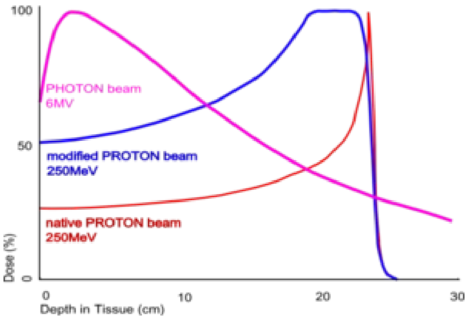
Proton therapy

Proton therapy is a type of radiotherapy developed for the treatment of oncological diseases. The main advantage of proton therapy should be better targeting of the transmitted energy to the tumor, less damage to the surrounding tissue and thus less side effects than with conventional radiotherapy. The corpuscular nature of protons, unlike photons, causes the protons to transmit relatively little energy to the tissues in front of the tumor and, after transferring the maximum of their energy to the target site (Bragg's peak), they practically stop. This should allow the use of a larger dose of radiation and increase the likelihood of tumor destruction. These benefits should be greatest when irradiating tumors near sensitive structures (tumors of the brain, neck, eyes, pancreas, liver, or prostate). The extent to which proton therapy actually meets these expectations is still the subject of research; the results so far are controversial.

Proton production requires a cyclotron or synchrotron and other very expensive equipment. Since Bragg's peak is only a few millimeters wide, the protons need to be scattered to cover the entire deposit. This is achieved by means of aids (scattering filters, modulation disks, compensators), which are also very expensive. The first experiments with proton therapy began in the 1950s, and more extensive research did not begin until the turn of the 20th and 21st centuries.

Physical nature



Bragg's peak is indicated by the red curve for the tumor at a depth of 25 cm. The pink curve indicates the irradiance distribution under conventional radiation

Proton radiation is a designation of radiation caused by a stream of protons, so it is corpuscular radiation. Protons are positively charged particles with a charge equal to +1 e and have a non-zero rest mass. Due to their physical properties, the proton beam is in some cases more advantageous than conventional photon radiotherapy. The source of protons is hydrogen, the source of the proton beam is the particle accelerator. The bundle has almost no lateral scattering and can be very precisely targeted and adapted to the shape of the tumor. The penetration of the beam varies between α and β radiation. Upon entering the tissue and passing through, the accelerated protons transfer only a small amount of their energy, about 30%. Through nuclear reactions and collisions with nuclei and atomic electrons, protons lose speed and their ionizing effects intensify. The maximum radiation dose is passed to the tissue just before the end of the range in the area of the so-called **Bragg peak**, where the tissue absorbs approximately 70% of the beam energy. The range of the beam, ie the depth of the Bragg peak, is precisely determined by the input energy of the protons, which can be regulated, depending on the depth of the tumor deposit (up to 30 cm). After all the energy is released, the particles stop and do not continue in flight, so the tissues behind the tumor are not damaged by radiation.

By proton beam we mean a set of charged particles moving in close orbits, which has bounded transverse dimensions. For its preparation, two types of accelerators are used in proton therapy - cyclotron and synchocyclotron. Their task is to increase the kinetic energy of charged particles to the required level and unify their paths to create a single beam. These are circular (cyclic) accelerators. Compared to a linear accelerator, it is possible to use a lower accelerating voltage. The principle of particle acceleration in a cyclotron is based on the circulation of particles in circular orbits - the particle thus gains much more energy than would be allocated to it in a single linear flight through the tube. Proton energy ranges from 70 to 230 MeV. In accelerator devices, it is adjustable for different types of tumors, for example, in an eye tumor, a proton energy of approximately 70 MeV is sufficient. If the accelerator is able to give the particle energy around 300 MeV, it can also be used for proton tomography.

The stream of protons passing through the tissue causes direct ionization and excitation of tissue molecules and atoms. This ionization damages the DNA molecules, either directly or indirectly (ionization creates free radicals and they can react with the DNA molecules and cause damage). Cells have repair mechanisms that are able to repair the resulting DNA damage. In tumor cells, these mechanisms are disrupted and the tumor cells do not have sufficient DNA repair capacity. This makes the tumor cells more sensitive to radiation. From this it can be concluded that the aim of the therapy is to cause sufficient damage to the DNA of the tumor cells so that they disappear or stop dividing. This effect is not necessarily achieved by a single irradiation, but the damage may accumulate due to the reduced repair capacity of the tumor cells.

Technical design

The proton irradiator is a relatively expensive and complex device. Its development is closely linked to the development of cyclotrons, which are the most common way of creating an accelerated proton beam for irradiation.

Most modern devices today consist of three basic parts:

- **Cyclotron**
- Particle transport and energy modulation system

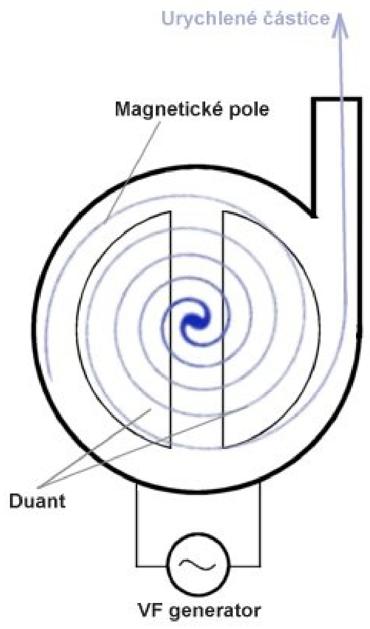
- Nozzle

The proton irradiator itself is complemented by technical solutions of individual proton centers. The following in particular play a very important role:

- Diagnostic devices (eg CT, MRI)
- Irradiation room

Cyclotron

The cyclotron is a cyclic high-frequency accelerator of charged particles (it does not accelerate eg neutrons, because they have no charge). It contains two hollow semicircular electrodes - duants, a strong electromagnet and a source of high-frequency voltage. The duants turn the holes against each other, but they have space between them. Particles (in our case protons) are fired into this space, which are accelerated by a high-frequency electric field (voltage 10kV - 1000kV [1]) until they enter the duant. Duants act like Faraday cages, so they are not exposed to an electric field on the particles. Only the magnetic field, which is oriented perpendicular to the direction of their movement, acts on them. The magnetic field curves the movement of particles - it causes a circular curvature. In the cavities of the duants, the particles are not accelerated, they are only directed. The movement of protons is accelerated only in the space between the duants. The particles cycle through the system duant 1 - gap between duants - duant 2 - gap, etc. Over time, they increase in speed and the radius of the path increases. When the maximum speed is reached, the particles reach the edge of the cyclotron, from where they are directed by special deflection magnets into the transport system of the proton irradiator. The proton beam can reach a kinetic energy of up to 230 MeV at maximum velocity [2]. The velocity and energy of the particle beam are constant before entering the transport system.



Scheme of the cyclotron

Particle transport and energy modulation system

Proton transport takes place in a vacuum tube, in which these particles are assisted by electromagnets, which serve both to focus the beam and to bend it towards the therapy room. Since the cyclotron also produces particles with other than the required energy, beam modulation is required, which in newer devices is precisely adjusted by the magnetic field of the coils on the path through the vacuum tube and older types use rotary modulators (mechanical separation) to prevent protons from moving at other than the given speed.

Nozzle

The nozzle is a very complex device that stands at the very end of the proton beam radiation process. Since the tumors that are the subject of proton radiation treatment have a certain volume and usually irregular shape, the principle of proton radiation had to be modified. For comprehensive tumor coverage, the bundle needs to be extended in two directions - laterally and distally, with irradiation performed from multiple angles. The proton centers are equipped with universal nozzles, which must include a fixed scattering filter and a secondary scattering filter, which take care of the scattering of the beams. There must also be a modulation disk, which is responsible for splitting the beams into certain energy intervals in order to hit the tumor in its entire depth. Other parts that are used for correct radiation are scanning magnets, compensator and aperture. There are currently two types of these devices, namely passive beam scattering nozzles and active scanning nozzles.

Irradiation room

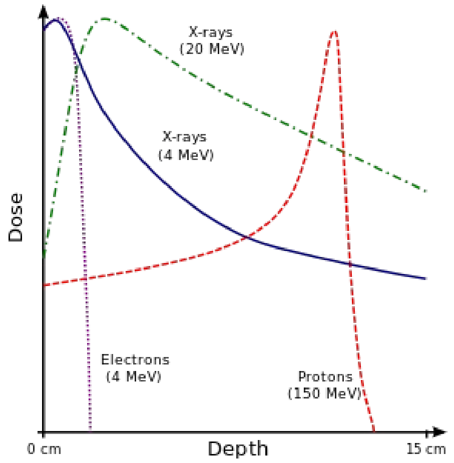
The nozzles are located in rooms - irradiation rooms. There are two types of irradiation facilities most often - with fixed beam (Fixed beam treatment rooms) and with moving beam (Gantry treatment rooms) [1]. In a moving beam irradiation room, the tumor is irradiated with moving nozzles from several angles. The proton beams intersect at an isocentric point oriented at the tumor site. Fixed beam irradiation facilities have the nozzle firmly anchored, only the patient's position is modulated. A special type of irradiation room is, for example, an irradiation room for eye tumors. The patient has his head fixed in a chair and the movements of the nozzle are synchronized with the gentle movements of the eyeball.

Indication

The use of proton therapy is tested mainly in tumors that are located near sensitive structures. So far, proton therapy is considered the most appropriate for many childhood tumors, but according to some recent studies, it does not bring therapeutic benefits over standard approaches. Furthermore, proton therapy is recommended in the treatment of ocular melanomas, chondromas and chondrosarcomas. Promising results have been published for many other tumor types, but are based on studies with small numbers of patients.

Comparison with conventional irradiation

Proton radiation and conventional radiotherapy differ in the effectiveness of targeting a given place in the human body. In general, the greatest possible dose of radiation is required to destroy cells in the shortest possible time. The maximum radiation dose that can be used in a particular case depends on the possibility of damage to the surrounding healthy tissue.

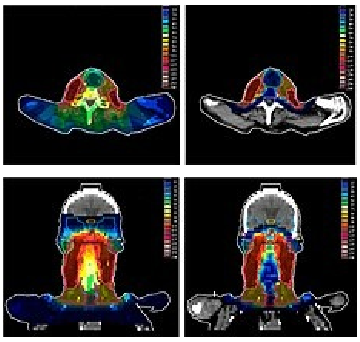


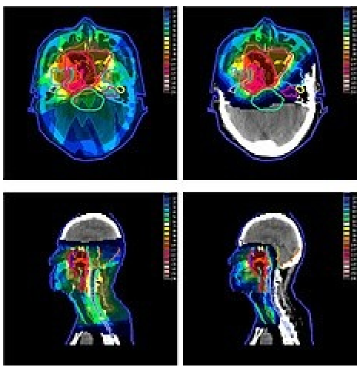
Comparison of the curves of passage of individual types of radiation through tissues depending on the depth

Conventional radiotherapy transmits the largest dose of radiation as it enters the tissue. In the targeted area, the dose is then medium and a smaller dose is passed on. It could be said that the dose decreases steadily from the source. Irradiation of healthy tissues results in side effects of the treatment. These affect the overall condition of the body, quality of life and thus the speed of healing.

In proton therapy, about 20-30% of the energy is transferred to the tissue and 70-80% [1] of energy is delivered to the target area. Targeting is possible with millimeter accuracy. The tissue behind the target area is irradiated very little. The design of the irradiators and the planning of the therapy make it possible to irradiate even intricately shaped areas with high precision.

Based on the above, it can be assumed that in proton therapy, it is possible to deliver several times higher energy to the target area than is possible using conventional irradiation methods. The radiation exposure of the surrounding tissues is relatively low. This should be advantageous especially in cases where the target area is close to tissues very sensitive to radiation (gastrointestinal and urinary tract mucosa, lymphatic tissue, bone marrow, gonads, tissues of the developing organism of children). However, strong data are currently lacking to confirm this assumption, and some authors point out that due to the different nature of radiation, experience with photonic therapy cannot be uncritically based on the estimation of proton radiation effects.


Comparison of radiation dose with conventional (left) and proton (right) radiotherapy(1)


Comparison of radiation dose of conventional (left) and proton (right) radiotherapy (2)

Development of the field

Proton therapy is currently considered a novelty in the treatment of cancer, however, the idea of using protons for therapeutic use, said the American physicist Robert R. Wilson, Ph.D in 1946, when he participated in the construction of the Harvard Cyclotron Laboratory).

In 1948, the Berkeley Radiation Laboratory conducted an extensive study of protons, and confirmed R. Wilson's assumptions. A few years later - in 1954, protons were first used to treat patients. In this laboratory, protons reached a kinetic energy of 100 MeV. Successes were repeated in 1958 in patients in Uppsala, Sweden - protons could reach a kinetic energy of 185 MeV, Harvard cyclotron did not treat the first patient until 1961. Although this cyclotron was put into operation in 1949 and should be able to accelerate protons so much, that their kinetic energy was to reach up to 160 MeV, however, due to technical difficulties it often reached only 95 - 110 MeV. The cyclotron did not reach full functionality until 6 years later.

However, treatment in physics laboratories was limited to a few places on the body because accelerators were not primarily built to treat patients. The particles did not have enough energy to cure tumors that were deeper in the body. During the 1970s, therefore, research focused on the development of more advanced cyclotrons, which was greatly aided by the assembly of more advanced computers in the late 1970s. Much of the technology that is now considered a standard part of proton therapy originated between 1970 and 1990.

In 1990, the first accelerator, located directly in the hospital, was opened at Loma Linda University, California, to improve patient care.

Thus, the differences in what tumors the center treats are mainly due to how much the cyclotron is able to accelerate the protons (increase their kinetic energy). Protons with lower kinetic energy are not able to penetrate so deep into the tissues, so they can only be used to treat tumors that are closer to the body surface (such as eye tumors).

Europe

One of the first centers built in Europe was the Paul Scherrer Institute in Switzerland, opened in 1984, however, it specialized only in eye tumors. In 1991, the Center de Protontherapy de l‘Institute Curie was opened in Orsay, which treats patients with various types of cancer. After the year 2000, the number of proton centers increased dramatically, this is related to the increase in the number of private companies engaged in the development of new cyclotrons. Until now, research has been funded mainly from state or university money.

Centers in Europe	Maximum achievable kinetic energy (MeV)	what heals	Year of origin	Country	Web
The Clatterbridge Cancer Centre	62	Eye tumors only	1989	Great Britain	http://www.ccotrust.nhs.uk
Centre de protonthérapie de l'Institut Curie	235	Tumors of the eyes, head and some tumors of the spine. There are also some types of tumors of the chest and abdomen in pediatric patients.	1991	France	https://curie.fr/liste/centre-de-protontherapie
Centre Antoine Lacassagne	63	Eye tumors only	1991	France	http://www.centreantoinelacassagne.org/
Paul Scherrer Institut	250	Tumors of the eyes, head and some tumors of the spine. There are also some types of tumors of the chest and abdomen in pediatric patients.	1984	Switzerland	https://www.psi.ch/protontherapy/
Instytut Fizyki Jądrowej PAN	60	Eyeball tumors	2009	Poland	https://www.ifj.edu.pl/ccb/radioterapia/
Rinecker Proton Therapy Center	250	Tumors of the lungs, liver, esophagus, pharynx, head, eyes, pancreas, prostate, gynecological tumors, bone tumors	2009	Germany	https://www.rptc.de/de/
ISL	250	Eye tumors	1998	Germany	http://www.helmholtz-berlin.de/isl
Westdeutsches Protonentherapiezentrum Essen	230	Tumors of the head, spine and pelvic area	2013	Germany	https://www.wpe-uk.de
Proton Therapy Centre Prague	230	Tumors lying in the area of the spine and in the area of the cranial base, tumors of the eye, prostate, head and neck, lungs	2012	Czech Republic	https://www.ptc.cz/cs/

Planned centers

It is currently planned to build another 12 proton centers in Europe for clinical use. The activities of these centers are coordinated by the Proton Therapy Cooperative Group, which recommends building one proton center for the needs of approximately 10 million inhabitants. One new center should be established in: Austria, Germany, Russia, Italy, Poland, Sweden, France, Slovakia and four centers are planned in the Netherlands.

Costs

Proton therapy, unlike traditional forms of irradiation, uses a stream of protons. Although it uses the same principle of beam production as the conventional method, in proton therapy, the energy distribution of protons can be directed and stored in tissues in a three-dimensional pattern from each beam used. Therefore, the cost of proton therapy is about 2.4 times higher than with the photon method. Specific figures are derived from the region, appliances and health insurance companies. The price increase arises mainly with the purchase of all required devices, such as cyclotron, the price of which is around 2 billion Czech crowns. One-patient care after treatment costs US $ 34,000. Compared to health care after another cancer treatment, it's almost half as much, as it costs an average of $ 16,000.

Links

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