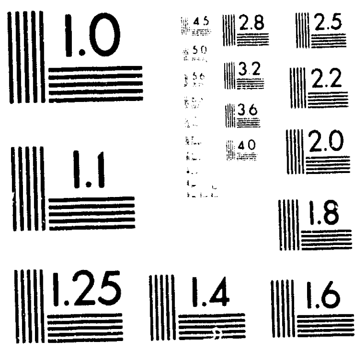
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PARTICLE THERAPY

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Introduction

Particle therapy has a long history. The experimentation with particles for their therapeutic application got started soon after they were produced in the laboratory. Physicists played a major role in proposing the potential applications in radiotherapy as well as in the development of particle therapy. A brief review of the current status of particle radiotherapy with some historical perspective will be presented and specific contributions made by physicists will be pointed out wherever appropriate. Detailed reviews can be found in books by Catterall and Bewley (1979), Raju (1980), and Fowler (1981).

The rationale of using particles in cancer treatment is: 1) To reduce the treatment volume to the target volume by using precise dose distributions in three dimensions by using particles such as protons, 2) To improve the differential effects on tumors compared to normal tissues by using high-LET radiations such as neutrons. Pions and heavy ions combine the above two characteristics.

Fast Neutrons

Two hundred and twenty six patients with advanced tumors were treated in Berkeley by Stone during 1939-1943. Although the neutrons were found to be quite effective in sterilizing the tumor, the effects on normal tissues were found to be severe (Stone 1948).

Dr. Harold Gray, the student of Dr. Rutherford was perhaps the first physicist that switched to biomedical field. Gray and his associates conducted a series of radiobiological experiments to demonstrate the importance of oxygen tension in radiotherapy and concluded that hypoxic cells may be a limiting factor in radiotherapy. In the light of radiobiological knowledge regarding the oxygen effect and its reduction with fast neutrons, Gray and his associates in U.K. felt the need to reinvestigate their use in radiotherapy in spite of the discouraging findings by Stone. A cyclotron was built exclusively for medical research in Hammersmith Hospital in London. After a careful study of fast neutron effects on normal tissues and tumors, patient treatments were started in 1969. After the initial encouraging results, a randomized clinical trial was undertaken to treat head and neck tumors with fast neutrons and the results were compared with megavoltage radiation results (Catterall et al 1975). The results from this clinical study stimulated great interest around the world in the clinical application of fast neutrons and emphasized the need for medically dedicated neutron facilities.

One of the exciting developments in radiobiology came from the pioneering work of late Prof. Breur and his associates using pulmonary metastasis in human patients (Van Peperzeel et al 1974). They found a wide range of RBE values (1.2 to 4.0). The RBE for slowly growing well differentiated tumors were found to be much higher compared to fast growing poorly differentiated tumors.

More than 15,000 patients were treated world wide using about 15 fast neutron facilities. Fast neutrons are found to be the treatment of choice for inoperable salivary gland tumors with local control rate of 67% compared to 24% for x rays (Wambersie 1992). Neutron treatments are also found to be beneficial in the treatment of well differentiated slowly growing soft tissue sarcomas, and locally extended prostatic adenocarcinoma. By contrast, the results of fast neutron treatment on brain tumors are disappointing. It is estimated that about 10% of the patients undergoing radiation therapy may be benefited by fast neutron treatments (Wambersie 1992). Selection of patients that could be benefited by fast neutron treatments remains to be a problem. Predictive assays are being developed to over come this problem.

Protons

Proton beams were proposed for radiotherapy by the physicist Wilson (1948). Radiobiological and clinical studies by Tobias, Lawrence and their associates led to the use of protons, deuterons and helium ions in treating human diseases associated with the malfunctioning of the pituitary gland. The subsequent improvements of the cyclotron led to the acceleration of protons to higher fixed energies thereby making it unsuitable for proton radiotherapy.

The clinical application of proton beams got started in Uppsala in 1957. Radiosurgery techniques using protons were pioneered by Larsson, Leksell and their associates (1958). Larsson and his associates also developed techniques for large field radiotherapy and treated about 60 patients (Graffman 1975). They demonstrated that almost any volume in the body can be uniformly and selectively irradiated using proton beams.

The Harvard cyclotron group headed by Koehler developed precise techniques to treat human pituitary using the proton Bragg peak in collaboration with Kjellbeg and his associates. They treated patients with acromegaly, Nelson's syndrome, diabetic retinopathy and Cushing's disease. Kjellberg and his associates (1988) also developed techniques to treat arteriovenous malformations in the brain using proton Bragg peak. Koehler in collaboration with Massachusetts Eye and Ear Infirmary and Massachusetts General Hospital pioneered the technique to treat uveal melanoma. This technique was so successful (local control rate >95%), it eventually became the treatment of choice (Gragoudas et al 1978). These successful results in treating uveal melanoma with protons led to the use of proton beams from the cyclotrons used for neutron radiotherapy and pion radiotherapy for eye melanoma treatments. The new isochronic machine built in the Institute of Nuclear Physics in Krakow is currently being prepared for proton therapy for eye melanoma in addition to neutron treatment. Suit and his associates in collaboration with Koehler from Harvard cyclotron group initiated fractionated radiotherapy using large fields of protons. Their impressive clinical results of the treatment for sarcomas of the skull base (91% local control) added further excitement and interest in proton radiotherapy (Suit 1991).

The use of proton beams in radiotherapy and radiosurgery in Russia has a long history since 1964. They have been using three of their accelerators located in Moscow, Dubna and Gatchina.

The sustained effort by various groups played a key role in maintaining an international interest in proton radiotherapy. More than 12,000 patients were treated with protons around the world using about 15 facilities. The first medically dedicated proton accelerator is installed and in operation at Loma Linda University in California.

Heavy Ions

The potential application of heavy ions in radiotherapy was also proposed by the physicist Tobias. Two accelerators, a low energy heavy ion linear accelerator and a high energy proton accelerator, (located nearby at Lawrence Berkeley Laboratory), were connected together with a beam line in 1974. This combined facility is known as BEVELAC. After extensive radiobiological investigations, patient treatments have been in progress since 1979. Most of the heavy ion treatments were given with neon ions. Around 450 patients were treated with heavy ions. The clinical results after treatment with heavy ions for several advanced tumors of the salivary gland, paranasal sinus, soft tissue sarcoma, and bone sarcoma were found to be promising (Castro 1991). The effects of heavy ions on slowly growing tumors were found to be comparable to the effects of neutrons but the sparing of normal tissues are expected to be better for heavy ions. The clinical impression is that heavy ions may play a useful role in the management of slowly growing sarcomas, chordomas and prostate cancers, consistent with the observation made earlier by Breur and his associates from human lung metastasis studies. Berkeley BEVALAC was the only heavy ion facility in the world doing clinical work, but it is now shut down for lack of funds. However, a heavy ion facility, mainly for physics research, but with some biomedical facilities is in operation in Damstadt, Germany. An ambitious medically dedicated heavy ion facility is nearing completion in Chiba, Japan.

Pions

Application of pion beams for radiotherapy was also proposed by cosmic-ray physicists Fowler and Perkins (1961). Three pion facilities built mainly for physics research but with adequate facilities for therapy are located at Los Alamos, USA, Vancouver, Canada and Villigen, Switzerland. The program in Los Alamos was discontinued in 1982 after treating about 230 patients and the program in Switzerland is also recently discontinued after treating about 500 patients. Although some favorable tumor responses were obtained, the results were inconclusive. Pion therapy is still being carried out heroically in Vancouver. Two randomized trials for treating astrocytoma and prostate are in progress. The accrual of the patients required for these two studies are expected to be completed by 1995. No definitive statements can be made at this time.

Conclusions

The developments of particle therapy programs to a large extent is due to an international cooperation. These programs have helped to attract many talented high energy physicists that contributed to these programs and medical physics in general. Particle radiotherapy has moved quickly to clinical stages and medically dedicated facilities of all particles with the exception of pions are being built. The ability to control dose at depth gave an impetus to develop three dimensional treatment planning. The introduction of high LET beams in radiotherapy helped to improve our understanding on acute and late effects as a function of dose fraction.

Recent developments in sophisticated imaging techniques helped to make use of the excellent dose distributions of heavy charged particles. These developments helped to obtain impressive clinical results with protons and helium ions for some selected tumors. Because of the biological complexities of tumors and their variations, the optimum utilization of high LET beams have been difficult. Predictive assay methods need to be developed to identify tumors that have a better prognosis for high LET radiations.

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