

High-Energy Neutron Therapy for Radioresistant Cancers

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Abstract

Randomized prospective clinical trials have demonstrated that high energy neutron therapy is superior to low dE/dx radiation such as photons or protons for certain cancers, including salivary gland tumors, melanoma, sarcoma and locally advanced prostate cancer. Neutrons exhibit a biological advantage because their interactions in tissue are quite different from those of photons and protons. For best clinical results, proton linacs or cyclotrons are used to generate an ~70 MeV proton beam with average intensity ~200 microamperes. The proton beam strikes a beryllium target to produce a high energy neutron beam that, unlike reactor-generated neutron beams, is well collimated and can be used for conformal neutron therapy or intensity modulated neutron therapy. This paper discusses the radiobiology of neutron-tissue interactions, presents clinical results of national/international trials, and describes some issues related to designing a modern high-energy neutron therapy facility, including the possibility of generating medically useful radioisotopes.

1. Introduction

International clinical trials with fast neutrons were enthusiastically embraced from the mid-1970's through the mid-1980's, only to be nearly abandoned in the late 1980's as clinicians observed unacceptable side effects. The problem was analyzed by Griffin *et al* in a 1986 publication showing that neutron generators using primary deuteron beams with energies below 50 MeV produced beams with tissue-penetration properties that made it difficult to achieve good clinical results [1]. By the late 1980's only one of the facilities described by Griffin continued to operate, namely the p(66)Be(49) beam at the Fermi National Accelerator Laboratory (Fermilab). In 1984 a new p(50)Be(25) beam was commissioned at the University of Washington in Seattle, Washington. These two high-energy beams continue to operate as clinical beams because the clinicians recognize the value of fast neutron therapy for otherwise intractable cases. In addition, a fast neutron beam modeled on the Fermilab beam continues to operate at iThemba Laboratory in South Africa and a lower-energy fast neutron beam is used to treat salivary gland tumors at the University Clinic in Essen, Germany. The next section describes the unique biological properties of fast neutron therapy.

2. Radiobiological Aspects of Neutron Therapy

Extensive research leading to an understanding of the radiobiology of neutrons was conducted in England during the 1970's. A summary of the most important findings is given in reference [2]. Specifically

- Neutrons are more effective per unit dose than x-rays
- Cell survival curves for neutrons are more nearly exponential than those of x-rays
- The modifying effect of hypoxia is smaller for neutrons than for photons
- Cell sensitivity to neutrons is much less dependent on cell growth stage than cell sensitivity to photons

These phenomena can be explained by comparing the interactions of neutrons and x-rays (photons) in tissue. Because protons interact with tissue in much the same way as x-rays, the limitations mentioned above for x-rays also apply to protons.

2.1 Neutron Interactions with Tissue

With conventional photon or proton therapy, the radiation beam interacts with atoms in human tissue primarily via electromagnetic interactions that may disturb the molecular bonding in cellular DNA. Or the photons or protons may interact with water molecules in the body to form the OH^\cdot radical, that, in turn damages DNA. The presence of oxygen in the cell facilitates the formation of OH^\cdot ; this explains why smaller, well-oxygenated tumors are more likely to respond to photon or proton irradiation while larger hypoxic tumors are less affected by these types of radiation. Because the amount of energy transferred to the cell is relatively small in a single interaction, these interactions are called low Linear-Energy-Transfer (LET) reactions. Low LET damage to tumor cells is often repaired, and the tumor continues to grow.

In contrast, neutrons interact primarily via (n,p) or spallation interactions, depositing a large amount of energy, (high LET), and often transforming the atom in the DNA strand into a completely different atom. A tumor cell whose DNA is damaged to this extent cannot repair itself and will ultimately die. This inability for the tumor to repair is one factor accounting for the higher relative biological effectiveness (RBE) of neutron therapy and for the differences in the shapes of cell-survival curves. Many of the early radiobiology textbooks hypothesized that the number of double-strand breaks in DNA was greater for high LET neutrons than for low LET radiation. It was believed that the greater number of double strand breaks was responsible for the smaller amount of repair observed with high LET radiation. In fact, as several radiobiological experiments at Fermilab have shown, the number of single and double strand breaks is about the same for high and low LET radiation. The smaller incidence of repair with high LET radiation is due to the more extensive nature of the damage at an interaction site rather than a larger number of interaction sites. The high RBE associated with high LET radiation has also been attributed to the fact that for high LET radiation, cell killing is relatively independent of cell growth-cycle stage [3].

With any type of radiation some healthy tissue will also experience a sub-lethal dose during the process of treating a tumor. In cases where a damaged healthy cell cannot repair, other healthy cells in the neighborhood of a damaged healthy cell counteract the damage by generating new cells (repopulation). Thus, as will be seen in the following section, healthy tissue that has received a sublethal dose of neutrons will recover, just as healthy tissue damaged by sublethal doses of photons or protons will recover. In both cases the extent of long-lasting damage (late side effects) depends on the given dose. A detailed comparison of the interactions of photons and neutrons in tissue is given in reference [4].

2.2 Illustrative Radiobiological Results

Figure 1 shows a simple example of the difference between neutron and photon cell-killing properties for two different human prostate cancer cell lines, both of which are classified as being radioresistant. DU145 and PC3 human prostate cancer cells were irradiated to a single 3 Gy dose of either $\text{p}(66)\text{Be}(49)$ neutrons at Fermilab or photons from a cesium source at Rush-Presbyterian-St. Luke's Medical Center [5]. Two characteristics are immediately noticed. First, neutrons were more effective than photons at killing both types of tumor cells, with the small difference in survival not being statistically significant. Second, there is a considerable difference in survival in the two cell lines when photons are used. The cause of this difference was not examined, but it is consistent with earlier observations that with photons the amount of cell-kill can vary with factors such as cell growth-cycle stage and oxygen levels.

In a more realistic follow-up experiment, the DU145 cells were irradiated with either photons or neutrons using a multiple-fraction schedule corresponding to the multiple fraction schedule typically used to treat prostate cancer patients in the clinic. Using 0.001 survival as an endpoint, Figure 2 shows that 7 Gy of neutrons are equivalent to 28 Gy of photons, corresponding to an RBE of 4 for this prostate cancer cell line [6]. These results are consistent with the RBE value obtained in a randomized clinical trial involving prostate cancer patients [7].

Survival curves for two human prostate cancer cell lines.

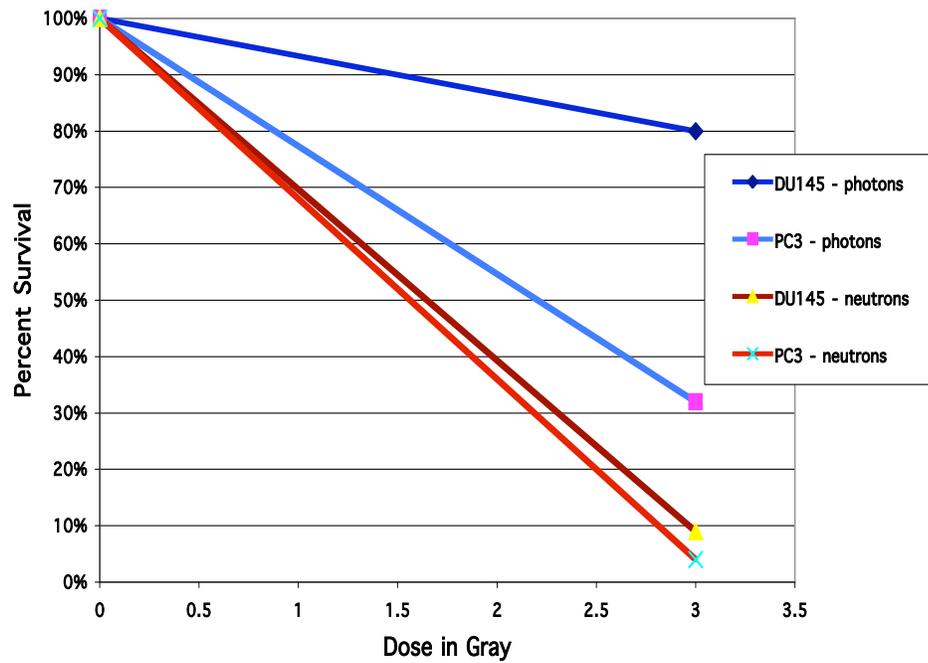


Figure 1: Simple example of survival of two radioresistant human prostate cell lines in vitro following a single 3-Gray dose of either photons or neutrons.

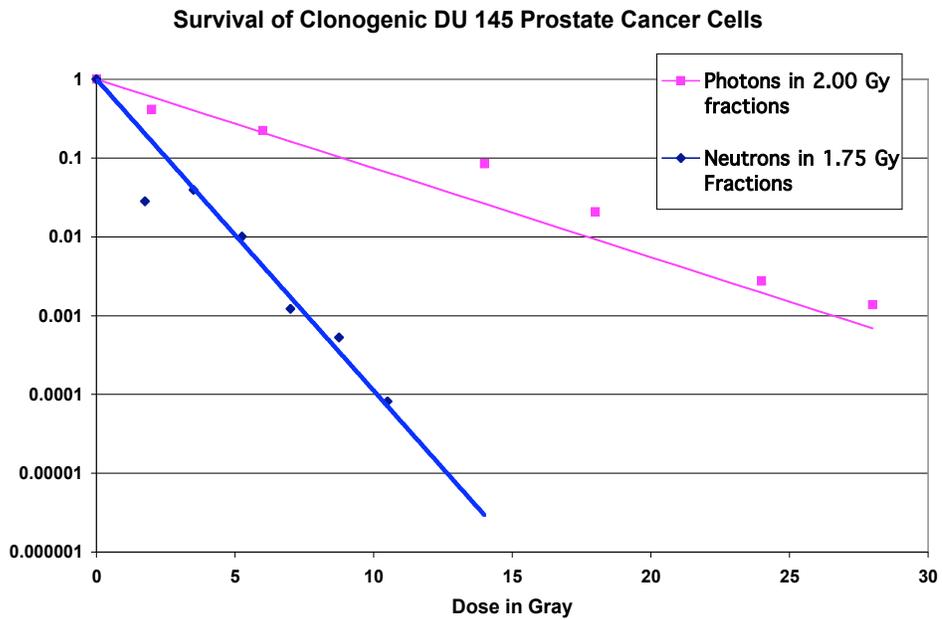


Figure 2: Using a survival endpoint of 0.001 neutrons exhibit an RBE of 4 for this human prostate cancer cell line. Seven Gray of neutrons exhibit the same “killing power” as 28 Gray of photons.

Experiments with other human cancer cell lines exhibit the same trend seen with prostate cells. For example, Figure 3 shows results for human brain tumor cells. These irradiations were performed using the neutron beam at Fermilab and a cesium source at Northern Illinois University [8]. As with the prostate cells, survival curves for brain tumor cells harvested from two different patients vary for photon irradiation but are the same for neutron irradiation. This reinforces earlier observations that neutron cell-kill is less dependent on cell stage and oxygen levels than photon (or proton) cell-kill.

Finally, Figure 4 shows results of an experiment using a γ H2AX biomarker to study the development of double strand breaks for photons and neutrons. The vertical axis shows the number of double strand breaks identified by the biomarker at various times after the end of radiation. For both types of radiation double-strand breaks continued to develop for about ten minutes after irradiation, but after that period the number of neutron-induced breaks remained constant, while the photon-induced breaks continued to repair. Further experiments are needed to determine the time at which the photon-induced damage is no longer repaired [8]. These results support the interpretation that neutrons do not produce more double strand DNA breaks compared to low LET radiation, but that there is no repair of neutron-induced double strand breaks.

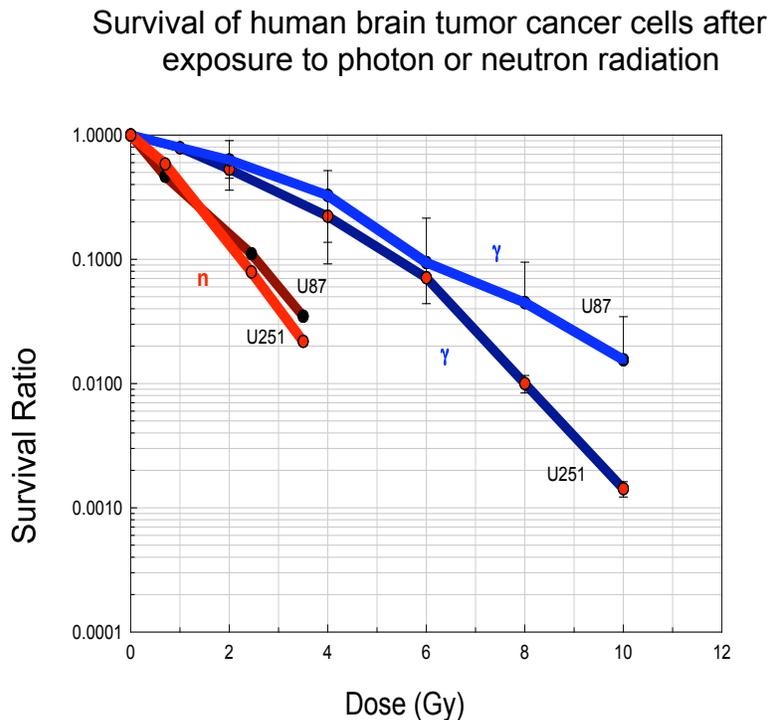


Figure 3. Different human brain tumor cell lines exposed to neutron therapy experience the similar probabilities of being killed. Those exposed to photon therapy have differing cell-kill probabilities.

γ H2AX Biomarker Shows Presence of Double-Strand Breaks

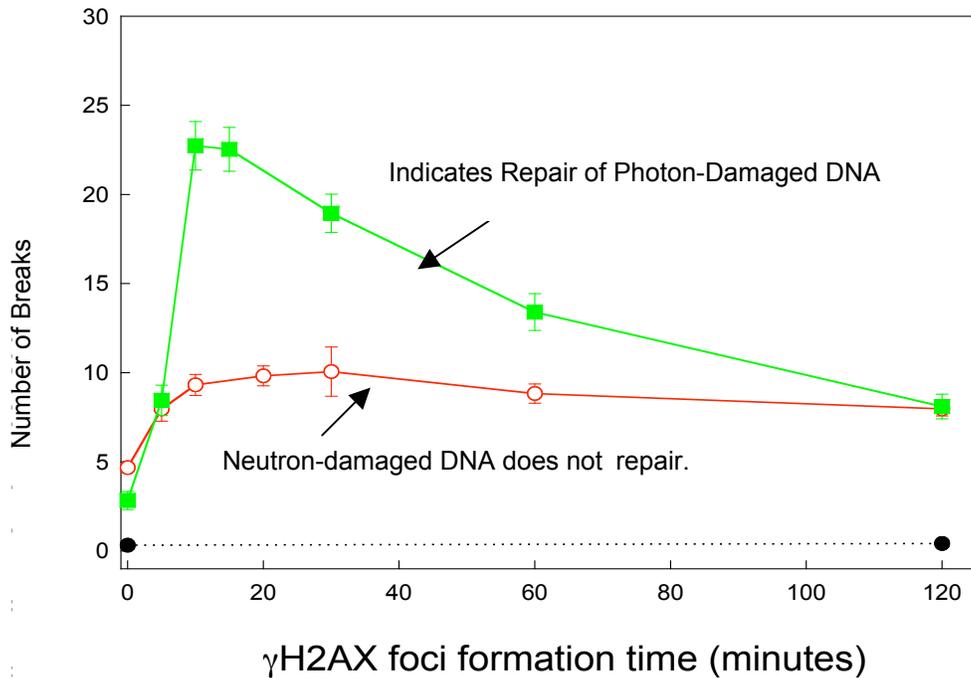


Figure 4. γ H2AX biomarker indicates the number of double-strand DNA breaks in Chinese hamster ovarian cells after irradiation with photons or neutrons.

3. Clinical results

In 1987 the International Atomic Energy Agency organized a Coordinated Research Program (CRP) on Nuclear Data Needed for Neutron Therapy. The CRP met between 1987 and 1993 and prepared a report (TECDOC-992) that included an evaluation of all clinical trials conducted with fast neutrons until that time [9]. The document provides a good summary of clinical results, because funding for clinical trials terminated in the mid-nineties and the handful of studies conducted after 1995 obtained results that were consistent with the earlier findings. The CRP concluded that

Tumors where fast neutrons are superior to photons are:

- Salivary glands - locally extended, well differentiated
- Paranasal sinuses - adenocarcinoma, mucoepidermoid, squamous, adenoid cystic
- Head and Neck - locally extended, metastatic
- Soft tissue sarcoma, osteosarcoma, and chondrosarcoma
- Locally advanced prostate
- Melanomas Inoperable/recurrent [10]

Tumors for which more research is needed are:

- Inoperable Pancreatic
- Bladder
- Esophagus
- Recurrent or inoperable rectal
- Locally advanced uterine cervix
- Neutron boost for brain tumors [11]

Most significantly they concluded that: “The proportion of patients suitable for neutrons ranges from 10-20%, but this is probably a lower limit ...with high energy modern cyclotrons neutron therapy will be useful for a larger proportion of patients.” [12] In fact, most of the neutron patients today are being treated with a high-energy proton linac.

Additional clinical results are summarized below.

3.1 Salivary Gland tumors

The best statistics are available for salivary gland tumors, probably because even those accelerators whose energy was too low to treat deep-seated tumors could be used to treat salivary gland tumors, which tend to be fairly superficial. Table 1 summarizes international data collected in the TECDOC-992 report. The term “local control” means that the tumor completely disappeared in the treated volume and did not recur in or near that volume. It does not address the issue of distant metastasis. A person could achieve local control of the tumor and still have cancer elsewhere in his/her body.

Table 2 has fewer statistics than Table 1 but is interesting because it was terminated early based on ethical considerations. After two years follow-up the results with neutrons were so much better than those with photons that it was considered unethical to randomize patients to the photon arm [13]. Figure 5 shows an example of a salivary gland tumor treated with fast neutrons at Fermilab. Note that the tumor is inoperable and is large, implying that it may be hypoxic and may have cells in the resting stage.

Table 1: Loco-regional control of malignant salivary gland tumors. International clinical trials 1972-1990.

	Number of Facilities	Number of Patients	Local Control ($p = 3.7E-25$)
Neutrons	10	310	67%
Photons	10	254	24%

Table2: Loco-regional control of inoperable salivary gland tumors: an international prospective randomized trial.

	Photons	Neutrons
Number of Patients	12	13
Loco-regional control at 1 year at 2 years ($p=0.01$)	17 ± 11% 17 ± 11%	67 ± 14% 67 ± 14%
Survival at 1 year at 2 years ($p=0.06$)	67 ± 12% 24 ± 14%	77 ± 12% 62 ± 14%

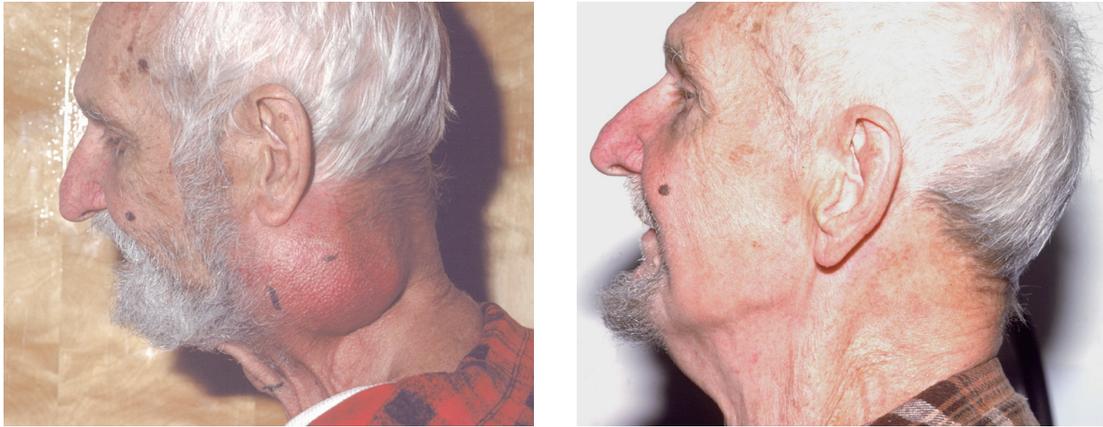


Figure 5: An inoperable salivary gland tumor before and after treatment with fast neutron therapy at Fermilab.

3.2 Prostate cancer

Figure 6 shows results of multi-institutional clinical trials showing that locally advanced stage prostate cancer patients treated with a combination of neutrons and photons had better long-term survival than those treated with photons only. [14] A similar study involving over 700 early stage prostate cancer patients showed that the order in which patients receive the radiation influences disease-free survival. Disease free survival was 93% for those receiving neutrons before photons and 73% for those receiving photons before neutrons [15].

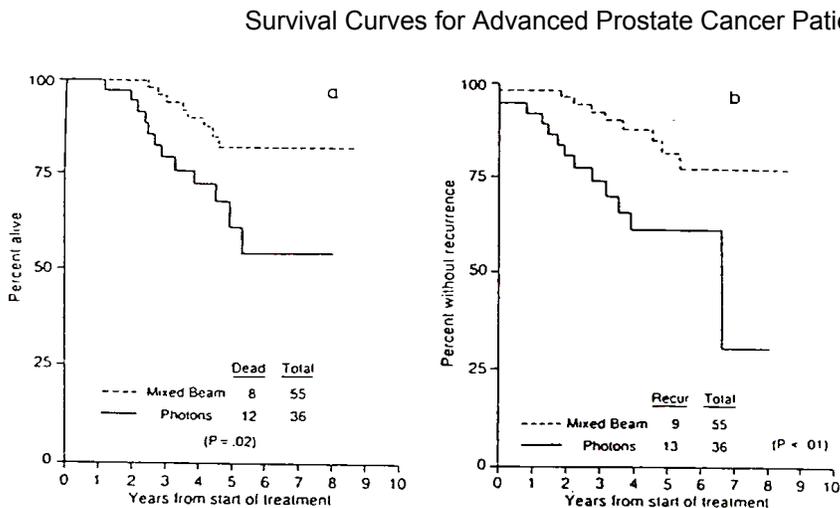


Figure 6. Actuarial survival curves for advanced stage prostate cancer patients treated with photons only or a combination of neutrons and photons. National clinical trial RTOG 7704.

3.3 Sarcoma

Figure 7 shows a soft tissue sarcoma located on the buttock, before treatment at Fermilab, just after treatment and at the two-month follow-up. The term “sarcoma” refers to a malignant tumor arising in connective tissue, bone, cartilage or muscle. This figure is an example of a large tumor whose progression was controlled by fast neutron therapy. The photo taken at the end of treatment shows damage to healthy tissue, but the third photo shows that healthy tissue can repair sublethal damage from neutron therapy. Tables 3 – 5 present results of prospective randomized clinical trials for various types of sarcoma [16].

Table 3: Loco-regional control of unresected osteosarcoma – 2-year actuarial data - International prospective randomized clinical trials.

	Number of Facilities	Number of Patients	Local Control ($p = 9.1 E-6$)
Neutrons	8	97	54%
Photons	3	73	21%

Table 4: Loco-regional control of unresected chondrosarcoma – 2-year actuarial data - International prospective randomized clinical trials.

	Number of Facilities	Number of Patients	Local Control ($p = 0.28$)
Neutrons	7	25	49%
Photons	2	10	33%

Table 5: Loco-regional control of unresected or partially resected soft-tissue sarcoma - 2-year actuarial data - International prospective randomized clinical trials.

	Number of Facilities	Number of Patients	Local Control ($p = 0.047$)
Neutrons	11	297	53%
Photons	5	49	38%



Figure 7a. Large soft tissue sarcoma on the hip. This tumor is radioresistant. It contains hypoxic cells and cells in various stages of development.



Figure 7b. Same patient after being treated with fast neutrons at Fermilab. Note residual skin reddening just at the end of treatment. This is characteristic of any radiation if a high dose is given.



Figure 7c. Same patient at two-month follow-up. Note repair of reddening, but presence of long-term scar tissue.

4.0 Design of a Modern Fast Neutron Therapy Facility

In designing a modern fast neutron therapy facility, two issues must be considered: the accelerator/beam transport design and the collimation and beam shaping system. Design parameters for the accelerator are well understood and at least two options are available for accelerating the proton beam needed to generate the fast neutrons. The collimation and beam shaping system still requires some research and development, the primary issue being the problem of providing good beam shaping using materials that have minimal radioactivation properties and do not allow neutrons to penetrate cracks in the collimators.

4.1 Accelerator/Beam Transport Parameters

Clinical trials have shown that clinically useful fast neutron beams are best generated by an ~ 70 MeV proton beam impinging on a water-cooled semi-thick cylindrical beryllium target. There are no clinical data for beams greater than 70 MeV, though it is expected that such beams would have deeper penetration capabilities at the expense of RBE. Deeper penetration would be advantageous for tumors such as prostate tumors, but disadvantageous for head and neck tumors because of increased exit dose. Typical proton beam currents at existing neutron facilities range from 20 – 70 microamperes, but to be competitive with dose rates available at photon facilities, the proton current in a new accelerator should be at least 200 microamperes. Target-to-patient distance for existing facilities ranges from 150 – 190 cm. At Fermilab, the original patient position was 153 cm, but the distance was increased to 190 cm to allow easier access for the therapists to set up the patient. Table 6 summarizes accelerator/beam transport requirements for an optimized fast neutron facility.

Table 6: Accelerator/beam transport requirements for a modern fast neutron facility.

Accelerated Ion	H^+ or H^-
Beam extraction energy	~ 70 MeV
Production target	Beryllium cylinder, 2 cm diameter, 2 cm length
Average ion current	~ 200 microamperes
Target-to-patient distance	190 cm

Logistics for installing a neutron therapy facility at a hospital are still difficult because no commercial firm is manufacturing neutron therapy systems. As will be described in the next section, some research and development is still needed to optimize a clinic. Hence it is still appropriate for a neutron facility to be located at or be affiliated with a large physics laboratory where there is access to engineers and specialists in neutron shielding and collimation. One particularly cost-effective way to generate neutrons is to divert a proton beam from the linac injector used at large research proton synchrotron facilities. This approach is used at Fermilab, where 66 MeV beam is diverted from the drift tube linac to treat patients, Figure 8. Under computer control the dipole switching magnet ramps on or off in less than 1/15 second, allowing therapy beam when it is on and high-energy physics beam when it is off.

Both cyclotrons and proton drift-tube linacs have been used to generate clinical 70 MeV beams. A proton linac optimized for clinic-based fast neutron therapy and capable of producing medical radioisotopes is described in reference 17.



Figure 8: At Fermilab a curved dipole magnet located between linac drift-tube tanks switches beam between high energy physics research (straight ahead) and neutron therapy (toward the right). One-fifteenth of a second is required to switch between modes.

4.2 Beam Collimation and Shaping Systems

Neutrons produced by the $p(66)\text{Be}(49)$ interaction are nearly isotropic, with neutrons generated in every direction. As shown in Figure 9, only those neutrons traveling in a small cone centered on the forward direction are clinically useful.

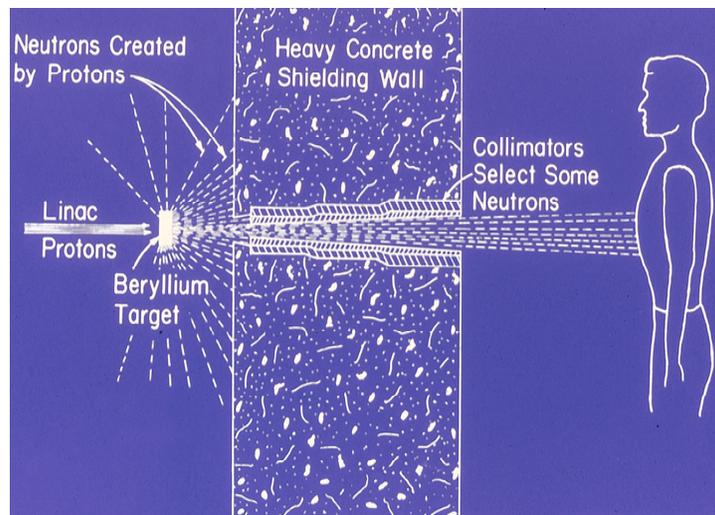


Figure 9: Forward moving neutrons are collimated to fit the size of the tumor. Remaining neutrons are stopped by a heavy concrete shielding wall. Removable collimators made of concrete and polyethylene have various sized openings to fit large or small tumors.

Following the standard beam configuration used in conventional photon therapy, the neutron collimators are rectangular in shape. As shown in Figure 10, low carbon steel “blocks” are inserted into the collimator to customize the beam shape for each patient. The use of concrete/polyethylene collimators and low carbon steel blocks is an excellent way to confine the dose to the region of the tumor and to shield the patient’s body from unwanted whole-body radiation. Furthermore, the use of low atomic number (low Z) materials prevents long-lived radioactivation in the treatment room, thus minimizing radiation dose to the staff. However, the collimators are cumbersome to handle, and inserting the multiple blocks needed to produce the complicated beam shapes required for modern conformal treatments greatly increases the time required to treat a patient.

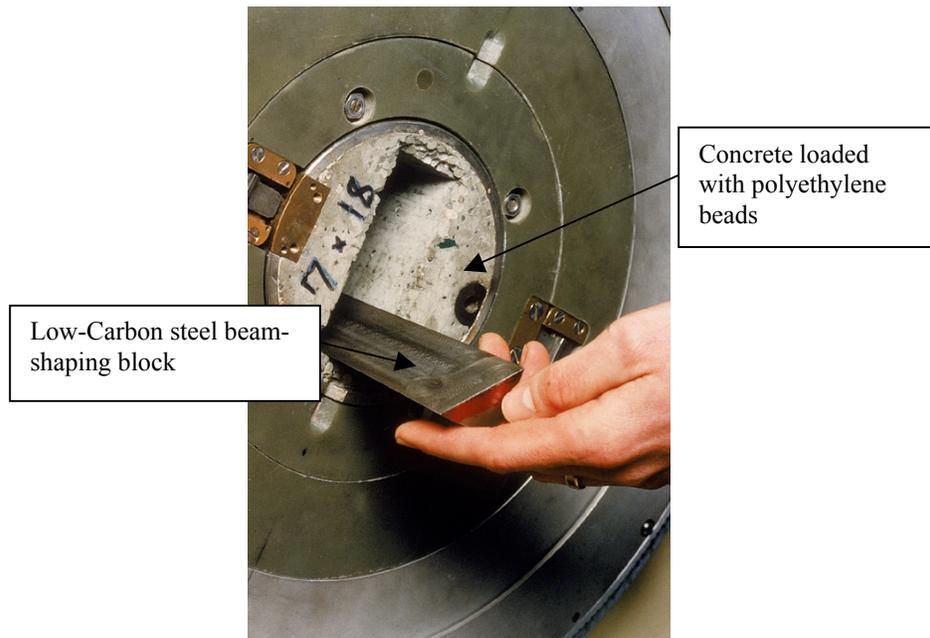


Figure 10: Concrete/polyethylene collimator and low-carbon steel beam shaping block to deliver a conformal treatment beam to the tumor while minimizing total body dose.

Some neutron clinics have developed beam delivery systems more closely resembling those used in conventional photon therapy. These involve mounting the beryllium target in the head of a gantry and rotating the beam about a recumbent patient. The drawback of these systems is that shielding around the beryllium target is reduced to minimize the size and weight of the gantry head. Thus, the beryllium target is under shielded, and the gantry head becomes a large radioactive source that is always present in the treatment room, exposing both patients and staff to unwanted total body dose.

The use of hand-blocks as shown in Figure 10 was routine in most photon radiation therapy clinics when Fermilab developed its neutron therapy facility. Since then photon therapy clinics have adopted the use of gantry heads containing metal leaves that slide over each other to shape the beam under computer control. This greatly reduces patient setup time at the expense of increasing total body dose to the patient. The use of sliding leaves is essential to the newest form of photon beam shaping, Intensity Modulated Radiation Therapy (IMRT). However,

even with photons, whose ability to traverse cracks in the shielding leaves is much less than that of neutrons, there is concern that the additional total body dose may lead to the development of new cancers in IMRT patients [18-19]. A neutron therapy facility that used a photon-like gantry head along with sliding leaves to shape the beam would deliver more total body dose to both the patient and the staff than the system currently in use at Fermilab. For example, Rosenberg *et al* measured the therapist dose to average of 5 microsieverts per treatment [20] at Fermilab. Risler measured an average of 6 microsieverts per field at the University of Washington, which has a gantry head containing moveable leaves [21]. Assuming an average of three fields per treatment, the comparable dose to staff per treatment is 18/5 or 3.6 times greater when the gantry is used.

The technological challenge is to devise a system where the patient could be treated in a recumbent position and still keep the total body dose comparable to that achieved using a fixed horizontal beam. Choice of shielding materials is important. The high-Z materials used for shielding photons are not appropriate for a neutron therapy facility. New materials and better manufacturing techniques have been developed since Fermilab's clinic was built in 1974-76. These materials and techniques are well understood by specialists at large physics laboratories.

5.0 Production of Medically Useful Isotopes

The use of medical radioisotopes for both diagnosis and treatment of disease is becoming increasingly important. Many of these isotopes have production thresholds of 50-70 MeV and are best produced in this energy range to avoid contamination with isotopes whose production threshold is above 70 MeV. Any accelerator that can provide a clinically useful fast neutron beam can also provide protons to generate these isotopes. Because most of the time the patient spends in the treatment room is used for setup rather than actual treatment, the accelerator is idle about two-thirds of the time during the treatment day. The setup time between treatments as well as the evening and night shifts could be used to generate isotopes. Tables 7 and 8 list medical isotopes that could be produced using a proton beam designed for fast neutron therapy.

Table 7: Short-lived Isotopes with Medical Applications. These isotopes are easily produced using the same accelerator that provides a clinical fast neutron therapy beam.

Isotope	Production Reaction	Application
$^{52}\text{Fe}(8.2\text{h})$	$^{55}\text{Mn}(p,4n)$	Bone Marrow Scanning
$^{62}\text{Zn}(9.1\text{h}) \rightarrow$ $^{62}\text{Cu}(9\text{ min})$	$^{63}\text{Cu}(p,2n)$	Positron emission tomography of heart or brain
$^{67}\text{Ga}(78\text{h})$	$^{67}\text{Zn}(p,n)$ $^{68}\text{Zn}(p,2n)$	Detection of cancer, infection or inflammation
$^{111}\text{In}(67.2\text{h})$	$^{112}\text{Cd}(p,2n)$ $^{113}\text{Cd}(p,3n)$ $^{115}\text{Cd}(p,4n)$ $^{116}\text{Cd}(p,6n)$	Molecular labeling
$^{123}\text{I}(13.3\text{h})$	$^{127}\text{I}(p,5n) \rightarrow$ $^{123}\text{Xe} \rightarrow ^{123}\text{I}$ $^{123}\text{Te}(p,n)^{123}\text{I}$	Thyroid Scan
$^{210}\text{Tl}(74\text{h})$	$^{203}\text{Tl}(p,3n)$ $^{205}\text{Tl}(p,5n)$	Heart Imaging

Table 8: Long-lived Isotopes with Medical Applications. These isotopes are easily produced using the same accelerator that provides a clinical fast neutron therapy beam.

Isotope	Production Reaction	Application
$^{68}\text{Ge}(280\text{d}) \rightarrow$ $^{68}\text{Ga}(68\text{min})$	$^{69}\text{Ga}(p,2n)^{68}\text{Ge}$ $^{71}\text{Ga}(p,4n)^{68}\text{Ge}$	Calibrate positron emission tomography imaging devices
$^{82}\text{Sr}(25\text{d}) \rightarrow$ $^{82}\text{Rb}(1.5\text{min})$	$^{85}\text{Rb}(p,4n)^{82}\text{Sr}$	Cardiac perfusion studies
$^{103}\text{Pd}(17\text{d})$	$^{103}\text{Rh}(p,n)^{103}\text{Pd}$	Prostate Cancer treatment seeds
$^{127}\text{Xe}(36.4\text{d})$	$^{133}\text{Cs}(p,2p,5n)^{127}\text{Xe}$	Lung Ventilation Studies

6.0 Summary and Discussion

International, prospective, randomized clinical trials have shown fast neutrons to be superior to photons for treating radioresistant tumors such as salivary gland tumors, sarcomas, melanomas and locally advanced prostate tumors. More research is needed to evaluate neutron therapy for tumor types that were not adequately investigated during the clinical trials. The higher efficacy of neutrons is due to the fact that their interactions with tissue are significantly different from photon (or proton) interactions with tissue. More research is needed to understand the biological response to these different interactions.

Because there are only a few clinical fast neutron beams in the world only a limited amount of research is being conducted. In addition, there are engineering challenges to be addressed with respect to neutron beam collimation and shaping before neutron therapy becomes practical and efficient for more extensive clinical use. National laboratories that are already developing accelerator and beam line technology are well qualified to address the engineering challenges associated with making neutron therapy more widely available.

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