

Neutron radiotherapy in South Africa

Neutron radiotherapy: a different perspective

To the Editor: As the director of one of the longest running neutron radiotherapy programmes in the world (27+ years and 2 900 patients treated) and a member of an international team that reviewed the iThemba laboratories particle radiotherapy programme on behalf of the National Research Foundation in 2010, my view of neutron radiotherapy and the iThemba-Faure facility differs from that of Abratt.^{1,2}

Fast neutron radiotherapy has not proved to be the panacea in cancer therapy as was hoped in the 1970s and 1980s. Most early clinical trials showed no advantage to fast neutron radiotherapy over standard photon radiotherapy for common tumours; therefore, interest waned. Long-term side-effects of the early studies were often more severe with fast neutrons, but this was largely attributable to primitive treatment facilities (e.g. laboratory-based, fixed horizontal beams, primitive collimation and blocking). The University of Washington and iThemba facilities have more sophisticated isocentric rotational gantries with movable floors and multi-leaf collimators which allow treatment configurations comparable with conventional photon radiotherapy. This allows for more normal tissue sparing, resulting in a lower incidence of side-effects than quoted in the older literature.

Salivary gland malignancies are one example where improved outcomes have consistently been reported.³ As Abratt noted, the initial, multi-centre randomised trial accrued only 32 patients before it was closed for ethical reasons. At closure, there was a statistically significant improvement in local and regional control in the neutron-treated group and a trend towards improved survival. With longer follow-up time, the survival curves came together (everyone eventually dies of some cause). However, the cause of death differed with the largest factor being local/regional disease in the photon-treated group and distant metastases in the neutron-treated group. The improved local/regional control in the neutron-treated group allowed time for the manifestation of distant metastases. Since 2000, our research group has documented its research outcomes in 25 articles and invited book chapters. Recently, we showed that 80% of salivary gland tumours with inoperable, skull-base disease can be controlled with a multi-leaf collimator and a Gamma Knife boost.⁴ We also use our neutron beam to treat inoperable sarcomas, anaplastic thyroid cancers, mucosal melanomas, and other 'radioresistant' tumours in selected clinical situations.

There is a continuing role for high linear energy transfer (LET) radiotherapy in treating human malignancies. The University of Washington, through the Seattle Cancer Care Alliance and ProCure, is building a proton radiotherapy centre that will be operational in 2013. However, we intend to keep our neutron radiotherapy facility operational as we feel that there are many instances where this will better serve patients. The iThemba-Faure neutron facility needs to be maintained as a resource for Africa, with improved patient recruitment for increased utilisation and sufficient resource allocation for optimal programme functioning.

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2. Abratt RP. The fast neutron therapy programme for patients in South Africa should come to an end. *S Afr Med J* 2012;102(2):58.
3. Laramore GE, Krall JM, Griffin TW, et al. Neutron versus photon irradiation for unresectable salivary gland tumors: final report of an RTOG-MRC randomized clinical trial. *Int J Radiat Oncol Biol Phys* 1993;27(2):235-240.
4. Douglas JD, Goodkin R, Laramore GE. Gamma knife stereotactic radiosurgery for salivary gland neoplasms following neutron radiotherapy. *Head Neck* 2008; 30(4):492-496. [<http://dx.doi.org/10.1002/hed.20729>]

Neutron radiotherapy should continue

To the Editor: Abratt's letter¹ needs a response. We are currently – or have been directly – involved in treating patients with fast neutrons for decades; some with more than 20 years' experience in proton therapy, and others working at major hospitals with modern, high-end facilities for radiotherapy with photons and electrons.

Prof Abratt's opinion was held in the late 1980s when severe late effects of fast neutron therapy (FNT) were recognised, resulting in the early enthusiasm for this modality abating. FNT was introduced into clinical practice after careful radiobiological work, particularly by LH Gray. FNT, the first high linear energy transfer (LET) radiation used in radiotherapy, has not fulfilled the early optimistic laboratory-based expectations. Initial treatment beams had inferior physical characteristics. However, clinical FNT now has facilities with high-energy beams, individually shaped fields, isocentric beam delivery and full 3D treatment-planning systems and image guidance, and it can be applied safely at dedicated centres. However, well-trained personnel are needed who understand the particles' biological effects and complex physical behaviour.

Proven indications for FNT are limited and will benefit few patients. However, for some indications, neutron therapy remains superior to other modalities, despite advances in oncology. The early closure of the one prospective clinical trial,² due to the unexpected demonstration of superior results of FNT over conventional low-LET radiotherapy for salivary gland tumours, precluded more patients being recruited. Had the trial continued, it may have led to a better understanding of the effects of neutrons on survival. Nevertheless, today, FNT is the standard and established evidence-based treatment for adenoid cystic carcinoma of the salivary glands, and should be maintained for patients who will benefit from high LET FNT. This knowledge is advantageous for such a rare disease; in most other similar situations, treatment is based on opinion rather than facts from randomised trials. Other FNT indications should be regarded as research or prescribed as an individual treatment decision.

Research is another important role for neutron therapy facilities, e.g. basic physics (interactions of neutrons with biological materials), dosimetry, technological developments and radiobiology, clinical trials and treatment application.

Few highly industrialised countries have the financial and technical capacity to explore carbon ion therapy, which combines a high LET effect with an excellent dose-distribution profile. Their clinical results will take time to guide the radiotherapy community in its use and prove the superiority of delivering expensive high LET radiation.^{3,4} FNT history also shows that new developments which excite great enthusiasm may not always be justified; they need careful evaluation over time before becoming irrefutably beneficial for patients. The medical community must accept this less exciting period as essential. It is easier to demonise neutrons and conclude that they should not be used than to spend a long time learning how to use them safely.

Prof Abratt rightly notes the effective and safe use of proton (low LET) therapy but that is not a relevant argument against FNT. Different particles are needed for optimal treatment of different tumours.

iThemba LABS offers high LET radiation to South Africa and its neighbours at a fraction of the cost of carbon ion facilities. It has the infrastructure and knowledge to deliver this therapy safely, and its neutron therapy facility is regularly used for patients from Europe. Prof Abratt calls for fiscal responsibility – it would be fiscally irresponsible not to use South Africa's high LET facility and to send patients overseas for such therapy.

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Neutron radiotherapy: Abratt reply

To the Editor: The clinical fast neutron therapy programme in South Africa (SA) should be discontinued because:

- (i) Many experimental and clinical studies show an increase in serious late normal tissue complications with neutron therapy,^{1,2} which can be reduced in part by using the technology described in the letters by Laramore³ and Sauerwein *et al.*⁴ Nevertheless, its ability to deliver irradiation to tumours and spare normal tissue is inferior to that of other contemporary radiation modalities. More importantly, these complications arise from the interaction of neutrons with normal tissue, and are progressive with time. A patient's perspective of the debilitating morbidity after modern neutron therapy for adenoid cystic carcinoma of the parotid has been described.⁵
- (ii) Continuation of the neutron therapy programme cannot be supported based on the results of Phase III studies. The authors of the aforementioned letters refer repeatedly to the 1993 study of 32 patients with salivary gland tumours,⁶ but its data do not support the use of neutron therapy. In the study, neutron therapy was administered to 13 patients, resulting in severe toxicity in 9 patients and life-threatening toxicity in 2 patients. This toxicity was much higher than in the photon therapy arm. The trial was discontinued due to decreased referrals.
- (iii) Due to the disappointing outcome of patients treated with fast neutron therapy, all such facilities – except for 2 in the USA – have been discontinued in England, Europe, Canada and the USA.
- (iv) There are few peer-reviewed publications in the PubMed database on clinical studies of fast neutron therapy over the last 10 years.

Although the subject is the neutron therapy programme in SA, none of the 13 co-authors of the letter by Sauerwein *et al.* practice as a radiation oncologist in SA. They present no additional data to justify the continuation of this clinical fast neutron therapy programme. The radiobiological research programme is a separate matter.

Prof Laramore argues for further patient recruitment, continued resource allocation and for the neutron therapy programme to serve as a resource for Africa. The call for increased recruitment is unrealistic as the strong trend is of decreasing referrals to the programme. The average radiation oncology department in SA sees 150 - 300 new patients per month, whereas patient accrual to the neutron therapy programme is reportedly 1 - 2 patients per month in the last year.

Advocating the maintenance of resources for the programme is counter to our need for fiscal responsibility within our resource-constrained environment. Moreover, the failure of neutron therapy to meet its goals is not due to a lack of resources, but rather the biological nature of the therapy.

The neutron therapy programme, as a resource for Africa, has no basis; its shortcomings are as relevant to patients from Africa as they are elsewhere and are compounded by the distance of the site for patients. African studies give no weight to neutron therapy in cancer control programmes, but rather value conventional cancer prevention strategies and therapies.⁷

There have been exciting new developments in the technologies of other radiation modalities including proton particle therapy, and in the concurrent use of radiation with biological therapy and chemotherapy. The latter requires high precision radiation administration by contemporary radiation techniques with other modalities. Phase III studies with large numbers of patients document the safety and efficacy of these approaches for most of the common solid tumours, e.g. cancer of the cervix, lung, rectum, oesophagus,

1. Abratt RP. The fast neutron therapy programme for patients in South Africa should come to an end. *S Afr Med J* 2012;102(2):58.
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