose is needed to produce the same effect.[2,3]

Besides the advantages of protons there are some drawbacks as well. The biggest problem is range uncertainty in treatment planning and delivery. The stopping point of protons called range is influenced by tissue density along the beam path. Even the slightest positioning error or organ motion might cause a range variation which can result in a significant dose deformation with respect to the planned dose distribution (Fig 1). The tumour volume might change over treatment due to tumour shrinkage or extension and will affect the dose distribution as well. Anatomical variation and heterogeneous regions along the beam path can lead to a decrease or increase of delivered dose compared to the planned dose distribution. Therefore it is very important to use a technology to monitor the tumour position and anatomical changes in the beam path during treatment, to make sure the actual dose delivery is similar to the planned dose distribution. This technique is called Image-Guided Radiation Therapy (IGRT). The current IGRT technique for proton therapy is stereoscopic kilo Volt (kV) x-ray, because most existing proton facilities were designed 10 years ago when modern IGRT techniques (i.e. Cone Beam Computed Tomography (CBCT))were not developed yet. With the stereoscopic kV x-ray technique it is difficult to distinguish soft tissue structures. Therefore it is not possible to monitor and rectify anatomical variations in the beam path. The ultimate IGRT technique for proton therapy would be proton CT.[3] Besides providing information about the patient geometry it would be a direct measurement of proton attenuation in the patient. The technical challenge is the poor spatial resolution of the images due to interactions between protons and electrons along the beam path causing multiple scatter. This requires higher energetic protons than currently available.[3]

Another problem of proton therapy is related to the RBE. The RBE depends on the tissue type and the amount of administered dose. The RBE determines the biological effect of protons. Variation in RBE could lead to inaccurate estimation of biological effects such as the Normal Tissue Control Probability NTCP, Tumour Control Probability TCP and radiation related side effects.[4]

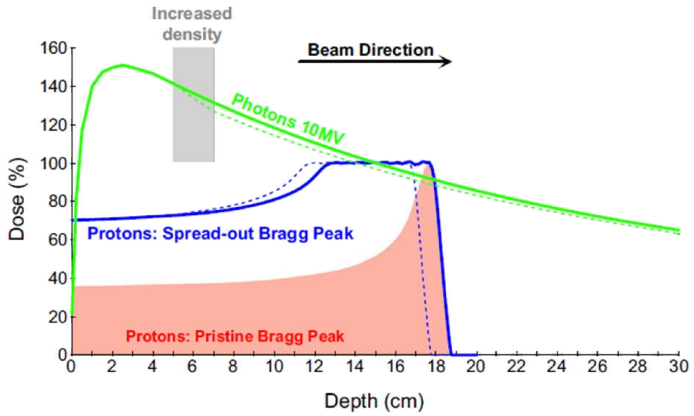

Figure 1 Range uncertainty in proton therapy. Dose-depth curves with (dashed lines) and without (solid lines) density variation along the beam path. A dense structure that shifts into the beam path during treatment affects the proton range. Protons travel less far in the tissue and the dose is deposited less deep as planned. Range uncertainty does not apply for photon therapy.[3]

Beam production and delivery

The proton energies required for clinical applications are between 70 – 250 Mega electron Volts (MeV).[5] An accelerator is used to generate a proton beam with the desired energy. Accelerators that produce reliable beams for clinical applications are cyclotrons and synchrotrons.
A cyclotrons accelerates charged particles in spiral direction by a constant Radio Frequency (RF). Protons can be accelerated up to 250MeV. A synchrotron accelerate charged particles in circular direction by a varying RF and produces a pulsed beam and the beam energy can be modified. The proton energy ranges from 270-330 MeV. The maximum energy is determined by the

diameter of the synchrotron. The disadvantage of synchrotrons over cyclotrons is that they are technologically much more complicated.[5]

There are two methods to deliver the proton beam to the target area, passive scattering and active scanning.
Passive scattering is the most frequently used method. The Bragg peak of the mono-energetic protons is very narrow so that the dose will be deposited over a very small area. To broad the Bragg peak over the entire target area and generate a so called spread out Bragg peak (SOBP), the beam is modulated by a variable degrader (Fig 2). The degrader consists of absorbers of varying thickness and every absorber attenuates the beam in a different extent. A range shifter is used to shift the SOBP to the correct depth. Subsequently the small beam is spread out laterally to obtain a homogeneous coverage of the target area by using a double scattering system. To individually adjust the dose to the patient, patient-specific apertures such as a collimator and compensator are placed into the beam to account for the patients contour and tissue heterogeneities.[2]
A disadvantage of this method is the external production of high-energetic secondary neutrons due to proton interactions with the material of the collimator and apertures in the beam line. Due to secondary neutrons there is an increased risk of developing secondary cancers. Neutrons have a high quality factor resulting in a high RBE so that even the smallest amount of dose may lead to biological damage.[6,7]

With active scanning the pencil beam is shifted across the target area by two deflecting magnets. By changing the beam energy the range of the protons can be modified to adjust the dose distribution to the target area in 3 dimensions. Energy changes can be made when a synchrotron is used or with an energy selection system when a cyclotron is used. No degraders and patient specific apertures in the beam line are needed anymore for depth modulation. The problem of external production of secondary neutrons is dissolved. [2,6,7]

Cost-effectiveness

To build and operate a proton therapy facility is significantly more expensive than a photon therapy facility.[8] Although the potential advantages of proton therapy in clinical applications in comparison with the conventional photon therapy are promising, the question is whether the clinical gain is worth the additional costs.

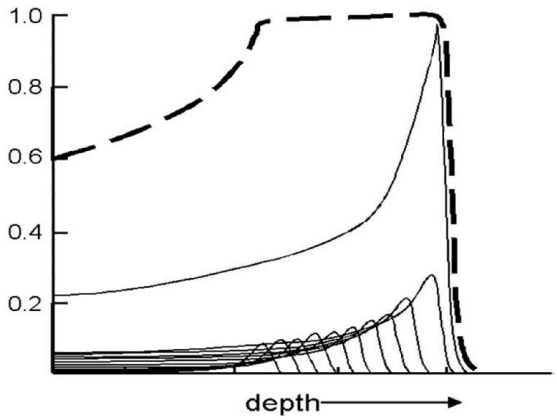

Figure 2 A number of Bragg peaks (solid lines) with different energies can be added up to produce a SOBP.[2]

The costs can be divided into construction costs and operations costs. Construction costs consist of project management during the construction, building, equipment and treatment infrastructure (e.g. imaging modalities, software and computers). Operation costs consist of personnel, utilities, servicing and business costs (e.g. repayment of loan).[8,9] The most dominant cost is the proton therapy equipment and is determined by the technology used for beam production and delivery. To produce a proton beam this includes a cyclotron or synchrotron. This is one of the main reasons that proton therapy is much more expensive than photon therapy for which a linear accelerator will be sufficient.[8] Another important reason is the

lower number of patients treated per year with proton therapy.
However, there are a couple of factors that influence the costs and make it plausible to expect a reduction in costs over the upcoming 5-10 years. They include time efficiency, market competition and development of technology.
Proton therapy is less developed compared with photon therapy and thus has a greater scope for improvements in time efficiency. Improvements can be made due to a higher workflow through experience and improved facilitation and due to automation (hard- and software) because both are not fully developed yet.
Another factor is the number of proton therapy facilities. If there is more demand for proton equipment, the acquisition costs of the equipment will be reduced due to competition on the market. Therefore it is feasible to assume that an extension of the number of facilities will reduce the costs of the equipment.
The last factor is development of technology. The delivery time of a proton beam is twice as high as the delivery time of a photon beam.[8] Subsequently, the set-up time, which is the time to set up and treat a patient when the proton beam is available, is considerably higher than for photon therapy. Because of the longer treatment time, less patients can be treated per year and this results in higher treatment costs. Due to technology improvements, the delivery time and set-up time will be shortened. Additionally patients can be treated with fewer fractions due to hypo fractionation. As a result more patients can be treated per year and the treatment costs will be reduced.[8,9,18]

Clinical applications

The advantages of proton therapy over photon therapy are lower dose to normal tissue proximal to the target area and less radiation related side effects.
Many cancer related indications may benefit from the specific characteristics of protons but especially tumours in difficult to treat regions such as the brain.[11] Treatment of central nervous system (CNS) tumours is very challenging because there are many critical structures proximity to the tumour. Specifically brain that is still in development is very sensitive to radiation. Radiation of the CNS can result in irreversible functional loss including neurocognitive impairment, changes in socio-behaviour and intelligence, hearing and ocular loss and endocrinologic deficiencies.[14] The risk for radiation induced secondary malignancies are particular relevant for children and young adults. Childhood survivors of brain tumours have an increased mortality.[11]
Proton therapy is able to reduce the volume of normal tissue that receives radiation and decreases the risk for adverse side effects and secondary malignancies. Therefore children and young adults with CNS tumours have great potential for proton therapy including medulloblastoma, glioma, craniopharyngioma, ependymoma and neuroblastoma. [12,13]

Medulloblastoma is the most common paediatric CNS tumour among children. It is a very aggressive embryonic brain tumour and the whole craniospinal axis has to be irradiated.[12,13] The risk for damage of normal tissue is severe. Merchant[13] published results about treatment of medulloblastoma with protons. He reported dose reduction in normal tissue and predicted reduced incidence of secondary malignancies and reduced intelligence quotient (IQ) loss by sophisticated models and simulations.
Beltran et all [15] studied the differences in treatment of craniopharyngioma with protons and photons. Craniopharyngioma is an intracranial aggressive tumour and includes cystic components. The challenge in treating this tumour with radiotherapy is the change in volume during treatment caused by cystic extension. The compared techniques were Intensity Modulated Radiation Therapy (IMRT) for photons and passive scattering for protons. The study shows a reduction in dose to normal tissue and critical structures using proton therapy. Nevertheless, the possible

expansion of the target area during treatment remains to be a problem . An integrated image modality such as magnetic resonance imaging (MRI) combined with adaptive radiotherapy is necessary to avoid target compromise.[13,15]

Other potential suitable indications for proton therapy are prostate cancer, left-sided breast cancer, head and neck tumours and Hodgkin's disease.[10,16,17]
Prostate cancer is associated with high risk for adverse side effects due to radiation damage to the rectal and urinary areas. This limits the delivered dose to the target area. With proton therapy the dose to the target area can be increased without exceeding the tolerance dose to critical structures.[10]
Left-sided breast cancer has plausible potential because proton therapy may decrease radiation induced cardio toxicity and pneumonitis. This is particular advantageous for patients suffering from cardiac- and lung diseases.[10]
Head and neck tumours are frequently difficult to be surgically removed because they are surrounded by multiple critical structures. These include tumours in the nasal cavity, paranasal sinuses and hypofarynx . Additionally it is often impossible to remove the tumour or only part of the tumour is removed. Larger volumes have to be irradiated to control the tumour. Radiotherapy of head and neck tumours affect critical structures such as the optic nerves, optic chiasm, temporal lobes and the salivary glands. Proton therapy might allow higher prescription dose resulting in better TCP and decreased radiation related side effects due to dose reduction in normal tissue.[10,16]
Hodgkin's disease often occurs in young adults and has a cure rate of 90%.[17] Long-term survivors have an increased risk for radiation related side effects and secondary malignancies. For this patient group proton therapy might be a better alternative than conventional photon radiotherapy.[17]

Discussion

The evidence of proton therapy in clinical use has been built on the assumption of the superior physical properties of protons and small retrospective studies rather than on evidence-based randomized controlled trials (RCT).[4,10] The major problem is the limited number of published reports with clinical outcomes of patients treated with protons. Although the sparse available data is promising and shows a reduction in dose to normal tissue, the reduction of radiation related side effects and secondary malignancies are not proved yet in clinic. Further research is necessary to demonstrate the advantages of proton therapy over photon therapy and should be based on randomized trials. Research should be focused on treatment-related uncertainties in proton range and RBE and on long-term radiation related side effects and secondary malignancies.[3] Range uncertainty are dominated by current limitations of technology. To deal with range uncertainty, IGRT techniques such as proton CT or MRI combined with adoptive radiotherapy should be further developed. This will allow an active monitoring of treatment by making online corrections and the target area can be determined with millimetre precision. [3,18]
A reduction in costs is assumed because of improved time efficiency and technology, market competition and an increase in patients treated per year. Despite the reduction in costs, the cost-effectiveness will be determined by the clinical efficacy and is still a remaining question.[8,9,10]
This is related to the current situation in The Netherlands as well. The health insurances are considerable dubious about the clinical- and cost-effectiveness of proton therapy. The lack of evidence for a clear benefit in clinic is the main reason why only one hospital has permission to build and operate a proton facility instead of the planned 4 hospitals. This is a justified decision considering the obstacles that still have to be overcome.

Conclusion

Protons have superior physical properties compared with photons. For specific patient groups and indications proton therapy has great potential. A few studies proof a reduction in dose to normal tissue and critical structures. The current clinical outcomes do not proof that proton therapy is more effective or has less adverse events and secondary malignancies than photon therapy. Subsequently, at the moment there are still too many uncertainties regarding to the actual delivered dose distribution compared with the planned dose distribution.
Until more evidence-based data is available and technology with respect to proton therapy is more mature, it is not possible to offer clinical- and cost-effective proton therapy.

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