PROTON AND HEAVY ION THERAPY

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Abstract

Penetrating ion beams are considered interesting supplements to the types of radiation, mostly electrons and gamma rays, that have dominated in radiation research and radiotherapy during the last decades. Biomedical experimentations and clinical studies at larger ion accelerators (100-1000 MeV/amu) are therefore undertaken in order to exploit their possible clinical use in cancer therapy. It is concluded that an accelerator that permits effective use of protons (ca. 200 MeV) and deutrons (ca. 50 MeV,for neutron therapy) located in a central hospital would represent a convenient tool for clinical investigations at a larger scale.

Introduction

Megavoltage photons and electrons from various sources have almost replaced therapeutic kilovoltage X-rays in many hospitals. Partly due to these developments, during the last two decades, there has been considerable improvement in the quality of life and survival of cancer patients[1]. It is nevertheless highly relevant, at a time when cyclotrons no longer are rare and exclusive experimental instruments, to ask for the potentialities of various accelerated ions and their secondary radiations in the radiotherapy of tomorrow. This and the following two papers [2,3] illustrate radiobiological and clinical research activities aiming at understanding and evaluation of the partly unique physical qualities offered by these "new" radiations.

The present importance of radiotherapy is evident from the fact that nearly one half of all patients with cancer disease are sooner or later subject to radiation treatment. That future which may see immunotherapy, chemotherapy, improved surgery and early diagnosis substantially change this situation is probably far away. This is because ionizing radiation is the only modality that permits adequate and, in the same time, more or less uniform treatment of any chosen target volume. If ion accelerators will be accepted for routine applications, it will take a long time before they become obsolete, at least when they have been conveniently located in or near medical centers of lasting standards[4]

Beams of protons and "heavy" ions such as oxygen or neon particles presently considered in pre-therapeutic research, are from the point of view of macroscopic treatment planning, very similar (Fig. 1). They are characterized by near-straight line penetration and a " Bragg peak" that may conveniently be transformed into "Bragg plateaus" of almost any chosen shapes at the end of the well-defined range of penetration. On the other hand protons and heavy ions may under almost the same macroscopic conditions be used to irradiate extended structures uniformly with radiation of low and high average linear energy transfer (LET), respectively. At the necessary energy, several hundred MeV/amu, protons deliver most of their dose at LET < 10 keV/µm and neon ions at LET > 100 keV/µm. These values represent, effectively, the clinically relevant extremes of a scale of LET on which all radiations, "new" or "conventional" can be placed. With our present knowledge, this is a relevant and, for any practical purpose, unequivocal way of presenting the radiobiological quality of the various radiations[5]. From this point of view, that is with regard to microscopic distribution of dose, the protons are classified as low-LET radiations together with all conventional kilovoltage or megavoltage radiations, while heavy ions, together with fast neutrons

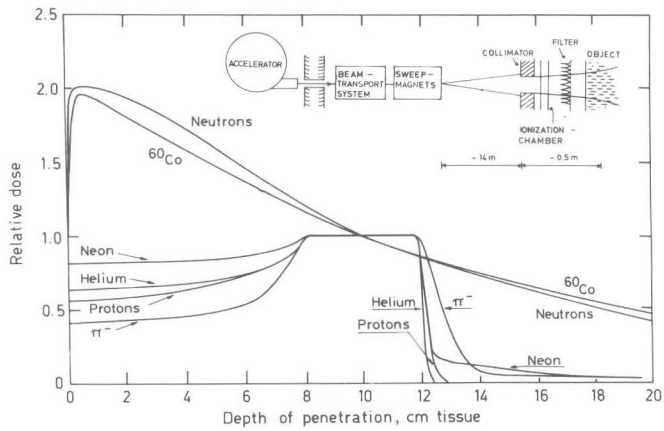

Fig. 1. The dose planning is very much facilitated by radiations that permit a free choice of depth of penetration and of adaptation of the dose maximum to the area suspected of tumour growth. Many ion beams have, in these respects, particularly advantageous absorption characteristics. Both protons and heavier aions (such as helium or neon) of varying LET can be made to deliver their dose uniformly within a plateau of maximum dose, that can be varied almost at will by a technique outlined in the inset drawing.[8,16]

Proc. 7th Int. Conf. on Cyclotrons and their Applications (Birkhäuser, Basel, 1975), p. 414-418

and negative pions, may be called high-$\overline{LET}$ radiations. The latter assignation is, in fact, not entirely correct, fast neutrons[6] and negative pions[7] are both representatives of an intermediate class. This is easily understood, considering that these latter particles are mainly acting indirectly through non-uniform mixtures of secondary protons and other ions of varying $\overline{LET}$.

The out-lined important macroscopic and microscopic characteristics are the main reasons for radiotherapeutic research with ion beams for direct irradiation of living targets as illustrated here with examples provided by investigators at Uppsala and Berkeley working with the 190 cm synchrocyclotron[8] and the Bevalac installation[9], respectively. Clinical research with high-energy protons or other light ions has also been reported from Berkeley[10], Harvard[11], Dubna[12] and Moscow[13], and other laboratories have made pre-therapeutic developments. My intention is to illustrate how the experimental and clinical findings and the associated theoretical and technical progress may influence general strategies in radiotherapy. The present state of ion beam therapy and future prospects are also summarized and reference is given to a model for a 200 MeV proton clinic for radiotherapy and other medical applications[4]. First it is important, however, to recall, briefly, the radiobiological and clinical principles of radiotherapy and the physical requirements that emanate from them.

General aspects

A minimum basis for the understanding of the requirements that govern the choice of therapeutic radiations is here provided. The biological and clinical elements suffer necessarily from oversimplification.

Radiobiological principles. The general aim of all radical treatment for tumour disease is to achieve a high probability of preventing tumour tissue from growth without causing, in the same time, undue harm to the patient. This is almost equivalent to saying that we should eliminate efficiently the proliferative capacity of all tumour cells without causing irreversible damage to normal tissues within a "target volume" supposed to contain all viable tumour cells. (This is not necessarilty equivalent to saying that we should kill all tumour cells.)

Let us assume, to get a general idea of some typical figures involved, that the initial number of tumour cells is $10^9 \simeq 2^{30}$ per cm^3 and let the absorbed dose necessary to reduce, in one single sitting, the number of tumour cells with proliferative capacity to half the original be 200 rad. Assuming now (not very realistically) that no repopulation is taking place between sittings, we have got a fair chance of sterilizing 1 cm^3 of tumour tissue in 30 sittings, giving a total absorbed dose of 30 x 200 = 6000 rad. This would in fact be a typical treatment protocol as 6000 rad is a representative tolerance dose for several healthy tissues.

This crude model shows that the choice of target dose is the result of a critical compromise between our ambition of killing the tumour and our fear to hurt the patient. Even minor deviations from the conditions out-lined may give raise to major disturbances of our predictions, however. A mere glimpse at the real biological situation will destroy whatever confidence we may have had in mathematical models of complicated biological systems. When we consider the facts that our chosen tumour was unusually small, that cell density and intrinsic radiosensitivity both show large variations; that proliferation during the treatment period more than likely occurs; that immune factors or variations in the microenvironment of the cells may drastically alter the prospects of surviving cells, and that even healthy tissues may show varying radiovulnerability, it is indeed difficult to understand why predictions are at all possible in radiotherapy.

It is, in fact, difficult to explain why radiotherapy is at all working, on the sole basis of dose-survival curves seen in experiments on free cells in vitro. Such experiments show that there are no important systematic differences in intrinsic radiosensitivity between normal and tumour cells when cells are scored for proliferative capacity after irradiation. Explanations for the clinically seen differences in "radiovulnerability" of healthy tissues and tumours that respond favourably to irradiation have to be sought among the factors that regulate the repopulation of normal cells and tumour cells in vivo. In contrast to neoplastic cells which are more or less autonomic, the normal cells of healthy tissues are subject to efficient feedback control by various means. For example, removal of cells due to killing by irradiation often stimulates the mitotic activity of the remaining cells population so as to compensate for the loss (cf. skin, intestinal epithelium, blood-forming tissues). Without this difference in "restoration pressure" between tumour cells and normal cells radiotherapy would probably be impossible, except in a few extreme situations when malignant cells show exceptionally high intrinsic radiosensitivity.

The biological effects are results of the production of radiation-induced chemical changes in important biomolecules (such as DNA). The spatial (and probably also chemical) patterns of such changes and the distribution of ions and free radicals along the particle tracks are drastically different at low and high $\overline{LET}$, in conformity with a general concept of "radiobiological quality". In the therapeutic dose range, normally both the malignant and healthy cell populations are subject to serious radiation effects. The width of the restricted useful dose interval can be changed both through careful modelling of the macroscopic dose distribu-

tion within the patient (physical selectivity) as well as through various other measures (radiobiological selectivity). Among the latter we may recognize the choice - when indicated - of high LET radiation instead of low LET radiation.

Clinical experience[14] as well as radiobiological considerations based on more sophisticated models[15] indicate that even very small changes in absorbed dose or uniformity of dose distribution may decisively alter the probability of tumour sterilization. The same should be true for changes in radiobiological variables that induce changes in the efficiency of the treatment.

Clinical conditions. There are more than hundred types of tumours, as they are being classified as to cellular origin and degree of malignancy. Clinically, the disease is also characterized by the localization of the primary tumour and its stage of spread (i.e. whether tumour tissue is seen only locally at the primary site, has invaded surrounding tissues or has spread to or beyond local lymph stations). The dose necessary to sterilize a tumour of given size or number of cells may vary considerably. Radiation effects on healthy tissues are easier to predict although the dose that can be given is often related to the fraction of an organ irradiated. In principle, each patient represents a unique biological and physical problem, which has to be carefully considered.

The degree of accuracy at which tumour extension is to be given depends on site, type and stage of the malignancy. Wide security margins are often important and extreme accuracy therefore of little value. On the other hand, say in early stages of carcinoma of the larynx or small intracranial tumours, accuracy of a few millimeters can be achieved and exploited. Under circumstances changes in anatomical relationships could also occur during the course of fractionated treatment.

Another parameter of importance is the patient outline that could be measured and defined by various techniques. Variations between sittings and movements could be controlled by individual casts of supports. Bolus material has sometimes to be introduced for "correction of body contours".

The parameters of the tumour disease, that are needed for dose planning and clinical evaluation of the effects refer to tumour localization and extension. Radiographs, tomographs and scintigrams, sometimes findings in connection with surgery or, in case of a superficial growth, palpation, are the main sources of information.

Physical requirements

Macroscopic distribution of dose. The macroscopic distribution of dose determines the physical selectivity. The "best" technique would be one that provides maximum probability of tumour sterilization without untoward irradiation of tissues outside the chosen target volume. Although other types of criteria would be more relevant (i.e) when realistic assumptions can be made about tumour structures within the target volume), a homogenous dose within the target volume and minimum energy deposition in neighbouring tissues are conditions that characterize, generally, the ideal situation. Protons and heavy ions permit flexible and precise arrangements according to the simple criteria, and offer, similarly, flexibility in the design of more sophisticated distributions of dose (Fig. 2).

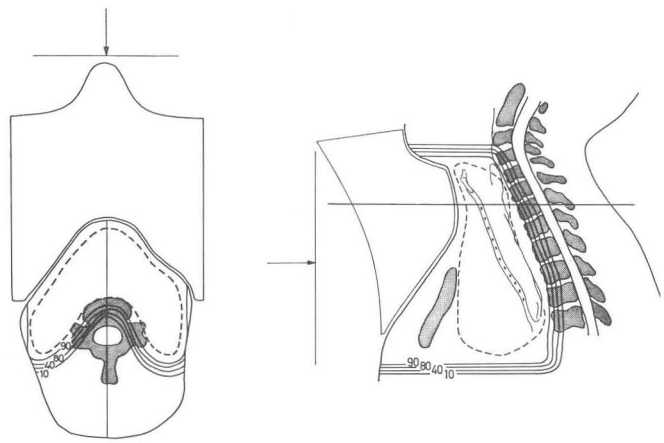

Fig. 2. This case, from a series of therapeutic applications with 190 MeV protons at Uppsala, illustrates the tailor-made dose distributions which can be obtained with ion beams of high energy. The dotted curve indicates the target area, the figures and the full lines represent "isodoses" The area within the isodose 90 % is almost uniformly irradiated while surrounding tissues (e.g. in the lungs and in the spinal cord) are spared. (From Sten Graffman, Thesis, Uppsala 1975.)

Microscopic distribution of dose. The microscopic distribution of dose, as it is characterized by the LET, determines, at present knowledge, fairly well the radiobiological qualiyy of the radiation. It is trivial to say that the best LET is that which gives the best radiobiological selectivity, i.e. leads to highest relative radiosensitivity of the tumour cells as compared to the most critical normal cells in the target volume. What is, however, the best LET? Low or high? Perhaps intermediate?

So far we have to base our considerations mainly on results from experiments on simple organisms and cultured mammalian cells 16). Such findings permit us to predict that, at radiotherapy with high-LET radiations, both tumour and normal cells (i) will have

great difficulties in recovering from sublethal damage between sittings; (ii) will be more easily killed by a given dose of radiation (unfortunately the relative biological efficiency, RBE, seems to increase in the same way for most cells studied), (iii) will express less variation in radiosensitivity with the position in cell cycle: (iv) will express less variation in radiosensitivity with varying oxygen tension and, supposedly, also with varying concentrations of other chemicals known to be effect-modifiers. These predictions are fairly safe but qualitative. We cannot predict to what extent the various factors will be able to contribute to the desired increase in radiobiological selectivity. This has to be tested in measurements on patients or in clinical trials.

There are reasons to believe that under varying circumstances the above-mentioned general decrease in sensitivity of radiation effects to the various effect-modifying factors (i-iv) may be exploited to advantage. For example, the early interest centering around the possibility to reduce the effect-enhancement due to oxygen is still valid, since ineffective oxygenation of cancer cells in poorly vasculated tumour tissue is considered to sometimes be an important cause of failure in conventional radiotherapy[17]. The observations on patients irradiated with fast neutrons, the only high-LET radiation that has been available for thorough clinical investigations so far, will be of great importance in this context[18]. Awaiting such and other significant information on the various factors out-lined we must admit that a reliable judgement as to the place of high LET in radiotherapy cannot be given.

Radiological merits of ion beams

Protons. Theoretical considerations, as outlined above, supported by a multitude of biological experiments and clinical observations, indicate that no important differences in radiobiological specificity exist between ion beams of low-LET and conventional therapeutic radiations. The possible merits of protons depend, for example entirely of physical selectivity[19]. In many cases the extra features offered in this respect by the highly flexible proton fields may be clearly non-significant. In several tumour localizations, however, the proton radiation seems to offer specific advantages, as judged from generally accepted clinical criteria. This view cannot yet be supported by statistical analysis of a patient material that is both limited and heterogenous. The situation would not be improved by integration of material from other therapeutic research groups active in the field [10-13], as no equivalent material permitting comparison with conventional treatment methods could be constructed in retrospective.

We believe presently, that as has been the case for conventional radiations, the merits of new radiations can be appreciated only by large scale applications. To this end we have made a thorough analysis of the biomedical, technical, economical and practical prerequisites for routinary proton therapy intended to serve the 8 million people in Sweden[20]. From a model design it seems clear that about 200 proton sittings per day could be used to more or less obvious benefit as judged by conventional criteria. It is also estimated that such an alternative to the use of a corresponding arsenal of betatrons and linear accelerators for electrons would be economically reasonable. In Sweden, hoever, a project of that size would be realistic only if the patient basis were broadened to comprise a larger fraction of the requirements for radiotherapy. We consider this, at the present stage of development, too bold a step. We shall thus, also in the future, employ the protons only as a supplement to conventional resources, mainly when individual requirements for very "difficult" dose plans could be met by these particles. Such a continued small scale activity would permit us to study several basic medical - radiobiological problems that could be favourably tackled by use of the low-LET radiations from the existing accelerator.

Heavy ions. The Bevalac combination at Berkeley is presently the only apparatus that permits use of high LET radiation in the form of ion beams for direct treatment of tumours in the human body . As the installation requires large space and investments the experiences may be difficult to exploit at larger scale in the foreseeable future. The results of radiotherapy with heavy ions will nevertheless be of major clinical interest as this type of radiation offers very clean high-LET conditions. The activities will undoubtedly be of great importance in the elucidation of the conditions met with also in neutron and negative pion therapy.

The challenge to exploit high-LET radiations isnot yet felt in routinary clinical radiotherapy. However, depending on the outcome of present clinical research activities this situation may become subject to rapid change. If heavy ions then will be considered a possible alternative to fast neutrons and negative pions depends on advances in heavy accelerator technology not yet conceived.

Conclusions

In radiotherapy, direct irradiation with proton and heavy ion beams of suitable range of penetration offers outstanding flexibility and precision. Neither low-LET nor high-LET will probably come out as the "best" type of irradiation, as the choice in each case the type and extent of tumours and various radiobiological factors. Particularly important is the relative importance of the protective effect of hypoxia in tumour cells versus positive changes in radiobiological selectivity offered by procedures aiming at chemical or temporal effect-modification.

At the present state of development, the possibility of coordinated production and use of 200 MeV protons and 50 MeV (possibly 100 MeV) deutrons for fast neutron therapy seems attractive. A convenient design of an accelerator and beam transport system dedicated to these purposes would facilitate the further evaluation of the use of cyclotron-produced radiations in clinical medicine.

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DISCUSSION

H.G. BLOSSER: Would you comment on whether you have started clinical trials of using proton radiotherapy?

B. LARSSON: The prerequisites for clinical trials, in the strict statistical sense, do not seem to exist, irrespective of the fact that irradiation of hundreds of patients have been reported from Berkeley, Uppsala, Harvard, Moscow or Dubna.

M.A. CHAUDHRI: Which fractionation is normally used?

B. LARSSON: Typical fractionation schemes employed at all places are 2-5 irradiations per week for a period of several weeks.