

**AN INFORMAL REPORT OF THE 'NEUTRONS FOR THERAPY' SATELLITE MEETING HELD CONCURRENTLY
WITH THE FIRST DAY OF THE 11TH NEUTRON AND ION DOSIMETRY SYMPOSIUM (NEUDOS-11)
CAPE TOWN - 12TH OCTOBER 2009**

Introduction

A satellite symposium under the title "Neutrons for Therapy" was organised for the first day of the NEUDOS meeting. There were representatives from all fast neutron facilities worldwide. There are [7] centres delivering a service of Fast Neutron Therapy (FNT) in [5] countries. Additionally, delegates from centres offering Boron Neutron Capture (BNCT) in 6 countries attended.

Neutrons have been used for therapy for more than five decades with varying interest from the radiotherapy community. Sadly, because the number of fast neutron facilities has decreased, experience and potential from them are often unknown to the mainstream radiation oncologist.

BNCT meanwhile looks, at last, to be making the big step from experimental set-ups on reactors to accelerator-based facilities in hospitals but this needs to be widely understood.

The principal aim of the meeting was to bring together this relatively small community to ensure that the quality of neutron applications is at the highest level, to maintain its skills and knowledge and to develop this modality to achieve the best outcomes for patients.

Summary report

More than thirty people from seven countries attended the meeting. They heard reports from fast neutron facilities worldwide including all three in the United States, both centres in Germany, from one of the Russian centres and, of course, from the South Africa facility where the meeting took place. Boron Neutron Capture Therapy experience was shared with the group by experts from Germany/The Netherlands, Russia and Japan.

For FNT, the meeting learned on the one hand that patients continue to be treated successfully at all facilities whilst, on the other hand, it became evident that at least two centres are threatened with closure (Essen and Detroit). Each centre has significant differences in beam energy, diluents, modulation, planning and treatment protocols. This, and the problems of adapting stand alone facilities with very special technology to modern standards of treating with sub-optimal facilities – so-called 'legacy' installations which are found in some centres – were recurring themes. These issues complicate data analysis and comparison.

Patient numbers may surprise some readers: 2,750 in Seattle, more than 2, 200 in Detroit, 1,700 in Cape Town and... The figures from the United States are, of course, restricted by disadvantageous reimbursement protocols.

The plan from the meeting included the following primary actions:

- achieve more publications
- retrospectively develop an international register of patients treated and outcomes

- improve communication between centres and the development of more effective web presence for FNT

In so many ways, BNCT is in a more positive position. It is now possible to offer hospital-based therapy using epithermal neutron sources. Two demonstration projects with linac prototypes are already producing a beam at the Budker Institute (Novosibirsk, Russia) and at the Kyoto Research Reactor Institute, Japan. The fascinating work on treating explanted liver is moving closer to delivering a serious option for a difficult-to-treat tumour site. BNCT has suffered from its complexity and the need to bring together basic scientists and clinicians which obviously still is not an easy task. The report from Detroit and Essen for Boron Neutron Capture Enhanced Fast Neutron Therapy (BNCEFNT) with results indicating the possibility of considerable therapeutic gains is both encouraging and interesting. It brings together the two roles of neutrons for therapy, which were the subject of this meeting.

Report of the meeting

Fast Neutron Therapy (FNT): The context for the use of neutrons was set in a very important reminder session on the radiobiology of High-LET radiations given by Professor John Gueulette from Louvain-la-Neuve. He showed the possibilities and challenges in the use of high LET irradiation in cancer therapy, which are of increasing interest for the new Carbon ion beam facilities that are under construction around the world. He related the Relative Biological Effectiveness (RBE) to a number of factors and noted that inter-comparison of beams is not straightforward. He also observed that the variation of RBE with energy raises difficult bio-physical problems: especially for carbon ions where RBE varies with depth and, second, for both ions and neutrons with energy variations between installations. This raised a recurring theme as the day advanced.

Professor Kobus Slabbert of iThemba LABS in Faure, South Africa emphasised the safety of FNT compared with photons and went on to report on differences in the radiosensitivities of different prostate cell types stressing the need for further radiobiological investigations across the community using different beam qualities. He especially emphasised the need to make these experiments using neutron beams of “lower” energies that have a much higher biological effect. Currently such beams are available only in Essen, Germany and in Tomsk, Russia.

Professor Sauerwein from the University Hospital Essen presented a paper sent by Dr Jay Burmeister (Wayne State University/Karmanos Cancer Center, Detroit) setting out the major technical advances made over the last five years in the Detroit FNT facility, where the possibility of intensity modulated fast neutron therapy has been developed. The potential of this new approach was demonstrated by calculating dose distributions in prostate cancer, the principal disease treated in Detroit – some 1,600 successful cases. Due to economical reasons (fast neutron therapy is reimbursed in the US on the level of conventional irradiation) Detroit however never applied this outstanding approach in patients has treated only one single case in 2008.

Again to a recurring theme for the day, Dr Tom Kroc from the Fermi National Accelerator Laboratory, Batavia, Illinois described the challenges in operating a sub-optimal early design system. At the Fermi Lab Fast neutron facility some 30 to 40 patients are treated annually. These are now principally head & neck and sarcomas. Referral of prostate has declined – reflecting, as others noted in the discussions, that in the US the reimbursement rules can disadvantage better medicine.

Dr Ruedi Risler reported that 2,750 cases have been treated with FNT at University of Washington Medical Center in Seattle where the cyclotron downtime is about 1.5% - a pretty remarkable statistic for an installation that has been running for 25 years. Dr Risler noted with considerable pleasure that the clinical team delivering FNT has been strengthened with the addition of four 'new' clinicians: two specialising in head & neck and two in sarcomas.

Dr Birgit Loeper-Kabasakal from Forschungsneutronenquelle Heinz Maier-Leibnitz FRM II in Munich presented data from the superseded reactor FRM I (715 patients) as well as from the new reactor (58 patients to date). Superficial lesions are treated with the very special beam using fission neutrons, which, in practice, means that it is used only palliatively. She noted the excellent local effectiveness and the resulting benefit for the patients in different conditions: relapses of breast cancer on the chest wall, malignant melanoma, squamous cell carcinoma and adenoid cystic carcinomas. Professor Sauerwein then gave a very full report of the technical aspects of the Essen cyclotron, which, until 2003, was seen as a research facility and so did not attract reimbursement from the German health system. Though the Essen unit is closed for major maintenance, patients are being taken to iThemba for treatment – funded by the German health insurers. He stressed the importance of international use of the few available FNT facilities to assure the provision of medical care to the rare diseases, in which FNT have been proven to be superior as compared to conventional radiotherapy, but also to maintain the knowledge of the safe use of such complex beams in radiation oncology.

Professor Fred Vernimmen (Tygerberg University Hospital and University of Stellenbosch) chaired what was probably the most significant part of the meeting: 'Quo Vadis Fast Neutron Therapy'. He gave the initial talk reporting that some 1,700 patients had been treated at iThemba LABS (about 40% salivary gland carcinomas, 10% head & neck and a variety of other pathologies including breast, malignant melanoma, mesothelioma, osteosarcoma, soft tissue sarcoma and uterine sarcoma). For all of these, the outcomes have in general been good but the spectrum of staging and sub-pathologies makes comparison of results versus conventional radiotherapy difficult. He noted the technological improvements at the Cape Town facility and the parallel advances for photon radiation in the last twenty years.

The meeting heard a report of the operational aspects of FNT at iThemba from Dr Julyan Symonds which informed both the following discussion and the tour of the facility which followed later in the afternoon.

Professor Sauerwein presented a paper from Dr Michael Snyder of Detroit on Intensity Modulated Neutron Radiotherapy (IMNRT) vs. 3D Conformal Neutron Radiotherapy and a presentation prepared by Professor Musabaeva (Cancer Research Institute, Tomsk, Russia) on results of neutron and mixed beam therapy there. The former is a study in which retrospective IMNRT plans have been developed for

patients previously treated with 3D conformal neutrons. The result opens up the possibility of enhanced prostate treatments with IMNRT and suggests that it might allow neutron therapy to be effective at sites previously restricted by normal tissue toxicities. The latter indicated that 1500 patients have been treated in Tomsk using a 6.3 MeV beam over 25 years for patients with inoperable cancers with remarkable success: 2% local recurrence for breast cancer after 8 years with increased overall survival and no radiation-induced ulcers, Professor Musabaeva concludes that neutron therapy appears to be effective in the treatment of patients with locally advanced breast cancer and breast cancer local recurrence. This was the first time that the Russian results were presented to an international meeting. The presentation was made possible by the support from the ISTC (international Science and Technology Center Moscow), a G-8 office supporting international exchange for Russian Scientists.

Professor Vernimmen then posed difficult questions for FNT. Facilities generally are aging and it is difficult to justify new spending; the results from different centres are for the same pathologies but with differing beam qualities and different technical equipment.

In the ensuing discussion, Professor Sauerwein told of the need for new publications – one is expected on salivary glands from South Africa shortly – and the need to establish an international register of patients suitably anonymised. Centres should pool retrospective data categorised by sub pathology and then review the data to see if numbers are sufficient to make analysis meaningful. He shared Professor Vernimmen's view that prospective studies should be homogenous. The difficulties here were reprinted. Dr Slabbert suggested that only recent data be included where modern treatment planning has achieved excellent dose distributions. Dr Mark Swanepoel from iThemba raised the issue of DNA repair/damage.

There are enormous problems for neutron therapy: history, limited dissemination of excellent results, relatively few patients, disincentives in reimbursement protocols and the effects of all of these on motivation for those practising FNT. However, the meeting established that there is a much good work being done, real development and, above all a valuable FNT community.

In the main auditorium the following day, Professor Wambersie from the Université Catholique de Louvain, Belgium, presented a paper to the NEUDOS symposium entitled 'What can we learn from the neutron clinical experience for improving high-LET ion-beam techniques and patient selection?' He stated that radiotherapy will be improved by physical selectivity (accuracy) and differential effect (radiobiology). He noted that the greatest accuracy is currently achieved in proton therapy and that the best differential effect is achieved with neutron therapy. He suggested that the combination of these two advantages is why carbon ion therapy will prove to be very important. Professor Wambersie reflected on the history of neutron therapy noting that the damage to normal tissue that caused so much antipathy to the modality has largely been overcome by great improvements in collimation. He also noted, perhaps controversially, that advances in surgical techniques have meant that some of the patients for whom neutron therapy was indicated 30 years ago need not now be sent for such treatment.

Boron Neutron Capture Therapy (BNCT): BNCT now seems to be ready to offer hospital-based therapy using epithermal neutron sources. Two demonstration projects with linac prototypes already producing a beam at the Budker Institute (Novosibirsk, Russia) and at the Kyoto Research Reactor Institute, Japan were presented by Dr Sergey Taskaev and Dr Tooru Kobayashi respectively. Dr Taskaev advised that all the problems of lithium targets have been solved so that the facility is ready for the measurement of neutron spectra and for *in vitro* and *in vivo* investigations after modernisation. From this he concludes that a machine capable of generating the current needed to deliver therapy in a reasonable timescale can be built. Dr Kobayashi reported wide ranging work on technical subjects in accelerator-based BNCT and noted specific successes. There are three projects employing different types of accelerators and neutron generators: Dynamitron, FFAG and cyclotron. The latter started basic experiments in July 2009 and is expecting to become the first accelerator-based BNCT irradiation system in the world used for treating patients.

The session commenced with a presentation by Dr Andrea Wittig from University Duisburg-Essen setting out the rationale for BNCT and reporting the progress being made in bringing it into clinical practice. She summarized results from 7 centres in 5 countries drawing special attention to prospective controlled trials which will yield the much sought modern evidence base. The ability of BNCT to target single cells has the potential to enable the destruction of tumour cells protecting already irradiated normal tissues. Dr Wittig also noted the extension of BNCT indications away from brain lesions to cancers localized at the head and neck region, melanoma, sarcoma and the successful extracorporeal irradiation of an explanted liver with multiple metastases. High costs impede progress for BNCT but new hospital based accelerators for epithermal neutrons under construction in Japan will promote research for BNCT. Key is the strategy for clinical trials necessary to bring BNCT into routine clinical practice.

Anastasia Elyutina reported on dosimetry planning for BNCT at the Moscow Engineering Physics Institute (State University) where BNCT work started in 1993 where preclinical trials have been performed in animals with malignancies such as melanoma and osteosarcoma. Work on the development of dosimetry planning software is in progress, as well as BNCT treatment planning calculations using the existing special-purpose codes. Anastasia Elyutina described the computer modelling of the two therapeutic beams created and how the sources of experimental errors and computational time and how the beam models are used for planning a BNCT clinical trial for glioblastoma.

Dr Christian Schültz from the Institute of Nuclear Chemistry at the University of Mainz in Germany reported on work done with the University of Pavia, Italy, and other international partners on liver metastases of colorectal cancer. Research work is progressing on scientific, clinical, logistical aspects as well as on computational modelling, tissue and blood analysis, radiation biology, dosimetry and surgery. He reported a current study with 15 patients to determine boron uptake in both healthy and tumour tissue.

Professor Sauerwein presented a paper on Boron Neutron Capture Enhancement of Fast Neutron Therapy (BNCEFNT) at Wayne State University and at the Cyclotron Isocentric Neutron Therapy Facility Radiological Centre Essen (CIRCE) whose first author is Dr Jay Burmeister. The aim of the research is to gain the advantages detected for FNT in the treatment of glioblastoma multiforme which have proven

refractory to conventional radiotherapy without unacceptable doses to normal tissue. The provision of a boost using the BNC reaction to make a gain of 30% specific to the tumour was shown possible even assuming currently achievable boron concentrations. A different approach was used at CIRCE because its beam is of lower primary energy. It is possible to optimise the dose distribution at depth even when using boron compounds without high tumour specificity.

Professor Sauerwein then led a discussion on the future of accelerator based BNCT at hospitals. The progress made in the last two years was surprising. The Russian group estimated the actual costs of an accelerator for a high intensity epithermal neutron beam, based on their prototype in Novosibirsk, is approximately 4 Million Euro (without a gantry) which places such a facility close to the costs of a conventional linac and makes them in reach for hospitals. The Japanese group from Kyoto is not ready to commercialise their machine but would like, in a first step, to extend BNCT applications using their new accelerator at the Research Reactor Institute of the Kyoto University. It was expected that in the coming two years the number of patients treated will considerably increase, at least in Japan.

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