Motivation

Cancer is the second most frequent cause for disease in the developed countries. Every year, more than 1 million people in the European Union are diagnosed of having cancer. A general cure of cancer is not in sight because the term cancer stands for a large variety of diseases that can be characterised by an uncontrolled cell growth. Normally, cell growth is regulated by a number of specific genes that stop cellular growth after an organ has reached its normal size. Only a few cells in our body show permanent cell division like the stem cells of the different blood forming organs and skin cells as well as mucosa cells in the intestines. Most of the other cells in our body are not permanently dividing and some of them - as for instance the brain - stop dividing completely.

However, if the balance of the genetic growth regulations is impaired in a single cell by a genetic mutation and if this cell is not eliminated, infinite tissue growth will result from this single cell and tumor growth starts.

Figure 1: Distribution of the more than one million new cancer patients in Europe: Local disease (red fraction) are patients with only one well-defined tumor in the beginning. Generalized i.e. more than one tumor are given in blue. Nearly 50% of the patients yielded a 5 year tumor free survival by the different treatment modalities but 18% of patients with local desease in the beginning cannot be curied. These are the candidates for particle therapy.
Most tumors originate from such a single mutated cell. In contrast to a bacterial infection, when foreign cells invade the body, tumor cells are not foreign cells and are therefore almost indistinguishable from other cells of the body except for the fact, that one of the growth regulating genes, that are called oncogenes, is out of control.

There are also oncogenes in any normal cell but usually, their function is strictly controlled. Although the knowledge on the oncogenes and their regulation has dramatically increased in the last decades it is impossible - presently and probably in the next future - to use molecular therapy i.e. gene therapy for curing cancer on a molecular scale. Up to now, macroscopic treatments like surgery, irradiation and chemotherapy are successfully applied yielding a cure rate of mostly 50 %, i.e. a disease-free survival of at least five years after treatment (Fig. 1)

Surgery is the most efficient way to remove malignant tissue. But radiation alone and in combination with surgery improves the cure rate to about 40%. For a generalised disease, where the cancer has spread over a larger part of the body, a final cure is much less likely. But also in the fraction of localised tumors, 20% of all patients cannot be cured because the tumor cannot be resected completely by surgery nor can it - in conventional therapy - be treated with sufficiently high radiation doses. In principle, any tissue can be destroyed by radiation if only the applied dose is high enough. In practice, radiation therapy is limited by the radiation tolerance of the normal tissue surrounding the tumor. Consequently, the precision of dose delivery is the key of success for therapy: the more the dose is conformed and limited to the target volume and the more the normal tissue around can be spared, the higher can be the dose applied to the tumor and the more likely will be the success of the treatment (Wambersie 1998).

**Dose Delivery**

In conventional radiotherapy, dose delivery is limited by the physical parameters of the depth dose distribution and the scattering of the beam when penetrating a thick layer like the human body. For low energy x-rays the dose decreases exponentially with depth. For higher energies as for Cobalt gamma rays a build up effect shifts the maximum dose below the skin (fig. 2). For high energetic Bremsstrahlung finally the maximum dose is located 3 cm below the skin and followed by a slowly decreasing exponential curve, that allows a higher dose to deep setaeed tumors. Consequently, the trend in conventional radiotherapy with electromagnetic radiation went towards higher energies because of better depth dose profiles and reduced scattering.
Presently, sophisticated beam delivery methods are developed where a fine beam of high-energy Bremsstrahlung is delivered in an intensity-controlled way and is restricted to the target volume by a multileaf collimator. If many fields of such a beam are delivered to the target volume from many i.e. 6 to 10 directions, a very conform dose can be applied even to tumors of complex shape. However, the intensity-modulated radiation therapy with photons (IMRT) can only distribute the unwanted dose over a larger area of normal tissue but cannot increase the ratio of the total dose given to the tumor compared to that applied to the normal tissue.

**Ion Beam Therapy**

The transition from electromagnetic radiation to heavy particles like protons or heavier ions like carbon is the next step to improve the physical properties for an external radiotherapy (Kraft 2000).

The main differences between photons and particle beams are the depth dose profiles and the increased radiobiological efficiency (RBE). Particle beams show an inverse dose profile compared to photons: the dose is increasing with penetration depth up to a maximum value.
(Bragg peak) at the end of the range (fig. 2). Normally, the tumor and the target volume are much larger than the unmodified Bragg peak and the beam has to be adjusted to the target volume.

In the beginning of particle therapy, the size of the treated field was modulated in longitudinal and lateral direction by means of collimators, compensators and range modulators. Using these passive systems, the target volume can be shaped according to the tumor volume in such a way that the tumor is completely covered by the high dose area. But a perfect congruence between irradiated volume and tumor cannot be reached with passive beam shaping systems and frequently a large fraction of normal tissue is contained in the high-dose region causing lateron side effects. In order to improve the situation a novel irradiation technique by active beam shaping has been introduced for protons at PSI, Villigen, and for carbon at GSI, Darmstadt.

![Diagram](image)

Fig. 3: Principle of the 3d conformal beam delivery. The target volume is dissected into layers of equal particle range. These layers are covered with a net of pixels for each of which the intensity has been calculated before. The beam is switched from one point to the next after the precalculated number of particles has been reached. Together with a shift in depth, which is done by energy variation, a 3-dimensional target volume can be filled with high precision.

Ions are charged particles, and can thus be easily deflected by magnetic fields. Consequently, the principles of intensity-modulation can be reached by beam scanning using two fast driven electromagnets with fields perpendicular to each other and to the beam. This is the same technique as used in every TV-set where an electron beam is scanned over the screen and the intensity is modulated for each spot (Fig. 3). However, in the “ion TV” a third dimension is
introduced by changing the particle energy and irradiating a target volume layer by layer. Using this technique, a target volume of any shape can be irradiated within a precision of a few millimetres.

Using intensity-modulated delivery for particle beams an optimum conformity of the applied dose to the target volume can be reached. In fig. 4, a treatment plan of 9-photon fields is compared to a 2-field carbon therapy both using intensity-modulated techniques.

![Fig. 4: Treatment plan with 2 heavy ion fields](image1)  ![Treatment plan with 9 photon fields IMRT](image2)

The carbon plan has less dose in the normal tissue outside the target volume and steeper dose gradients to critical structures such as the brain stem. This is due to the smaller lateral scattering of carbon beams and - most important - due to the inversed dose profile i.e. the increase of dose with penetration depth into the body up to a sharp maximum at the end of the particle range.

**Patient Positioning and Quality Assurance**

This high precision of particle dose delivery has to be paralleled along with the same precision in patient positioning. In stereotactic treatment of patients with conventional therapy, patient fixation techniques have been developed that allow a precision of a millimetre in the head region and a few millimetres along the back bone and in the pelvic region., which are areas of no or negligible internal motion. Consequently these areas are the first indications for particle treatments up to now, but it seems to be possible to adapt beam scanning to moving organs.
Another important problem is the control system. The actual delivery has to be monitored in each treatment section and compared to the planned beam delivery. For this, two different and complementary methods have been developed: position-sensitive transmission detectors installed directly in front of the patient and gamma cameras as monitors for the positron decay that occurs inside the patient.

From high-energy nuclear physics the technology of position-sensitive detectors has been adapted for a fast control system for therapy. At GSI, for instance, two systems of a wire chamber combined with an ionisation chamber measure the beam intensity and the centre of the beam 6,000 times per second and compares the measurement to the requested data. In case of disagreement beyond a small tolerance limit, the beam is cut off within less than half a millisecond. This fast control system is the basis for a safe operation of the beam in a medical treatment.

Fig. 5: Comparison of planned dose (top) with expected (middle) and measured (bottom) positron activity. This comparison shows that no tissue in the critical regions like brainstem is affected.
The particle distribution inside the patient can be monitored in addition by means of PET techniques: during the passage of the primary carbon beam a small amount of radioactivity is produced by nuclear reactions. From this activity, the positron emitting isotopes like $^{10}$C and $^{11}$C are of special interest because they have almost the same range as the primary beam and can be monitored via the positron decay over two coincident gamma quanta. With this novel technique the position and range of the beam can be controlled inside the patient without applying any additional dose.

**Radiobiological Efficiency**

Finally, the use of ions heavier than protons has the advantage that the biological reaction of the cell can be potentiated. Heavy ions have a greater energy loss and consequently a higher density of locally produced electrons. At the microscopic scale of DNA as the sensitive target inside the cell the elevated ionisation density correlates with an elevated density of DNA lesions. Single and isolated lesions like single strand breaks can be repaired easily by the cell. Clusters of double strand breaks are frequently connected with information loss at DNA level and mostly irreparable (G. Kraft 2000).

Using carbon ions the energy loss and consequently the lesion density is distributed in a very favourable manner: At high energies in the entrance channel ionisation density is low and increases towards the end of the track. Thus, the quality of the damage differs along the track. At its beginning at high energies the DNA damage in the tissue in front of the tumor can be repaired to a large extent. At the end of the track, ionisation density is high and mostly irreparable lesions are produced in the tumor. Confining the track ends strictly to the tumor, the efficiency for tumor cell killing can be potentiated by a factor of two or more, which is most relevant for otherwise radioresistant tumors. The choice of carbon ions as the optimum ion is mainly determined by the gain in radiobiological efficiency between entrance channel and tumor. Lighter ions like protons lack the elevated RBE at the end of the track. Heavier ions like Neon have an additional increase in efficiency also in the entrance channel thereby causing severe late effects.

Carbon ions are best in the balance of the production of lethal lesion in the tumor on one hand and reduced damage to normal tissue on the other. Measurements of DNA double strand breaks as well as of cell survival have confirmed the high repair rate in the healthy tissue and the very effective cell killing in the tumor region.
However, the choice of carbon ion has the consequence that, first, the RBE variation complicates the treatment planning to some extent and second, that the beam delivery should be as conform as possible to the tumor and avoid any normal tissue to be hit by the very effective stopping ions. These conditions are fulfilled using the scanning systems and the biological optimized treatment planning. The clinical results achieved up to now confirm the theoretical benefits of target conformity for protons and carbon ions and the additional RBE gain for carbon beams.

These very advantageous properties of ion beams have prompted many facilities to introduce ion therapy. Since the rather reluctant and slow beginning of proton beams at Berkeley in 1958 this new radiation modality has now turned into a forefront activity of many advanced clinical units. The basis of this increased activity is the success of the ion therapy up to now. Up to now, approximately 30,000 patients have been treated, mostly with proton beams. Only for a small fraction of patients, heavy ions like carbon ions are used and approx. 1,000 patients are treated in Chiba, Japan, and 100 at GSI, Germany. Patients have been treated with ions in many centers (see chapter on hadron therapy in the world) and over a period of more than 40 years, during which particle therapy has made a large progress.

**Clinical Results**
Up to now, almost 30,000 patients have been treated with ion beams - mainly with protons. At the low-energy proton beams eye tumors, mainly uveal melanomes, have been treated extremely successfully (M. Krengli 1998).

These tumors occur in patients of all ages but are more frequent in older patients. The tumors are quite large, typically 13 mm in diameter and 15 mm in height and mostly in close proximity to the optical nerve which would be affected in conventional therapy. Therefore, the enucleation of the eye is the frequent alternative to radiation therapy, which results, however, in the total loss of vision but the radical tumor extirpation prevents a metastatic spread.

![Fig. 7: Local control rate as function of delivered dose. The local tumor control can be substantially raised for tumors in the base of the skull region by the application of ion beams (Svit H. et al 1995).](image)

Treatment with proton beams is in most cases similarly effective. Because of the small lateral spread of the proton beam a dose of 70 Gy can be given to the tumor, typically in 5 days, without a deterious effect on the optical nerves. Because it is possible to visually control the tumor localisation in the eye with great precision an excellent conformity of the treatment can be achieved. In the treatment of more than 10,000 eye patients, a local tumor control of 95% or better was reached connected with a high survival rate and a high rate of a useful vision. The treatment of eye tumors with proton beams yields by far the best clinical result. Thus, proton treatment is the best choice for these tumors.

The other fraction of tumors treated with protons is less homogeneous and spread over a few big centers like Harvard, Loma Linda and many smaller activities. Due to the very limited access to proton therapy mostly those tumors have been chosen for proton treatment where the greatest benefit in comparison to conventional therapy was to be expected. These are tumors that grow rather slowly and that are little radiosensitive like chordomas, chondrosarcomas and meningeomas.
Secondly, tumors have been chosen which were close to critical organs such as brain stem, spinal cord, etc. Consequently, tumors have been selected in the head and neck region and along the spinal cord or in other regions where the target dose is limited by the tolerance of the critical organs around. Having a better conformity, proton therapy was applied in these cases. Because of the lower contamination of the normal tissue the tumor dose could be increased yielding significantly better results. Since the escalation of dose was a very slow process, depending on the physical improvement of dose distribution over a period of 40 years, it cannot be characterized by a single number as it was the case with eye tumors, but in most cases an improvement of the local control of some 30-40% could be achieved. This increase of the tumor control rate with particle beams is a significant difference, especially, if this benefit in survival is not accompanied by a higher incidence of side effects. The good results of proton therapy confirm a general rule in radiotherapy: that better conformity of the irradiated volume with the target volume yields better results. This holds true for heavy-ion beams, too, where a superior conformity compared to protons can be achieved. But the main advantage of heavy ions is the increase in biological effectiveness that should provide a greater tumor control probability, especially for radioresistant tumors.

Heavy-ion therapy began in 1974 at the Lawrence Berkeley Laboratory. There, first patients were treated with argon ions at the Bevalac accelerator complex where a limited number of patients could be irradiated in time sharing with physics experiments. After a few patient treatments, however, the observed side effects proved to be not acceptable. Treatment then shifted to the lighter silicon and further on to neon beams, which were applied to approximately 400 patients. Tumors treated were radioresistant tumors close to critical organs and extended from brain tumors and other head and neck tumors to tumor incidences all over the human body. Because of the large diversity of the tumors treated a quantitative analysis is not possible, but the results were so convincing that they motivated the construction of a dedicated Heavy Ion Medical ACcelerator (HIMAC) at Chiba, Japan.

Since 1994 about 1000 patients have been treated with carbon ions for a variety of tumors in carefully conducted phase I/II and phase II trials. The sites treated with carbon ions at the HIMAC include patients with head and neck cancer, lung cancer, liver cancer, prostate cancer and tumors of the gastrointestinal tract. At the current point, most promising data are found in patients with base of skull tumors, head and neck cancer, soft tissue sarcoma and early stage lung cancer in the Japanese trials. The incidence of treatment-related toxicity was very limited in the phase II trials.
At GSI patient irradiations started in December 1997. So far 100 cancer patients underwent carbon ion irradiations and promising first results can be reported today (Debus 2000). At GSI, again, radioresistant tumors close to critical organs are treated but for the first time the active scanning systems are used in connection with a biology-based treatment planning system. This yields a dramatic reduction of dose to the normal tissue outside the tumor and in consequence a significant decrease in early side effects. Although the physical dose could be decreased because of a realistic RBE estimation, up to now, no tumor regrowth within the treated area has been observed in the Phase I/II study. Because of the short follow-up time and the limited number of patients it is too early to draw final conclusions from the heavy-ion treatment, but the results achieved so far are motivating. This reflects the increasing number of new ion beam units proposed for the near future (see the following chapter).

**Summary**

The use of heavy charged particles like protons or heavier ions was triggered by radiation physicists and radiobiologists. It was and is difficult to promote these new ideas in the medical community mainly because of the larger complexity and technical demand of these therapy units. In the beginning, particle therapy was feasible only with the generous help of the nuclear physics community that has developed the high-energy accelerators and also the equipment of beam monitoring that allows a safe patient treatment. At present, a separation of the medical application from the nuclear physics experiments is taking place and dedicated medical facilities become now available on the industrial market. With a few therapy units of modern standards being operational, this will be the largest success of a spin-off product of nuclear science.

**References**


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