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Fast Neutrons and High-LET Particles in Cancer Therapy

With 83 Figures and 36 Tables
Preface

The initial pioneer work in fast neutron therapy was performed by Stone at Berkeley in 1938. A fast neutron therapy programme was initiated in 1970 at the Hammersmith Hospital in London, and a few years later in several centres in Europe and in the United States. After almost 30 years of widespread experience, it is timely and useful to evaluate the results of neutron therapy in a comprehensive and objective way. That is the aim of this book.

In Europe, 14 centres have applied fast neutrons in cancer therapy, using different types of generators:
- “Low-energy” cyclotrons able to produce d(13-16)+Be neutron beams: Hammersmith and Edinburgh in the UK; Essen and Dresden in Germany; Krakow in Poland.
- (d+T) generators: Hamburg, Heidelberg, and Münster in Germany; Amsterdam in The Netherlands; Glasgow in the UK.
- “Higher-energy” cyclotrons: Louvain-la-Neuve in Belgium (p(65)+Be); Orléans in France (p(34)+Be); Clatterbridge in the UK (p(62)+Be); and, since 1997, Nice in France (p(50)+Be).

Some centres completed large clinical programmes from which important conclusions could be derived about the potential benefit of high-LET radiations. In other centres, the facility was shut down quite rapidly, in some cases because of patient recruitment problems but in most cases because of technical difficulties. In particular, all (d+T) facilities are now closed. Indeed, the low dose rates available with the (d+T) generators have always caused serious limitations in the selection of the treatment modalities.

In comparing the relative merits of fast neutron therapy and photon therapy, it has been recognised that fast neutron therapy has often been applied in suboptimal technical conditions. Poor beam penetration and collimation were compensated for in some institutions by sophisticated treatment planning and patient positioning for rather superficial tumours; for deep-seated tumours, however, they were definitely a handicap.
The situation has significantly improved during the past 15 years, in Europe and worldwide. At some facilities fast neutrons can be applied in the same advanced technical conditions and with the same physical selectivity as photons, as far as beam penetration, collimation and isocentric gantry are concerned (for example, Seattle and Detroit in the USA and NAC-Faure in South Africa).

The rationale for introducing fast neutrons (or, more generally, high-LET radiations) in cancer therapy in the 1970s was based on radiobiological considerations:
- Originally, reduction in the OER with increasing LET
- Reduction of differences in radiosensitivity related to the position of the cells in the mitotic cycle
- Furthermore, reduction of the relevance of the repair phenomena.

These arguments remain fully valid and have not been contradicted by more recent radiobiological findings. However, they imply the need for the development of "predictive tests" allowing the radiation oncologist to select the patients who could benefit most from high-LET radiations. This remains today an important research issue.

Most of the efforts in the field of hadron therapy in Europe were initiated and coordinated by the European Organization for Research and Treatment of Cancer (EORTC)-Fast Neutron Therapy Group. This group, founded in 1972 by the late Professor Klaas Breur from Amsterdam, became the European Hadron Therapy Group in 1995 (hadrons include fast neutrons, protons and heavy ions, i.e. non-conventional therapy beams). The aim of the group was to explore the possibilities of non-conventional radiations in cancer management and ultimately to initiate randomised clinical trials in order to be able to demonstrate the benefit of the new types of beams for some tumour types or sites.

An important achievement of the European Hadron Therapy Group was to initiate and coordinate intercomparisons at the different facilities, embracing dosimetry, microdosimetry and radiobiology.

As far as dosimetry is concerned, intercomparisons were performed at all the European neutron therapy facilities. As indicated in the first chapter of this book, an initial European protocol was established and applied. Because of significant discrepancies with the US AAPM protocol, efforts towards a common protocol were initiated under the auspices of the International Commission on Radiation Units and Measurements (ICRU) and an agreement was reached and accepted worldwide (see ICRU Re-

Intercomparisons aiming at specifying radiation quality at the different neutron facilities are dealt with in the second chapter. Radiation quality can be specified in terms of microdosimetric spectra and/or in terms of RBE values observed for well-defined biological systems. It is important to stress that both microdosimetric and radiobiological intercomparisons were performed by the same teams of biologists and experts in microdosimetry visiting the different facilities.

The side effects after neutron and high-LET therapy have always been a cause of concern. The complications observed at the level of the "treated volumes" and of the "irradiated volumes" (see definitions of these concepts in ICRU Report 50, 1993) are discussed for the different tumour localisations in the fourth to ninth chapter, and especially in the tenth chapter. However, of particular concern is cancer induction after neutron and high-LET therapy. No human data are presently available, and the best estimates derived from the radiobiological data are discussed in the third chapter.

The fourth to ninth chapters contain an extensive review of the published clinical data. There is emphasis on the data from the European centres; however, relevant data obtained worldwide are included. Neutrons were shown to be superior to conventional radiations for the treatment of some tumour types or sites, e.g. salivary gland tumours and prostatic adenocarcinomas. The most recent and complete data on this are presented. For other tumour types or sites, such as soft tissue sarcomas and chordomas, or for palliative treatment of inoperable/recurrent rectal carcinomas, the available neutron data are analysed and the clinical indications are discussed.

For some tumour localisations, data from different centres, in particular from Europe, have been pooled, analysed, and presented by a given group of authors. It is believed that this approach improves the quality and objectivity of the information.

The complications resulting from the fact that the first neutron treatments were often applied in suboptimal physical conditions have been mentioned above. In that respect, the logical trend in application of high-LET radiations in better physical conditions is to move towards heavy-ion beams, such as carbon or neon ions. This trend is equivalent to that observed with low-LET radiations, where proton beams have began to complement photon beams.

The first heavy-ion therapy programme was initiated in Berkeley in 1977 and ran until 1992. Although there were some limita-
tions in patient recruitment and in machine availability, important information was obtained about the potential value of heavy ions from the series of 433 patients who could be treated. At the time when, unfortunately, the Berkeley facility was being closed, a new carbon-ion therapy programme was started in Chiba, Japan. There is no limitation concerning the machine time, and three treatment rooms are planned. From the clinical point of view, the major efforts were focused on the treatment of the most frequent tumours in Japan, i.e. those of oesophagus, bronchus, and liver. The first patients were treated in 1994, and a total of 300 patients were treated by the end of 1997.

In Europe, a heavy-ion therapy programme was initiated at GSI-Darmstadt, in Germany, jointly with the German Cancer Research Centre (DKFZ) and the Department of Radiation Oncology of Heidelberg University. The clinical programme is orientated differently compared to the Chiba programme. There are strict limitations on machine time, but full advantage is taken of the scanning beam system and the possibility of modulating the carbon-ion beam energy. The selected clinical indications are thus, logically, radioresistant tumours that are irregular in shape and located close to critical normal structures for which there is at present no reasonable therapeutic alternative (e.g., some tumours of the skull base). For these types of localisations, the characteristics of the beam at GSI can be fully exploited.

The first two patients, with target volumes located at the base of the skull, were treated at the end of 1997. A chapter on heavy ions thus has a definite place in this book and helps to make it up to date.

The cost of the treatment facility will, for the moment, limit the development of heavy-ion therapy programmes. However, as has been observed with neutrons and protons, it can be expected that new technical developments will make the cost of heavy-ion therapy more affordable. It is recognised, however, that the investment, at present, is of another order of magnitude compared to that necessary for neutron or proton generators.

This book on high-LET radiations would not have been complete without a review of the present status of boron neutron capture therapy (BNCT) and a discussion of its future perspectives. BNCT is a special type of high-LET radiation therapy, with the intention of achieving selectivity at the cellular level.

BNCT was initiated at MIT (Boston) and at the Brookhaven National Laboratory (BNL) in the 1950s. It was introduced in Japan by Hatanaka in 1968 for the treatment of brain tumours, and more than 130 patients were treated, including at least 12 American patients. The results reported from Japan were severely questioned by the radiotherapy community, in particular in the USA.
However, the rationale for BNCT, and in particular its attempt to achieve selective irradiation at the cellular level, is attractive and could open new perspectives in radiation therapy, especially for some tumours for which no efficient treatment is available at the moment (such as glioblastomas).

For these reasons, the US Department of Energy has supported BNCT research programmes and clinical application programmes at MIT and at BNL. A total number of 40 patients with glioblastomas were treated between September 1994 and December 1997. In Europe, the European Commission has supported a BNCT project in Petten, The Netherlands. The first treatment was performed in October 1997, and three patients had been treated by the end of 1997.

Combination of BNCT with fast neutron beam therapy has also been proposed in order to enhance the selectivity of fast neutron therapy. This combination has indeed been used in some neutron therapy centres, such as Essen in Germany and Seattle in the USA.

The two closing chapters thus appear timely, making this book on cancer therapy with high-LET radiations as complete and up to date as possible, especially regarding the situation in Europe.

Rita Engenhart-Cabillic

André Wambersie
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