Recent Results in Cancer Research

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Fast Neutrons and High-LET Particles in Cancer Therapy

With 83 Figures and 36 Tables
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*
## Contents

The Physical Basis for Radiotherapy with Neutrons .............................. 1  
  S. Vynckier and R. Schmidt

Specification of Radiation Quality in Fast Neutron Therapy:  
Microdosimetric and Radiobiological Approach ................................. 31  
  J. Gueulette, H.G. Menzel, P. Pihet, and A. Wambersie

Relative Biological Effectiveness of Neutrons for Cancer Induction  
and Other Late Effects: A Review of Radiobiological Data ................. 54  
  H. Engels and A. Wambersie

Neutron Therapy in Malignant Salivary Gland Tumors:  
Results at European Centers ....................................................... 88  
  A. Krüll, R. Schwarz, S. Brackrock, R. Engenhart-Cabillic,  
  P. Huber, F.J. Prott, N. Breteau, A. Favre, A. Lessel,  
  H. Koppe, and T. Aubeger

European Results of Neutron Therapy in Soft Tissue Sarcomas ........... 100  
  R. Schwarz, A. Krüll, A. Lessel, R. Engenhart-Cabillic,  
  A. Favre, F.J. Prott, T. Aubeger, and R. Schmidt

Use of Neutron Therapy in the Management of Locally Advanced  
Nonresectable Primary or Recurrent Rectal Cancer .......................... 113  
  R. Engenhart-Cabillic, J. Debus, F.J. Prott, R. Pötter,  
  K.H. Höver, N. Breteau, and A. Krüll

Fast Neutrons in Prostatic Adenocarcinomas:  
Worldwide Clinical Experience .................................................... 125  
  K.L. Lindsley, P. Cho, K.J. Stelzer, W.-J. Koh,  
  M. Austin-Seymour, K.J. Russell, G.E. Laramore,  
  and T.W. Griffin

The Role of Fast Neutrons in the Treatment of Squamous Cell  
Carcinomas of the Head and Neck: The European Experience ............. 137  
  T. Aubeger and W. Reuschel
Sacrococcygeal Chordomas: Potential Role of High-LET Therapy  ...  148
   N. Breteau, M. Demasure, J. Lescrainier, R. Sabattier,
   and P. Michenet

Complications of Fast Neutron Therapy ..................... 156
   L. Cohen

Is There a Role for Heavy Ion Beam Therapy? ............... 170
   J. Debus, O. Jäckel, G. Kraft, and M. Wannenmacher

Boron Neutron Capture Therapy: Principles and Potential ...... 183
   R. Gahbauer, N. Gupta, T. Blue, J. Goodman, R. Barth,
   J. Grecula, A.H. Soloway, W. Sauerwein, and A. Wambersie

Subject Index ...................................................... 210
List of Contributors*

Auberger, T. 88, 100, 137
Austin-Seymour, M. 125
Barth, R. 183
Blue, T. 183
Brackrock, S. 88
Breteau, N. 88, 113, 148
Cho, P. 125
Cohen, L. 156
Debus, J. 113, 170
Demasure, M. 148
Engenhart-Cabillic, R. 88, 100, 113
Engels, H. 54
Favre, A. 88, 100
Gahbauer, R. 183
Goodman, J. 183
Grecula, J. 183
Griffin, T.W. 125
Gueulette, J. 31
Gupta, N. 183
Höver, K.H. 113
Huber, P. 88
Kraft, G. 170
Koh, W.-J. 125
Koppe, H. 88
Krüll, A. 88, 100, 113
Jäckel, O. 170
Laramore, G.E. 125
Lescrainier, J. 148
Lessel, A. 88, 100
Lindsley, K.L. 125
Menzel, H.G. 31
Michenet, P. 148
Piët, P. 31
Pötter, R. 113
Prott, F.J. 88, 100, 113
Reuschel, W. 137
Russell, K.J. 125
Sabattier, R. 148
Sauerwein, W. 183
Schmidt, R. 1, 100
Schwarz, R. 88, 100
Soloway, H. 183
Stelzer, K.J. 125
Vynckier, S. 1
Wambersie, A. 31, 54, 183
Wannenmacher, M. 170

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1 Page on which contribution begins.
The Physical Basis for Radiotherapy with Neutrons

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Abstract

Radiotherapy with neutrons requires a large quantity of physical information about neutrons and their interaction with matter. Primarily the absorbed dose at a reference point needs to be determined. For treatment planning the dose distribution in a phantom must be measured and algorithms for the simulation of the dose distribution in a patient must be available. As neutrons interact with matter in a more complicated way as high-energy photons and electrons commonly used in radiotherapy, biological effects based on microdosimetric data are used for treatment planning. This paper presents a brief summary of the neutron sources used in radiotherapy. The dosimetry of the clinical neutron beams is described. Special aspects of the treatment planning with fast neutrons are discussed. For further radiobiological interpretation the fundamentals of microdosimetry are described. Finally recent and future developments in the field of physics for neutron therapy are mentioned.

Neutron Sources for Radiotherapy

Physical Properties of Neutrons

The neutron is an uncharged nuclear particle and therefore cannot be accelerated or deflected. Because of its physical properties its interaction with matter is based on reactions with the nuclei of the matter, mainly by elastic or inelastic scattering or in the low-energy region by capture processes.

Neutrons are generally denominated according to their kinetic energy $E_n$:

- Thermal neutrons \quad $E_n < 0.5$ eV
- Intermediate neutrons \quad $0.5$ eV < $E_n < 10$ keV
- Fast neutrons \quad $10$ keV < $E_n < 20$ MeV
- Relativistic neutrons \quad $E_n > 20$ MeV
Three principally different neutron sources can be used in radiotherapy: fission and radioactive sources, nuclear reactors and accelerators.

**Production of Neutron Beams for Radiotherapy**

**Nuclear Reactor**

Neutrons produced in a nuclear reactor cover an energy range from thermal to fast neutrons (Fig. 1). Converters and filters can be used to absorb thermal and intermediate neutrons, thus hardening the beam so that a mean energy of 1–2 MeV can be obtained. Neutrons from reactor sources are used for the treatment of superficial tumours or for neutron capture therapy. In boron neutron capture therapy (BNCT) a $^{10}\text{B}$ carrier agent is used to concentrate the boron in the tumour. The irradiation of $^{10}\text{B}$ by thermal neutrons reveals high-linear energy transfer (LET) $\alpha$-particles via the reaction $^{10}\text{B}(n, \alpha)^{7}\text{Li}$. The neutrons from a nuclear reactor or the thermalized neutrons from a fast neutron beam can be used. In the latter case the BNCT can be handled as a concomitant boost to fast neutron therapy, whereas for BNCT with reactor neutrons the energy deposited by the $\alpha$-particles is the therapeutic basis. The mean free path length of the neutrons can be increased by appropriate filtering to obtain penetration into deeper sites.

![Fig. 1. Typical reactor neutron spectrum](image-url)
Radioactive Sources

The most common neutron-emitting isotope is $^{252}\text{Cf}$. The emitted neutrons have a mean energy of 2 MeV; the radioisotope has a half-life of 2.65 years. $^{252}\text{Cf}$ sources can be used in remote afterloading systems for interstitial and intracavitary therapy in a way comparable to gamma sources.

A second type of “radioactive” neutron sources uses the reactions $^{9}\text{Be}(a, n)^{12}\text{C}$ or $^{9}\text{Be}(\gamma, n)^{10}\text{Be}$. The $a$- or $\gamma$-particles required for these reactions are obtained from radioactive sources. As $a$-emitting source $^{238}\text{Pu}$ and $^{241}\text{Am}$ radioisotopes are used, as $\gamma$-emitter $^{226}\text{Ra}$. These sources are used not for radiotherapy, but for calibration purposes.

Neutron Production by Accelerated Particles

Fast neutron beams for radiotherapy are generated by accelerating protons or deuterons onto a target. Depending on the physical interaction process these reactions are either called fusion or stripping reactions. The processes with importance in radiotherapy are listed in Table 1.

The fusion reactions needs only slightly accelerated particles to enter the modest potentials. The DD reaction has a $Q$-value of 3.27 MeV. If neutrons with higher energies are required, the incident deuterons have to be accelerated to higher energies. But then a second reaction, called deuteron break-up $[^{2}\text{H}(d, np)^{2}\text{H} \rightarrow 2.2 \text{ MeV}]$, may occur, leading to lower energy neutrons in the spectrum. High-pressure gas targets mounted to a small cyclotron were temporarily used for radiation therapy. The applied energy distribution was separated into the two energy groups of the neutrons produced by both reactions, as can be seen from Fig. 2 (Höver et al. 1975; Schraube et al. 1975; Watermann et al. 1978).

The high $Q$-value of the DT reaction provides fast mono-energetic neutrons with a penetration in tissue almost equivalent to $^{60}\text{Co}$ photons. DT generators can be constructed in a compact way so that an isocentric design is possible. Two different generator designs are used for neutron therapy: sealed tubes and rotating targets.

In sealed tubes a mixture of deuterons and tritons is ionized by internal electrodes and accelerated onto an integrated target. The design of a system used at Heidelberg and Münster is given in Fig. 3. The tritium is regenerated so that the sealed tube can be used for several hundreds of beam-hours. Then the whole tube has to be replaced. The neutron tube housed inside a collimator is mounted onto an isocentric gantry. Different circular or rectan-

<table>
<thead>
<tr>
<th>Fusion reaction</th>
<th>Stripping reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{2}\text{H}(d, n)^{3}\text{He} \text{ (}+3.27 \text{ MeV)}$ DD reaction</td>
<td>$^{9}\text{Be} (d, n)^{10}\text{Be} \text{ (}+4.35 \text{ MeV)}$</td>
</tr>
<tr>
<td>$^{3}\text{H}(d, n)^{4}\text{He} \text{ (}+17.58 \text{ MeV)}$ DT reaction</td>
<td>$^{9}\text{Be} (p, n)^{8}\text{Be} \text{ (}–1.85 \text{ MeV)}$</td>
</tr>
</tbody>
</table>