Towards ion beam therapy based on laser plasma accelerators

Karsch, L.; Beyreuther, E.; Enghardt, W.; Gotz, M.; Masood, U.; Schramm, U.; Zeil, K.; Pawelke, J.;

Originally published:

November 2017

Acta Oncologica 56(2017)11, 1359-1366

DOI: https://doi.org/10.1080/0284186X.2017.1355111

Towards Ion Beam Therapy based on Laser Plasma Accelerators

Only few ten radiotherapy facilities worldwide provide ion beams, in spite of their physical advantage of better achievable tumour conformity of the dose compared to conventional photon beams. Since, mainly the large size and high costs hinder their wider spread, great efforts are ongoing to develop more compact ion therapy facilities.

One promising approach for smaller facilities is the acceleration of ions on micrometre scale by high intensity lasers. Laser accelerators deliver pulsed beams with a low pulse repetition rate, but a high number of ions per pulse, broad energy spectra and high divergences. A clinical use of a laser based ion beam facility requires not only a laser accelerator providing beams of therapeutic quality, but also new approaches for beam transport, dosimetric control, tumour conformal dose delivery procedure together with the knowledge of the radiobiological effectiveness of laser-driven beams.

Over the last decade research was mainly focused on protons and progress was achieved in all important challenges. Although currently the maximum proton energy is not yet high enough for patient irradiation, suggestions and solutions have been reported for compact beam transport and dose delivery procedures, respectively, as well as for precise dosimetric control. Radiobiological *in vitro* and *in vivo* studies show no indications of an altered biological effectiveness of laser-driven beams.

Laser based facilities will hardly improve the availability of ion beams for patient treatment in the next decade. Nevertheless, there are possibilities for a need of laser based therapy facilities in future.

ion, proton, laser, laser accelerator

Introduction:

Radiation therapy is an important pillar in the treatment of cancer, the second leading cause of death in the developed countries. Most patients treated with radiation therapy are irradiated with photon beams, produced as bremsstrahlung in clinical electron linear

accelerators (LINACs). Mounting these accelerators on a gantry allows the irradiation of the patient from different directions for improved dose conformity. These devices are compact (total diameter and length of about 3 m) and readily available worldwide. For instance, about 550 LINACs are operating in Germany, which is close to the recommendation of 6 units per million inhabitants [1].

Ion beams, i.e. protons and heavier ions, have physical advantages over photons for patient treatment. Ions have an energy dependent path length and deposit most of their energy at the end of their path, in the Bragg peak. Therefore, the undesired dose application to normal tissue can be reduced and the dose contour can be adjusted for better tumour conformality. Consequently, patients with an organ at risk close to the tumour and younger patients expecting a longer life span will profit most from ion irradiation. Current estimates suggest that about 14% of the radiation therapy patients can profit from ion irradiation [2], but for instance in Germany only 1% of the patients can be treated at 6 operating ion facilities. This under provision arises mainly from the large size and high cost of an ion facility necessitating a dedicated special building, whereas a LINAC fits into a medium sized radiation room.

The increased size arises from different facts: First, for the irradiation of deep seated tumours ions must have higher energy compared to the electrons used to produce conventional photons (230 MeV for protons vs. 20 MeV for electrons). To achieve those high ion energies circular accelerators in the form of cyclotrons, where the beam radius increases with beam energy during the acceleration, as well as synchrotrons, where the beam radius is constant but the magnetic field is increased during acceleration, are used for protons. For heavier ions, of which mostly carbon ions are applied clinically, only synchrotrons are used. Conventional proton cyclotrons have a diameter of about 4 m and a weight of 200 t. This can be reduced for the accelerator

itself to about 2 m and 50 t by using superconducting magnets requiring a cooling system down to a temperature of 4 K. Because of the huge size and mass, most of the conventional ion accelerators are not mounted on the gantry, like it is done for the LINACs with a length of the electron acceleration part of about 0.5 m. Therefore, an ion beam transport system is required to connect the immobile accelerator with the beam delivery unit mounted on the gantry.

Second, because of their much larger mass, compared to electrons, ions cannot be scattered and bent sufficiently in small devices. Consequently, even for proton beams the gantry has already a size of typically about 10 m (length and diameter). An isocentric gantry in clinical use for heavier ions (up to carbon) requires a diameter of about 13 m and a length of 25 m, which can be reduced by superconducting magnets to a diameter of 11 m and length of 13 m [3].

Third, protons as well as heavier ions with therapy relevant energies induce a lot of nuclear reactions, especially neutron production, requiring more effort on radiation protection than necessary for a LINAC based therapy. Accordingly, the walls of the rooms for ion accelerator, beamline and treatment are usually a few meters thick.

To overcome the limited spread of ion facilities and to treat more patients with ion beams, more compact facilities are desired. A promising approach is the use of laser plasma acceleration, which was predicted for electrons in 1979 [4] and for ions in 1985 [5]. The first experimental proof of ion acceleration was published 15 years later [6]. With the particle acceleration by laser light in principle the acceleration of ions up to the necessary maximum energy for radiation therapy application is possible on micrometre scale. However, to accelerate particles by light requires an ultra-high light-intensity, which in turn demands a high-power laser. The development of an ion therapy facility based on high intensity laser accelerators was and is the research focus of several

groups worldwide. This contribution summarizes the status established in the last decade.

The new technology and subsequent challenges

The particle acceleration process by high intensity lasers

The best understood and experimentally verified model to explain the ion acceleration process is the so-called Target-Normal-Sheath-Acceleration (TNSA). It bases on the following steps: First, an intense laser pulse is focused on the front side of a thin solid laser target. The electrically neutral atoms of the laser target are ionized by the electric field of the incoming light pulse and a plasma is generated. The electrons in this front-side plasma are accelerated dominantly in forward direction by the electromagnetic field of the laser pulse, because at sufficient high intensities the electron quiver motion in the oscillating laser field becomes fully relativistic and the Lorentz force bends the electron motion into the foil. The ions acceleration is negligible at first because their mass is more than three orders of magnitude higher than the electron mass. As the laser pulse cannot penetrate the foil, the electrons pass through the foil, leaving the target, which leads to a strong local charge imbalance. A local sheath field is formed at the foil surface, providing a quasi-static acceleration field for surface ions, several orders of magnitude higher than the electrical fields used in conventional accelerators. Ions from the back side of the laser target are finally accelerated by this electrical field. At the end, a neutral cloud consisting of different ions, either from (organic) contaminations or targeted coatings of the rear laser target surface or from the target itself, as well as electrons, is propagating perpendicular to the laser target.

Because the accelerated ions are originating from different positions on the rear laser target surface, they experience different electric field strengths over different time

durations. Finally, if the laser target is a plain foil the accelerated ions show an approximately exponentially decreasing energy spectrum up to an ion specific maximum cut-off energy. Another consequence of the acceleration process is a large laminar divergence of the ion beam (opening angles of few degrees).

The ion beam parameters can be influenced by the structure of the laser target. Examples are the usage of various types of micro structured laser targets, such as a titanium foil with small dots of a proton rich plastic (PMMA) at the backside, which can result in a proton beam with an energy width reduced to 30% (FWHM) [7], or the enhancement of the maximum ion energy by tailored target shapes like cones [8], optimizing the laser absorption process or small areas where accelerating fields are locally confined [9]. Furthermore, a beam consisting of only protons and electrons, instead of various different ions, can be obtained by substituting the foil with small frozen hydrogen droplets [10] or jets [11], resulting in a broad proton energy spectrum with superimposed narrow bands. It has to be noted, that almost all of the protons of a small frozen hydrogen droplet are accelerated allowing the control of the total number of ions accelerated by controlling the size of the droplet.

There are more sophisticated concepts to improve the acceleration process, which partly result in different beam parameters. They range from enhanced TNSA to Radiation Pressure Acceleration (RPA), where the electrons or even parts of the target en bloc are accelerated by the light pressure or scattering processes. These models predict a smaller ion beam divergence, but are much more demanding with respect to the necessary laser pulse and laser target parameters, which is the reason why a definitive experimental verification is still under investigation.

High intensity lasers

For ion acceleration a light intensity of more than 10^{19} W/cm^2 is necessary, which destroys every solid object. Therefore, the generation of a high intensity laser beam is performed by the chirped pulse amplification (CPA) method to avoid any damage of the optical elements of the laser: before amplification a laser pulse is stretched in time and enlarged in space, and following the amplification it is compressed in time again, and finally focused in space.

Main parts of a laser system are the amplifiers. An amplifier is usually a crystal pumped with pump light shortly before the laser pulse arrives, which is then amplified by the laser principle (light amplification by stimulated emission of radiation) when passing the crystal. To efficiently use of the pump energy and increase the amplification, the laser pulse usually passes the crystal several times in a short time interval. A high intensity laser consists of a number of multipass-amplifiers, which leads to the problem of the prepulse level. Prepulses can destroy the laser target before the main laser pulse arrives and therefore hinder the acceleration process. These prepulses are produced mainly by two processes spontaneous light emission of the pumped crystal (i.e. independent of an incoming laser pulse) or scattering of incoming laser light into the direction of the next amplifier, where it is amplified to a laser target damaging level.

The CPA principle together with the necessary laser output intensity as well as laser beam diagnostic and control define the size of the laser systems. Although labelled as “table-top”, because all elements are mounted on a table, the footprint of existing high-power laser systems usually occupies a size of several ten square meters. Furthermore, the repetition rate of existing high intensity laser systems designed for particle acceleration is limited to 10 Hz or less, because of thermal stability. Energy

efficient diode laser pumping of high peak power laser systems may in the near future allow for higher average power and repetition rate [12].

The steps to establish a new beam quality in clinic

Laser accelerated ion beams have different characteristics compared to the monoenergetic pencil-like beams delivered by conventional accelerators (Table 1). Before using a laser accelerator for the clinical radiation therapy five tasks have to be accomplished to fulfil clinical requirements and to minimize any unavoidable risk for the patient.

First of all, a laser accelerator has to be developed which delivers a defined number of ions within the therapeutic energy range with sufficiently stable and reproducible ion beam parameters.

Second, a beam transport and delivery system is required for cleaning the beam from undesired particles and for ensuring beam energy, beam intensity, beam direction and field size to deliver a prescribed dose to the patient.

Third, clinical application in radiation therapy demands precise dosimetric control. In clinical practice, several dosimeters are established. Most often used are ionization chambers for online monitoring, but also for absolute dose measurements. Semiconductors are used for relative dose measurements and several retrospective dosimeters, including films, thermal and optical stimulated luminescence dosimeters are used for special examinations of the system. Established dosimeters have to be investigated for compatibility with laser-driven beams, i.e. beams of short and very intense radiation pulses. If necessary new dosimeters have to be developed, which probably need more effort as adapting existing ones.

Fourth, dose delivery in clinical irradiation uses one of two procedures, pencil beam scanning or a scattering technique. Here, pencil beam scanning is technically more challenging but allows higher tumour conformity of the delivered dose which is why scanning sees an increased clinical application [13]. For pencil beam scanning the tumour volume is subdivided into several ten thousand voxels which are irradiated successively one voxel at a time with narrow monoenergetic beams of varying energy and intensity over a treatment time of few minutes. The new time structure of laser accelerated ion beams with the low pulse repetition frequency requires a new strategy for dose delivery, because the dose has to be delivered within at least the same (or possibly shorter) treatment time by a much lower number of pulses compared to conventional ion beams.

Fifth, the laser based acceleration leads to pulses with an outstandingly high pulse dose rate close to the source which may result in an altered radiobiological response. This has to be investigated first by *in vitro* studies with different tumour and normal tissue cell lines, and followed by *in vivo* studies with animal irradiations. A different radiobiological effectiveness needs also more effort to implement in the treatment planning system.

Limitations, Requirements and therapy unit designs

Ion beam parameters after the acceleration process

Over the last decade the research towards a laser based ion therapy was mainly focussed on protons, since developing suitable laser targets and accelerating ions to energies necessary for therapy is easier for protons than for heavier ions.

The highest proton energies obtained so far by laser plasma acceleration with ultra-short pulses are around 45 MeV with 1 PW class laser systems at 30 fs pulse

duration [14][15]. Based on analytical energy scaling laws confirmed with experimental data and simulation results (Fig. 1), it is expected, that a laser power of about 1 PW at medium pulse durations of about 100 fs or at shorter pulse durations of about 30 fs in combination with sophisticatedly structured laser targets is required for getting proton energies of about 230 MeV. Structured targets even resulted in quasi monoenergetic beams with energy widths in the order of 10 %. However, quasi monoenergetic beams have been generated for low energies (below 10 MeV) only. Additionally, the adjustment of proton beam parameters by laser beam and/or target parameters is very challenging and not yet established.

The achievable stability and reproducibility of laser accelerated proton beam can be derived from cell irradiations, in which many, successive beam pulses were delivered with the highest feasible repetition rate. Radiobiological *in vitro* experiments have been established by several groups in the world at fixed beam lines, using a magnetic energy selection system. An example of the currently achievable stability and reproducibility of the dose delivery by laser-driven protons is shown in fig. 2. With the rather simple transport beamlines cutting out a constant interval from the exponential proton energy spectrum a pulse-to-pulse fluctuation in proton number of ±30% (2σ) was achieved. Because of the always constant energy dependent transmission efficiency of the beamline in these experiments the dose fluctuations at the irradiation site may be a result of a change of the proton number or of the proton energy spectrum.

Transport Beamline and Gantry Design for Patient Irradiation

The transport beamline has to ensure the beam parameters (intensity, energy spectrum and field size) given by the treatment plan and beam delivery system used for patient irradiation. The smallest change from already established approaches and components

regarding beam transport and dose delivery strategy requires a processing of the laser accelerated beams to match conventional beam properties, i.e. filter out monoenergetic pencil-like beams from the divergent beam with broad energy spectrum after laser plasma acceleration. Accordingly, the first suggestion for a transport beam line with energy selection is a very compact beamline and produces a pencil-like monoenergetic beam by using four superconducting magnetic dipoles with a moveable aperture in between [17]. But, only a very small part, less than 0.1%, of the laser accelerated protons is used and transported to the irradiation site. Due to the very low efficiency and the very high level of secondary radiation resulting from dumping the large portion of unused protons, it is not suitable for a clinical facility.

More sophisticated approaches attempt to use two features of laser accelerated beams to develop a compact gantry with efficient beam delivery.

First, for patient irradiation a broad energy range, defined by position and expansion of the tumour in depth in the patient, is necessary. In conventional beam delivery systems the energy of the monoenergetic beams is changed, either by changing the accelerator setting (synchrotrons) or passing absorbing material (cyclotrons). Laser accelerators directly provide ion beams with a broad energy spectrum, which can be used for patient irradiation in the given broad energy range. This, however, requires a system for selecting broad energy beams with variable mean energy and width, and an achromatic beamline to transport these beams with energies widths up to about 20% to the irradiation site.

Second, the repetition rate of laser accelerated beam pulses is very low, which allows the use of pulsed magnets establishing the magnetic field only for parts of a millisecond. Pulsed magnets enable higher magnetic fields up to 50 T, which results in smaller beam bending radii compared to conventional magnets with a maximum

magnetic field strength of about 2 T.

There are suggestions for a transport beamline which exploit both advantages. Fig. 3 shows a gantry design for laser-driven protons, where laser target, an energy selection system and beam shaper are mounted on a gantry roughly halving the size of conventional gantry systems in both directions (length and diameter). Similar to another example with scanning option [18], it consists of three types of magnets: a solenoid for capturing the laser-accelerated divergent protons, dipoles for bending and energy selection as well as quadrupoles for beam shaping. First prototypes of each of the different pulsed magnets have already been designed, assembled and tested. In addition, a first simple beamline consisting of three pulsed magnets was recently setup and tested at a low energy proton beam.

Dosimetric Control

Different retrospective dosimeters in clinical use have been tested [19] and some were already applied within the framework of radiobiological experiments at laser accelerated beams [20]. Thermal and optical stimulated luminescence dosimeters as well as radiochromic films were found to be suitable for dose measurements at pulsed beams with pulse dose rate up to the order of 10^9 Gy/s [19].

The most important dosimeter in conventional radiation therapy is the ionization chamber, which provides an online readout in contrast to the retrospective dosimeters. Therefore, it is desirable to use an ionization chamber for laser based ion beams. Several corrections have to be taken into account for deviations from calibration conditions and to precisely measure absolute dose. Only one of them, the saturation correction, is influenced by pulse dose and pulse duration. While for conventional beams the effect of incomplete saturation is rather small and its correction is well

established, laser-driven beams result in a much larger effect, requiring proper saturation correction methods. Different theories were developed for this purpose. One method is the solution of a partial differential equation system by the recursive Euler method. Experimental data obtained with common plane-parallel therapy chambers for pulse doses up to 1 Gy are described very well [21]. A similar software expands the differential equations to 3 dimensions allowing also to consider initial recombination [22]. Another method is based on series expansion results in (more or less) handsome formulas to get an easy estimation about the saturation correction [23]. But all methods should be further verified by experiments with laser accelerated particles.

For online measurements semiconductor and scintillation detectors are in clinical use as well and have been tested for their compatibility at laser-driven beams. For example, a commercial photodiode array was tested at pulsed proton beams (energy up to 20 MeV, pulse duration of few ns) and has proven is operational reliability up to up to 10^7 protons/ns/cm^2 [24].

In conclusion, the measurements and theoretical developments indicate that the dosimetric control at a laser based therapy facility can be provided by established clinical dosimetric systems, but this has to be further verified with experiments at more progressed laser accelerators.

Dose Delivery Procedure

With laser-driven beams, the way pencil beam scanning is done at conventional accelerators would result in longer treatment times due to their very low pulse repetition rate (maximum 10 Hz). A promising approach to reduce the treatment time is to adapt the scanning procedure in such a way that clusters of several voxels are irradiated at once. These clusters can be setup by adjacent voxels in beam direction (axially) or

laterally or by a combination of both [25]. While laterally clustering requires larger beam spot size, axial clustering needs a broader energy width of the beam.

Delivery of a clinical dose has been studied for axial clustering. Supposing a typical TNSA energy spectrum from a laser accelerator and transport through the suggested gantry (Fig. 3) the number of beam pulses for patient irradiation is dependent on the number of protons accelerated by the laser [27]. For an initial proton number of about $3*10^9$ treatment plans with a sufficiently small number of pulses can be generated

for small or medium sized tumours. Pulse-to-pulse fluctuations in the initial proton number may cancel in some cases [27] but exact stability requirements need further investigation. Additionally, the laterally clustering has to be considered.

Nevertheless some requirements for a clinical application of the accelerated proton beam can be deduced: i) proton numbers in the order of 10^9 per pulse in the initial spectrum, ii) pulse repetition rate of at least 10 Hz, iii) reproducibility of few percent, and iv) need of controlled intensity modulation over at least one order of magnitude by the transport system or the source.

Radiobiological effectiveness of laser-driven particle beams

Several experiments were performed aiming to illuminate the radiobiological consequences of the high dose rate of laser accelerated ions. One of the first experiments was performed by the group of Yogo [28] using a 2 MeV proton beam filtered to an energy width of 0.66 MeV by a four permanent magnets chicane to measure the clonogenic survival of human cancer cells. The low proton energy corresponds to a penetration depth in water of about 100 μm, too shallow to allow for the application of online or retrospective offline dosimeter in parallel to cell irradiation. Instead, the dose applied to the cells was controlled by the number of pulses with the

pulse dose determined by irradiations before and after the cell irradiation.

The first in vitro study of the radiobiological effectiveness of laser-driven protons with an online monitoring of the dose delivery was performed by the Dresden based Oncooptics collaboration by Zeil et al. 2013 [29] following the concept introduced in Kraft et al. 2010 [16]. Compared to the studies by Yogo [28], this experiment resulted in a reduced overall dose uncertainty of <10 % for cell irradiation. A proton energy of about 9 MeV, i.e. with a penetration depth of about 1 mm, was applied to study the clonogenic cell survival and the induction of DNA double-strand breaks in human cancer cells after treatment with laser-driven relative to conventional proton beams. The energy selection took place by one magnetic dipole leading to an inhomogeneous dose distribution within the field which was compensated by rotation of the cell sample during irradiation.

Meanwhile some more groups performed experiments with laser accelerated protons using several human tumour [30][31][32] but also a human normal tissue cell line [33] and investigating different biological endpoints. Moreover, systematic *in vitro* experiments have also been performed with laser-driven electrons [34][35]. Additionally, a first *in vivo* experiment with laser driven electrons was performed again by the Oncooptics collaboration in Jena [36] comparing the radiation induced tumour growth delay of laser-driven electrons with conventional LINAC electrons.

Further experiments were conducted at research accelerators which can mimic the time structure of laser accelerated beams. These include *in vitro* experiments with electrons at a superconducting LINAC [37]. But also pulsed proton beams at a tandem accelerator focussed to a small spot size of 0.1 mm producing high dose rate beams have been used for cell irradiations [38] and animal studies [39].

To summarize all these studies, the investigation of the clonogenic survival as the so-called "gold-standard" in radiotherapy research indicates so far no significant difference between laser-driven and conventionally accelerated proton beams. This accordance should be verified by further *in vivo* studies with laser accelerated ions. Nowadays, the nominal proton energies of up to 40 MeV delivered by laser accelerators [15] are high enough for special small animal tumours [40], but so far no study has been published.

Discussion and Conclusion: The future of laser based ion beam therapy

Over the last ten years, progress was achieved in all of the tasks necessary to translate the laser acceleration process into a clinical facility for radiation therapy. The technology of laser accelerators was developed at such a rate that cell samples and small animals are being irradiated at fixed beam lines in the framework of radiation biology experiments. Further considerable progress is necessary to enable the conformal irradiation of large tumours in patients preferentially by rotating gantry systems. This demands a substantial improvement in beam generation, especially increasing energy but also enhancing stability and reliability of the laser-driven ion beam. Estimation, how long it will take to achieve clinical relevant energies of 230 MeV can be given by comparison to the establishment of other accelerators.

From the Livingstone chart (Fig. 4), where the maximum energy of different accelerator principles is plotted versus the year of commission of the respective accelerator, it is stated that the energy of a new accelerator technology increases on average by a factor of about 33 within 10 years almost independent from the acceleration principle. Limiting the consideration to ultra short pulse laser systems based on titanium doped sapphire operating at about 10 Hz, and considering the

maximum proton energy of 2 MeV in 2006 [7] as well as the above mentioned 45 MeV at 2013 [14], the laser plasma acceleration seems to have only a slightly lower value. Consequently, increasing the proton energy by an additional factor of 6 to the values necessary for therapy application can be expected within the next years. After achieving a sufficiently high energy a few more years will be necessary to stabilize the laser-driven beam for routine operation, which can be estimated on the basis of experience gained from existing laser systems.

Furthermore, conventional proton therapy facilities have also experienced a huge effort to compact the facilities within the last decade. The most important progress was achieved by the introduction of superconducting proton cyclotrons, which shrink the diameter of the cyclotron from about 4 m to less than 2 m connected also with a change in beam properties. For instance, the maximum current is decreased and the beam is delivered within macro pulses with duration of some μs and repetition rate about kHz. Nevertheless, one room solutions are now commercially available for protons by directly mounting the superconducting cyclotron on a gantry [43]. In contrast to protons, progress towards more compact conventional facilities for heavier ions, which require synchrotrons, is almost non-existent.

In conclusion, despite the considerable progress in the field over the last years a clinical operation of a laser based proton therapy facility can with high probability not be expected within one decade from now. A dedicated eye tumour facility which requires only protons up to about 70 MeV and a fixed beamline could be setup faster than a facility for deep-seated tumours and may be helpful for developing and establishing laser based technology. However, because of the low number of patients, an exclusive development of a laser-driven eye treatment facility itself would not significantly contribute to an improved treatment of cancer patients in total. Another

helpful possibility may be the establishment of a laser system for measurements of radiobiological effectiveness in vivo and in vitro without clinical certification (similar to [44]).

The progress of compact conventional proton accelerators over recent years leads presently to a rapidly increasing number of operating systems which may result in a saturation of the number of proton facility installations in developed countries in some years. Nevertheless, there are three possibilities for a still ongoing need of laser based therapy facilities. First, running and future clinical trials comparing the clinical benefit of ion versus photon beam therapy reveal an unexpected higher advantage of ion therapy, i.e. much more than 14% of the patients can profit from ion irradiation, which will increase the number of facilities required for saturation. Second, the reduction in costs by laser based therapy facilities compared to conventional ion therapy is so strong, that new installations in particular in the developing countries will use it. Third, heavier ions result in clinical benefit over protons for a larger number of patients, motivating the installation of cost-effective compact laser based ion therapy facilities.

The work was supported by German BMBF, grant nos. 03ZIK445, 03Z1N511 and 03Z1O511.

References

[1] Bentzen SM, Heeren G, Cottier B, et al. Towards evidence-based guidelines for radiotherapy infrastructure and staffing needs in Europe. Radiother Oncol. 2005;75(3):355-65.

[2] Glimelius B, Ask A, Bjelkengren G, et al. Number of patients potentially eligible for proton therapy, Acta Oncol. 2005;44(8):836-849.

[3] Noda K. Development of heavy-ion radiotherapy technology with HIMAC. Int J Mod Phys Conf Ser. 2016;44:1660219 10pp.

[4] Tajima T, Dawson JM. Laser electron accelerator. Phys Rev Lett. 1979;43:267–270.

[5] Mako F, Tajima T. Collective ion acceleration by a reflexing electron beam: model and scaling. Phys. Fluids. 1984;27(7):1815–1820.

[6] Snavely RA, Key MH, Hatchet SP, et al. Intense high-energy proton beams from Petawatt-laser irradiation of solids. Phys Rev Lett. 2000;85:2945-2948.

[7] Schwoerer H, Pfotenhauer S, Jäkel O, et al. Laser-plasma acceleration of quasi-monoenergetic protons from microstructured targets. Nature. 2006;439:445-448.

[8] Gaillard SA, Kluge T, Flippo KA, et al. Increased laser-accelerated proton energies via direct laser-light-pressure acceleration of electrons in microcone targets. Phys Plasma. 2011;18(5):056710 11pp.

[9] Zeil K, Metzkes J, Kluge T, et al. Robust energy enhancement of ultrashort pulse laser accelerated protons from reduced mass targets. Plasma Physics and Controlled Fusion. 2014;56:084004. https://arxiv.org/abs/1704.04311

[10] Gauthier M, Kim JB, Curry CB, et al. High-intensity laser-accelerated ion beam produced from cryogenic micro-jet target. Rev Sci Instr. 2016;87:11D827 3pp.

[11] Goede S, Roedel C, Zeil K, et al. Relativistic electron streaming instabilities modulate proton beams accelerated in laser-plasma interactions, Phys Rev. Lett. 2017;118:194801 5pp.

[12] Siebold M, Röser F, Löser M, et al. PEnELOPE - a high peak-power diode-pumped laser system for laser-plasma experiments. Proc. SPIE 8708. 2013;870805.

[13] Shiomi M, Mori S, Shinoto M, Nakayama Y, et al. Comparison of carbon-ion passive and scanning irradiation for pancreatic cancer. Radiother Oncol. 2016;119(2):326-330.

[14] Kim IJ, Pae KH, Kim CM, et al. Transition of Proton Energy Scaling Using an Ultrathin Target Irradiated by Linearly Polarized Femtosecond Laser Pulses. Phys Rev Lett. 2013;111**:**165003 5pp.

[15] Schramm U, Bussmann M, Irman A, et al. First results with the novel Petawatt laser acceleration facility in Dresden. Proc. IPAC'17, Copenhagen, Denmark MOZB1. 2017.

[16] Kraft S, Richter C, Zeil K, et al. Dose dependent biological damage of tumour cells by laser-accelerated proton beams. New J Phys. 2010;12:085003 12pp.

[17] Luo W, Fourkal E, Li J, et al. Particle selection and beam collimation system for laser-accelerated proton beam therapy. Med Phys. 2005;32(3):794-806.

[18] Masood U, Cowan T, Enghardt W, Hofmann K, et al. A light-weight compact gantry with a novel dose delivery system for broad-energetic laser-accelerated beams. Phys Med Bio. 2017;62(13):5531-5555.

[19] Karsch L, Beyreuther E, Burris-Mog T, et al. Dose rate dependence for different dosimeters and detectors: TLD, OSL, EBT films, and diamond detectors. Med Phys. 2012;39(5):2447-2455.

[20] Richter C, Karsch L, Dammene Y, et al. A dosimetric system for quantitative cell irradiation experiments with laser-accelerated protons. Phys Med Biol. 2011;56(6):1529-43.

[21] Gotz M, Karsch L, Pawelke J. A new method to determine volume recombination correction for pulsed fields at high dose-per-pulse. Submitted to Phys Med Biol.

[22] Christensen JP, Toelli H and Bassler N. A general algorithm for calculation of recombination losses in ionization chambers exposed to ion beams. Med Phys. 2016;43(10):5484-92.

[23] Karsch L, Derivation of formulas to calculate the saturation correction of ionization chambers in pulsed beams of short, nonvanishing pulse durations, Med Phys. 2016;43(11):6154-6164.

[24] Reinhardt S, Draxinger W, Schreiber J, et al. A pixel detector system for laser-accelerated ion detection. J Instr. 2013;8:P03008 13pp.

[25] Schell S, Wilkens JJ, Advanced treatment planning methods for efficient radiation therapy with laser accelerated proton and ion beams, Med Phys. 2010;37(10):5330-5340.

[26] Masood U, Bussmann M, Cowan TE, Enghardt W, et al. A compact solution for ion beam therapy with laser accelerated protons. Appl Phys B. 2014;117(1):41–52.

[27] Hofmann K, Masood U, Pawelke J, et al. A treatment planning study to assess the feasibility of laser-driven proton therapy using a compact gantry design. Med Phys. 2015;42(9):5120-5129.

[28] Yogo A, Maeda T, Hori T, et al. Measurement of relative biological effectiveness of protons in human cancer cells using a laser driven quasi-monoenergetic proton beamline. Appl Phys Lett. 2011;98(5):053701 3pp.

[29] Zeil K, Baumann M, Beyreuther E, Burris-Mog T, et al. Dose-controlled irradiation of cancer cells with laser accelerated proton pulses. Appl Phys B. 2013;110:437-444.

[30] Bin J, Allinger K, Assmann W, Dollinger G, et al. A laser-driven nanosecond proton source for radiobiological studies. Appl Phys Lett. 2012;101(24):243701 4pp.

[31] Doria D, Kakolee KF, Kar S, Litt SK, et al. Biological effectiveness on live cells of laser driven protons at dose rates exceeding 10^9 Gy/s. AIP Adv. 2012;2:011209

[32] Pommarel L, Vauzour B, Mégnin-Chanet F, et al. Spectral and spatial shaping of a laser-produced ion beam for radiation-biology experiments. Phys Rev Acc Beams. 2017;20(3):032801 10pp.

[33] Manti L, Perozziello FM, Borghesi M, et al. The radiobiology of laser-driven particle beams: focus on sub-lethal responses of normal human cells. J Instr. 2017;12(03):C03084 13pp.

[34] Rigaud O, Fortunel NO, Vaigot P, Cadio E, et al. Exploring ultrashort high-energy electron-induced damage in human carcinoma cells. Cell Death Disease 2010;1(9):e73 3pp.

[35] Laschinsky L, Baumann M, Beyreuther E, et al. Radiobiological Effectiveness of Laser Accelerated Electrons in Comparison to Electron Beams From a Conventional Linear Accelerator, Radiat Res. 2012;53(3):395-403.

[36] Oppelt M, Baumann M, Bergmann E, Beyreuther E, et al. Comparison study of in vivo dose response to laser-driven versus conventional electron beam. Rad Env Biophys. 2015;54:155-166.

[37] Beyreuther E, Karsch L, Laschinsky L, et al.. Radiobiological response to ultra-short pulsed megavoltage electron beams of ultra-high pulse dose rate. Int J Rad Bio. 2015;91(8):643-652.

[38] Auer S, Hable V, Greubel C, Drexler GA, et al. Survival of tumor cells after proton irradiation with ultra-high dose rates. Radiat Oncol. 2011;6:139 8pp.

[39] Zlobinskaya O, Siebenwirth, Greubel C, et al, The Effects of Ultra-High Dose Rate Proton Irradiation on Growth Delay in the Treatment of Human Tumor Xenografts in Nude Mice, Rad Research. 2014;181(2):177-183.

[40] Brüchner K, Beyreuther E, Baumann M, et al. Establishment of a small animal tumour model for in vivo studies with low energy laser accelerated particles. Radiat Onc. 2014;9(1):57 9pp.

[41] http://www.ischebeck.net/media/Accelerator%20Physics/Advanced%20Accelerator%20Concepts/Livingston%20Plot/Livingston%20Plot%201.png at 12th of april 2017.

[42] Chao A, Davidson R, Dragt A et al. 2001 Snowmass Accelerator R&D Report. Proceedings of the Snowmass 2001 Conference, eConf C010630, SLAC-R-599.

[43] Contreras J, Zhao Z, Perkins S, Sun B, et al. The world's first single-room proton therapy facility: Two-year experience. Prac Rad Onc. 2017;7(1):e71-e76.

[44] Dahle TJ, Rykkelid AM, Stokkevag CH, et al. Monte Carlo simulations of a low energy proton beamline for radiobiological experiments. Acta Oncol. 2017;56(6):779-86.

Figure 1. Expected scaling (lines) of achievable proton energy in dependence of laser power and laser pulse duration. Laser systems with short laser pulse duration are designed for a repetition rate of about ten shots per second (red points) and long pulse laser systems for only about 1 pulse per hour (black points). Blue points connected by a line to another point are taken from the same laser system with a structured target instead of a foil. Additionally, the influence of thickness for foils used as laser target is shown by the red solid (2 μm) and dashed (5 μm) line. Adapted from [15].

Figure 2. Typical fluctuation of the pulse dose of successive pulses during cell irradiation with laser accelerated protons, the solid line represents the mean value, the dashed lines the width of 2σ; adapted from [16].

Figure 3. Sophisticated gantry design based on pulsed magnets, the proton energy is coded by color; adapted from [26].

Figure 4. Livingstone chart showing the achieved energy for different accelerators in dependence of the year. With courtesy to R. Ischebeck [41], who adapted it from [42].

Table 1. Comparison of typical beam parameters of laser accelerator and cyclotron as an example of conventional clinical ion accelerators. With cyclotrons an additional beam time structure is superimposed to the given micro pulse structure.

	Laser accelerator	Proton cyclotron
Energy width	100 % (i.e. 0-E_{max})	0.1%
Pulse Duration	1 ps	2 ns
Repetition Rate	max 10 Hz	100 MHz
Peak dose rate	10^{11} Gy/s	10^{3} Gy/s

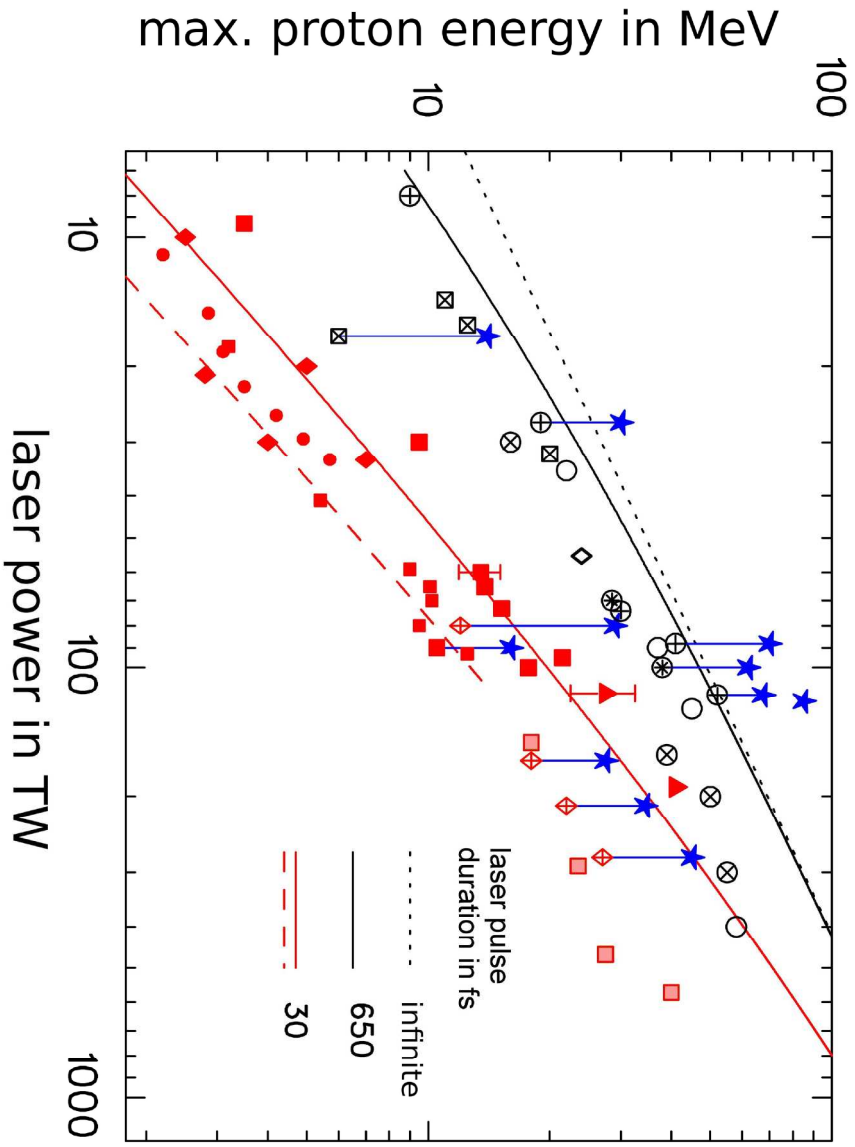

Figure 1. Expected scaling (lines) of achievable proton energy in dependence of laser power and laser pulse duration. Laser systems with short laser pulse duration are designed for a repetition rate of about ten shots per second (red points) and long pulse laser systems for only about 1 pulse per hour (black points). Blue points connected by a line to another point are taken from the same laser system with a structured target instead of a foil. Additionally, the influence of thickness for foils used as laser target is shown by the red solid (2 µm) and dashed (5 µm) line. Adapted from [15].

193x261mm (300 x 300 DPI)

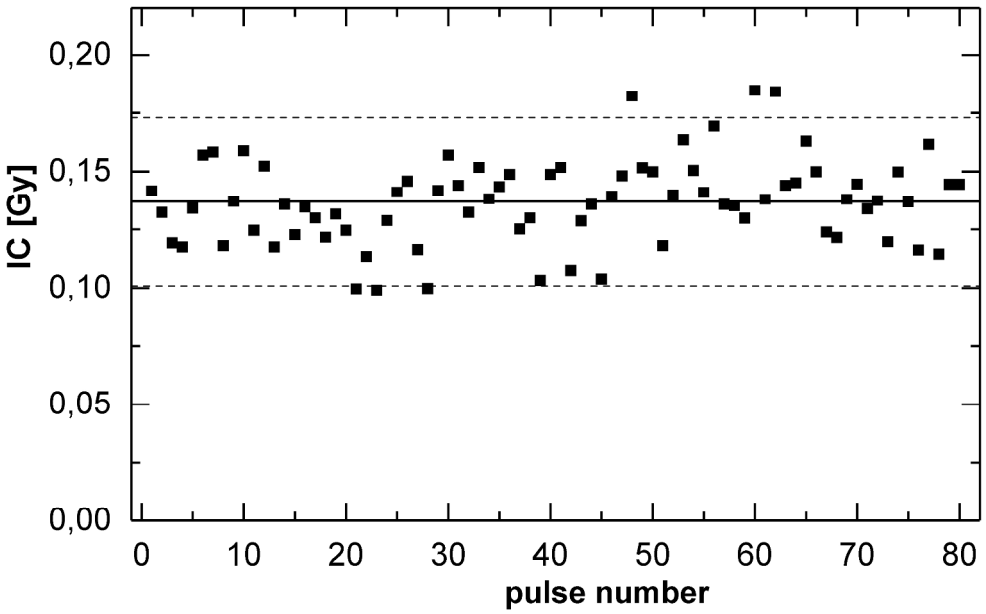

Figure 2. Typical fluctuation of the pulse dose of successive pulses during cell irradiation with laser accelerated protons, the solid line represents the mean value, the dashed lines the width of 2σ; adapted from [16].

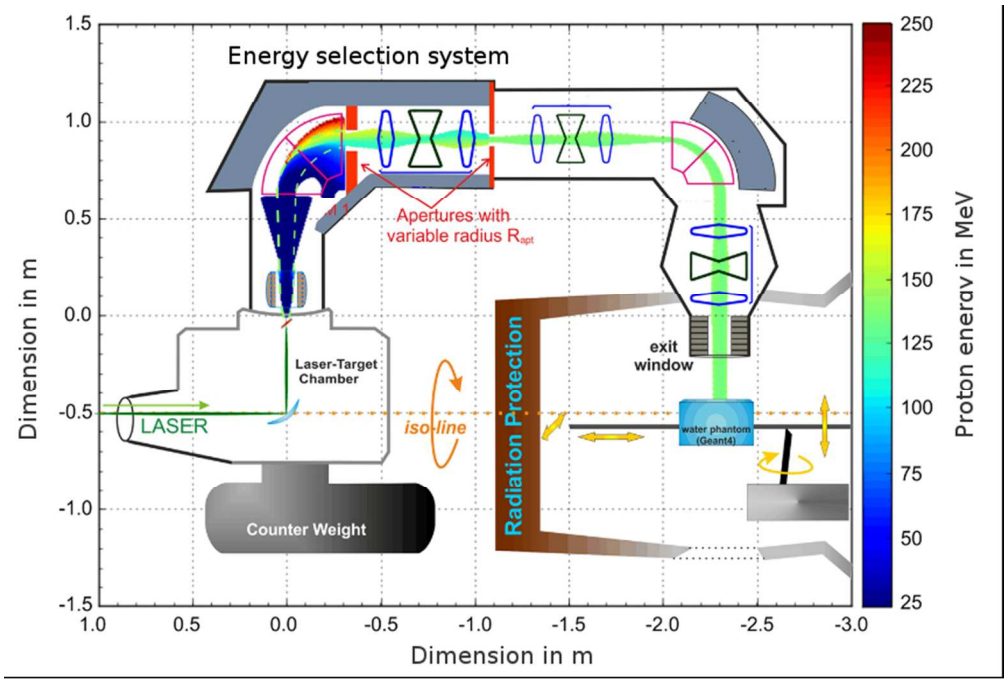

Figure 3. Sophisticated gantry design based on pulsed magnets, the proton energy is coded by color; adapted from [26].

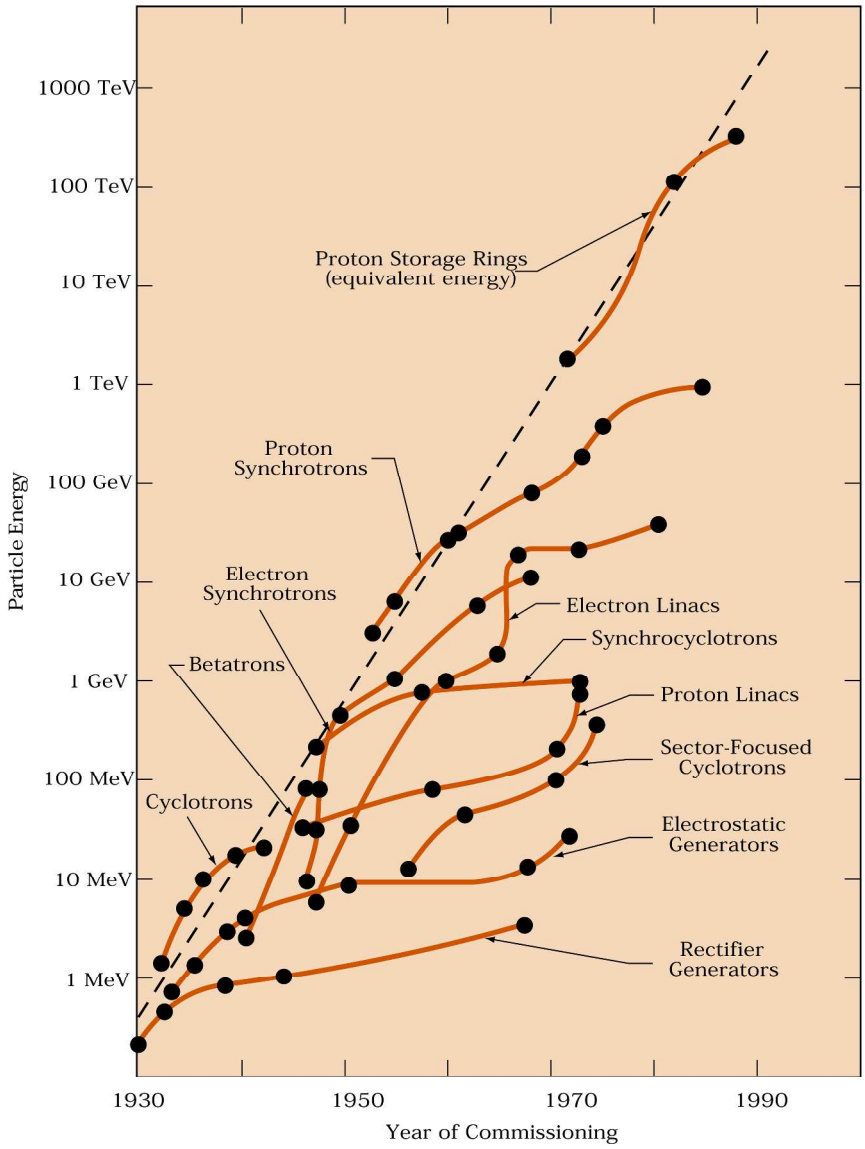

Figure 4. Livingstone chart showing the achieved energy for different accelerators in dependence of the year. With courtesy to R. Ischebeck [41], who adapted it from [42].