

Dear Editors,

With great interest I studied the editorial by Bengt Glimelius and Anders Montelius as well as the reviews by Mark Lodge, *et al* and Dag Run Olsen, *et al* in the May 2007 issue of *Radiotherapy and Oncology* concerning hadron and ion therapy. Mark Lodge correctly quoted my statement that at present no future fast neutron therapy facilities are being planned and he opted to leave a review of the effectiveness of neutron therapy for a separate analysis. Hence, I was surprised that Glimelius and Montelius quoted his article as saying that all the neutron trials were negative (*Radiotherapy and Oncology* **83** (2007) 106).

In fact, an extensive review of neutron clinical trials was commissioned by the International Atomic Energy Agency in 1992. It included an international review committee and the results were published in 1997 (1). The committee reviewed over one hundred documents, including international randomized clinical trials as well as status reports from individual clinics. For your convenience, I include a list of the most relevant references. (2- 18 ) Because funding for randomized clinical trials was not available after the mid 1990's, this document represents a good summary of the currently established role for neutron therapy. On page 23 the authors list "tumors for which fast neutrons were found to be superior to conventional x-rays:"

1. Salivary gland tumors (locally extended, well differentiated)
2. Paranasal sinuses (adenocarcinomas, adenoid cystic carcinomas)
3. Some tumors of the head and neck area (locally extended, metastatic adenopathies)
4. Soft tissue sarcomas, osteosarcomas, chondrosarcomas (especially slowly growing/well differentiated)
5. Prostatic carcinomas (locally extended)
6. Melanomas (inoperable/recurrent)

The report says more research is needed for inoperable pancreatic, bladder, esophageal tumors, recurrent or inoperable rectal tumors, locally advanced uterine cervix tumors, and neutron boosts for brain tumors.

The issue of complication rates was addressed by T. Griffin et al in *Bull. Cancer (Paris)* 73,5:582-586 (1986). The essence of the explanation is that most early trials were conducted using low energy neutron beams whose penetration was equivalent to orthovoltage or cobalt beams. Some trials conducted with these low energy beams were disappointing. High energy beams such as the 66 MeV neutron beam at Fermilab and iThemba lab have depth dose distributions and off-axis ratios similar to 8 MV photon beams. For beams in this energy range, complications are similar to those caused by

photon beams, and depend on total dose, volume treated and pre-existing conditions caused by previous treatments.

Though there currently are no plans for additional facilities, there is ongoing work to upgrade beam delivery capabilities. For example, for his thesis project, J. Farr designed and built a compact multileaf collimator for conventional and intensity modulated fast neutron therapy, (*Med Phys.* 33(9), Sept 2006), while Santanam *et al* developed software to calculate and compare intensity modulated neutron and photon therapy. (*Int. J. Radiation Oncology Bio. Phys.* 68(5), 2007). Here at Fermilab we are doing research related to compensator-based intensity modulated fast neutron therapy.

Without attempting a full-blown cost-effectiveness analysis, I will point out that fast neutron therapy is completed in twelve fractions, three per week for a total four weeks. If one set of patients is treated Monday-Wednesday- Friday and another set on Tuesday-Thursday-Saturday a single treatment room can handle twice as many patients as a single photon-therapy room per week. Completion of therapy in four weeks rather than the typical 6-8 weeks also allows for another factor of two in patient throughput, implying that a single neutron treatment room can be equivalent to four photon treatment rooms in terms of patient throughput. In addition, patients really appreciate a course of therapy involving only twelve treatments, compared to the typical 30-40 visits. A 70 MeV proton cyclotron for producing neutrons costs about \$12M, can service four treatment rooms and can also produce medically useful radioisotopes during the night and during patient setups. Costs for the gantries and shielding will be more than those for photon therapy (but less than proton or ion therapy), and can be offset by the extra patient throughput and production of radiopharmaceuticals.

Recent *in vitro* experiments at Fermilab with fractionated treatment of human prostate cells has shown a relative biological effectiveness (RBE) of 4. Clinical research with human subjects has also shown an RBE of 4 for prostate cancer, compared to an RBE of 3 for normal tissue. (J.D. Forman *et al*, *Journal of Brachytherapy Int'l*, 13:29-34(1997)). Mary Catterall has estimated an RBE for salivary glands as high as 7. (private communication).

In light of the well-known high RBE of neutrons, the ability to provide shorter treatment courses with fast neutrons and the still untried use of intensity modulated fast neutron therapy with a high-energy accelerator, it appears that research funds dedicated to hadron therapy would be more efficiently spent on a state-of-the-art 70 MeV fast neutron facility, rather than a proton facility, for which anticipated results can be inferred from photon results.

Sincerely,

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