A Brief History of Neutron Therapy Part III – Maturity: Technological Advancements, Appraising the Past, Considering the Future

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Abstract — **The history of neutron radiotherapy is characterized by cycles of great enthusiasm followed most often by discouraging outcomes. The ability of neutrons to eliminate even radioresistant tumors has been apparent since shortly after their discovery. The ability to accomplish this without unacceptable normal tissue toxicity has been the impediment to widespread implementation in radiation oncology. This article is the third in a series about the history of neutron radiotherapy. While the first two elucidate the early incarnation of neutron therapy, its biological rationale, and the expansion of technology, this article will examine the latest chapter in the history of neutron therapy. It will discuss the development of hospital-based facilities for the delivery of fast neutron therapy along with numerous technological advancements designed to improve our ability to capitalize on the advantages of neutron therapy. Finally, it will review some of the clinical successes and failures of fast neutron therapy, its role in providing data for other high-LET therapies, and its potential for future contributions to radiation oncology.**

Keywords — **Fast Neutron Therapy, Neutrons, Radiation Therapy, FNT, IMNRT**

I. Introduction

The history of fast neutron radiation therapy (FNT) has included periods of great excitement and great disappointment. The initial treatments at Berkeley represent the first example of this cycle. Indeed, Ernest Lawrence stated in 1938, "I personally believe, and this belief is shared by my medical colleagues, that this will be the beginning of a new method of cancer therapy which in a few years will be as widespread as that of x rays and radium." Within a decade, this sentiment stood in stark contrast to that of Robert Stone, the physician who delivered these treatments, who advised that "neutron therapy as administered by us has resulted in such bad late sequelae in proportion to the few good results that it should not be continued." This cycle has been repeated over the history of FNT, and while it currently appears to be at its nadir in terms of worldwide use, one may question whether we might expect another cycle. Regardless, we have learned many lessons from the history of FNT and can take a tremendous amount of associated data with us into the future of radiation therapy. This article is the third in a three-part series on the history of FNT in which we'll review the most recent phase of the development of FNT, including numerous technological advancements developed to better harness the biological advantages of FNT, along with a discussion of its current state and potential future directions.

II. Discussion

The potential biological advantages of FNT were well established in the early years of FNT. The ability to safely harness and capitalize on these advantages represented the impediment to the successful broad implementation of FNT as a standard component of our radiotherapy arsenal. The second phase of clinical implementation of FNT, ushered in by the Hammersmith experience, led to renewed excitement about the future of FNT. In general, however, the use of FNT facilities that developed from research accelerators led to shortcomings in our technical capabilities. As succinctly summarized by Catterall, "results were achieved using beams from primitive machines with serious disadvantages." [1] This fact was recognized by the National Cancer Institute who began a tremendous investment in FNT in 1971. The 20 year, $70 million project represented the largest investment in radiation therapy in the history of the NCI, involving the construction or modification of 10 neutron facilities.

Early experience in the US was led by the Neutron Therapy Facility (NTF) at Fermi National Laboratory (FNAL) which began treatment in 1976. Unlike other FNT facilities which were based on equipment designed for research, the NTF had a very high energy beam produced by 66 MeV protons on a beryllium target (p(66)+Be). It was recognized by this time that high energy beams would be necessary to exploit the biological benefits of FNT. The high energy protons for the NTF were extracted from the FNAL linac which provided 200 MeV protons for injection into the other accelerators. Since proton beam injection was required for only 0.8 seconds out of every 6 second cycle of the accelerator operation, the remaining beam was available for other use. The NTF was built along this beamline between the pre-accelerator and the booster ring and the proton beam was directed to an adjacent room where it struck a lithium target for neutron beam production. Patient treatment was delivered within an elevator shaft which would bring the patient to the level of the beamline. Since the biological effectiveness of FNT is strongly energy dependent, several other FNT facilities would later be built with accelerators designed to bombard a lithium target with proton energies at or near 66 MeV. The NTF beam was

shaped using a set of interchangeable regularly shaped polyethylene-concrete collimators placed in a steel and Benelex collimator assembly. The NTF treated over 3300 patients before its closure in 2013 and contributed tremendously to our understanding of FNT. The top panel in figure 1 provides an aerial view of the FNAL while the other panels depict the beamline and treatment room. The NTF was located just below and to the left of the high-rise Wilson Hall structure visible in the aerial image. Figure 2 shows a patient preparing for treatment at the NTF. An additional contribution of the NTF was the development of the first vertical CT scanner to allow 3D treatment planning for patients in the seated position necessitated by the nature of the treatment facility. This served as a precursor for the significant current research and interest in upright radiotherapy.

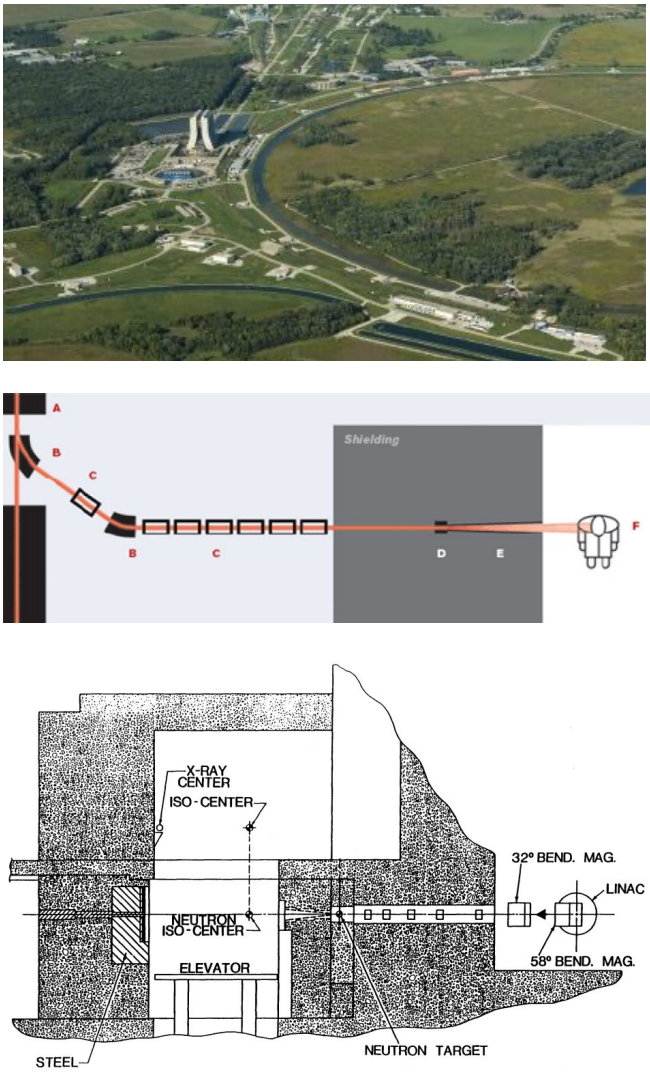


Fig. 1 Aerial view of Fermi National Accelerator Laboratory (top). The NTF was located just below and to the left of high-rise Wilson Hall. Top view of the proton beamline (middle) and cutaway view of the beamline and treatment room (bottom). (Reproduced from FNAL archives.)

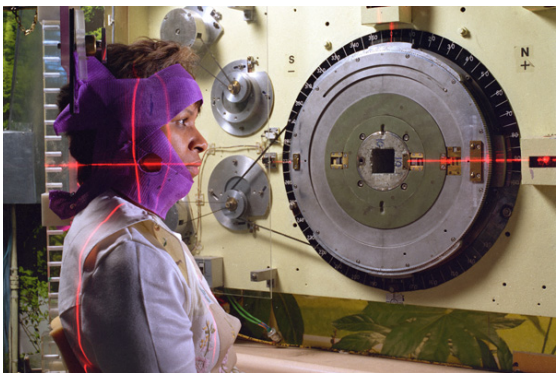


Fig. 2 Patient preparing for treatment at the FNAL NTF. (Reproduced from FNAL archives.)

As the investment from the NCI began to bear fruit, FNT moved from substandard laboratory-based delivery facilities in the 1970s to specially designed hospital-based facilities in the 1980s. This era saw the clinical implementation of the University of Washington FNT facility called the Clinical Neutron Therapy System (CNTS) in 1984. This p(50.5)+Be beam was shaped using a 40 leaf multi-leaf collimator (MLC) projecting a 1cm leaf width at isocenter. Figure 3 shows the treatment room and gantry. Figure 4 depicts the characteristics of the treatment head.

Fig. 3 Gantry and treatment couch for the University of Washington Clinical Neutron Therapy System (CNTS). (Reproduced from Wikipedia.)

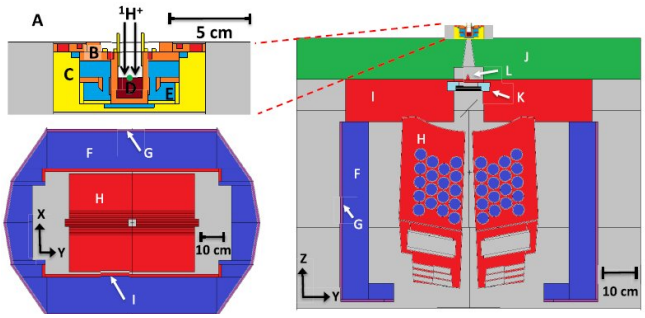


Fig. 4 Diagram of the UW CNTS target and MLC showing protons incident on the target (upper left), beam's-eye-view of the MLC (bottom left), and cross-sectional view of the beamline from target to MLC (right). (Reproduced from ref. 25.)

Figure 5 shows the UW CNTS MLC and a sample target with corresponding MLC shape. The CNTS is still operational and has now treated more than 3500 patients.

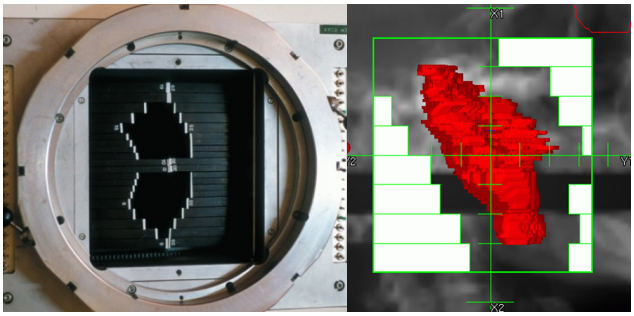


Fig. 5 UW CNTS MLC (left) along with MLC shape for representative radiotherapy target (right). (Reproduced from Wikipedia.)

Following in 1988 was the first treatment at the National Accelerator Center in South Africa, later to be renamed iThemba Laboratory. This p(66)+Be beam was shaped using variable jaws and a multi-blade trimmer. The gantry is shown in figure 6 while figure 7 shows a patient preparing for treatment next to the multiblade trimmer. The facility treated approximately 1800 patients before its closure in 2017.

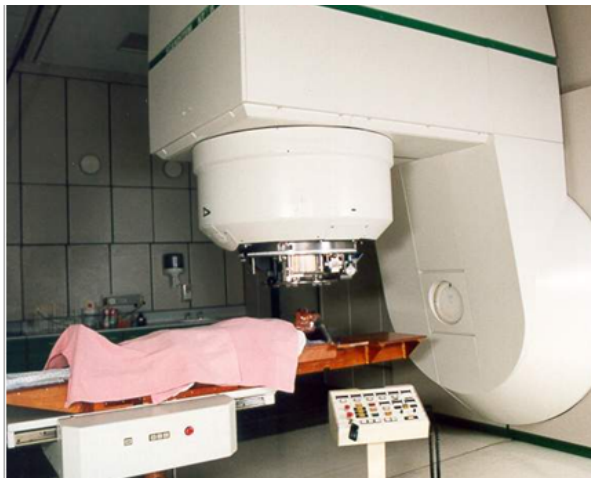


Fig. 6 Gantry and treatment couch for the iThemba fast neutron therapy facility. (Photo courtesy of Dan Jones.)

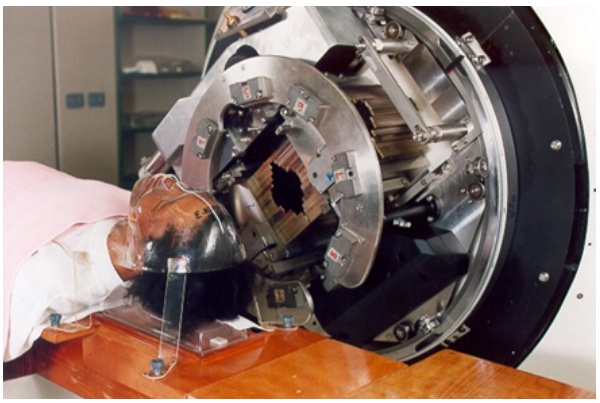
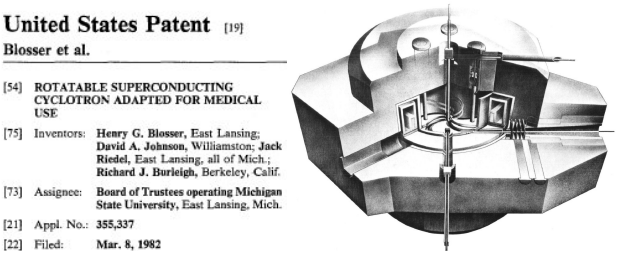


Fig. 7 Multi-blade trimmer for the iThemba fast neutron therapy facility. (Photo courtesy of Dan Jones.)

In 1991, the world's first gantry-mounted superconducting cyclotron was implemented for FNT at Harper Hospital, later to be named the Karmanos Cancer Center (KCC), affiliated with Wayne State University (WSU) in Detroit [2,3]. Michigan State University (MSU) had recruited Dr. Henry Blosser in 1958 to head a new cyclotron laboratory funded by the National Science Foundation. Dr. Blosser would create the world's first superconducting cyclotron and lead the development of the National Superconducting Cyclotron Laboratory (NSCL) at MSU. At the request of Dr. William Powers, radiation oncologist and chair of the Department of Radiation Oncology at Harper Hospital, MSU and Harper Hospital would begin a collaboration to create a neutron therapy facility. Blosser designed a gantry-mounted rotatable superconducting cyclotron for this facility. Figure 8 shows the patent for this device along with a cutaway view, while figure 9 shows the plan view of the accelerator.



United States Patent [19]

Blosser et al.

[54] ROTATABLE SUPERCONDUCTING CYCLOTRON ADAPTED FOR MEDICAL USE

[75] Inventors: Henry G. Blosser, East Lansing; David A. Johnson, Williamston; Jack Riedel, East Lansing, all of Mich.; Richard J. Burleigh, Berkeley, Calif.

[73] Assignee: Board of Trustees operating Michigan State University, East Lansing, Mich.

[21] Appl. No.: 355,337

[22] Filed: Mar. 8, 1982

Fig. 8 Patent and cutaway view of the superconducting cyclotron for FNT at WSU/KCC. (Images courtesy of the author.)

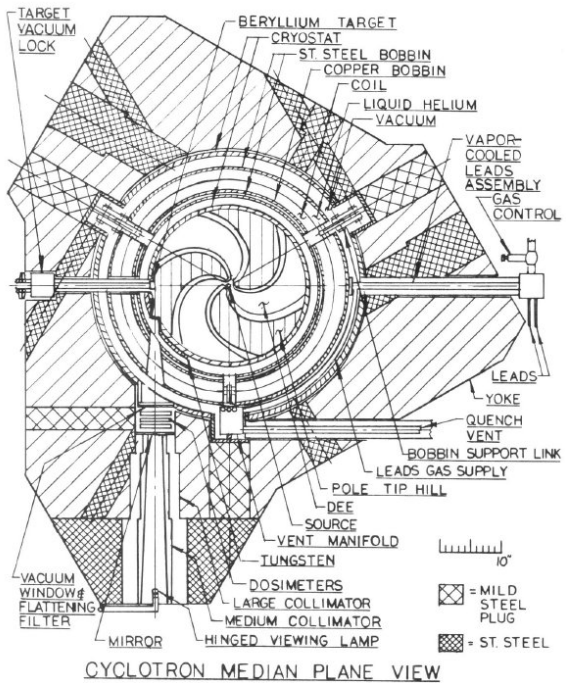


Fig. 9 Plan view of the superconducting cyclotron for FNT at WSU/KCC. (Image courtesy of the author.)

Figure 10 shows Drs. William Powers and Henry Blosser in front of a model of the treatment bore while figure 11 shows the two on the gantry structure during testing at the MSU NSCL where the unit was constructed and tested. Figures 12 and 13 show Dr. Richard Maughan next to the multi-rod collimator and Dr. Mark Yudelev in the treatment bore after clinical implementation.

Fig. 10 Drs. William Powers and Henry Blosser in front of a model of the WSU/KCC gantry and treatment couch. (Image courtesy of the author.)

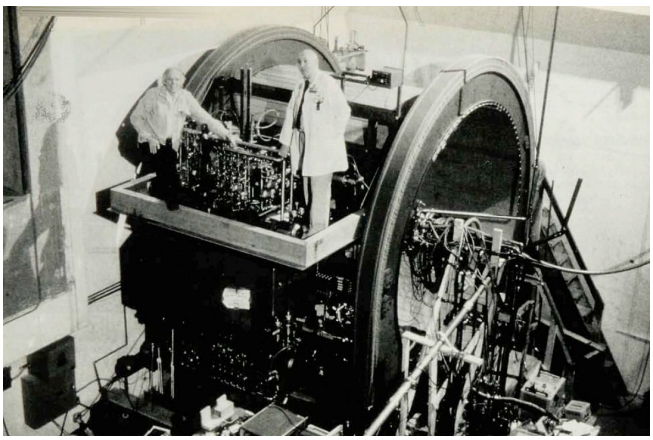


Fig. 11 Drs. Henry Blosser and William Powers on the gantry structure of the WSU/KCC FNT cyclotron during testing. (Photo courtesy of the author.)

While most accelerators developed for FNT used the p+Be reaction, the WSU/KCC cyclotron used a d(48.5)+Be beam since the d+Be reaction generates a neutron fluence rate roughly six times higher than the p+Be reaction. A novel multi-rod collimator was designed for this unit which allowed more detailed dose shaping characteristics than other facilities at that time [4]. Another unique feature of this treatment unit was the implementation of two gantry mounted x-ray tubes which facilitated pre-treatment image guidance.

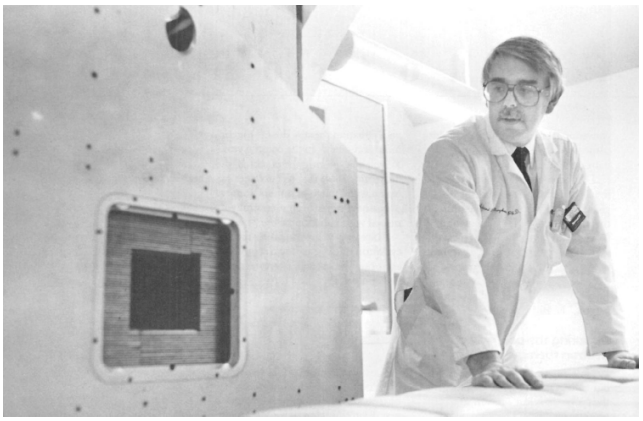


Fig. 12 Dr. Richard Maughan beside the tungsten multi-rod collimator for the WSU/KCC FNT unit. (Photo courtesy of the author.)

The WSU/KCC FNT facility was developed before CT simulation and 3D treatment planning were commonly available. The department had a wide bore CT and developed a novel laser marking device to facilitate CT-based simulation [5]. The CT data was then transferred to an in-house treatment planning system called VRSPlan which was originally developed from the GRATIS (trademark Sherouse Systems, Inc.) system [6]. This

allowed the unique opportunity to perform 3D conformal treatment planning for FNT using modern CT simulation processes, something that was extremely uncommon even for photon therapy at that time. The WSU/KCC facility treated over 2250 patients before its closure in 2011.

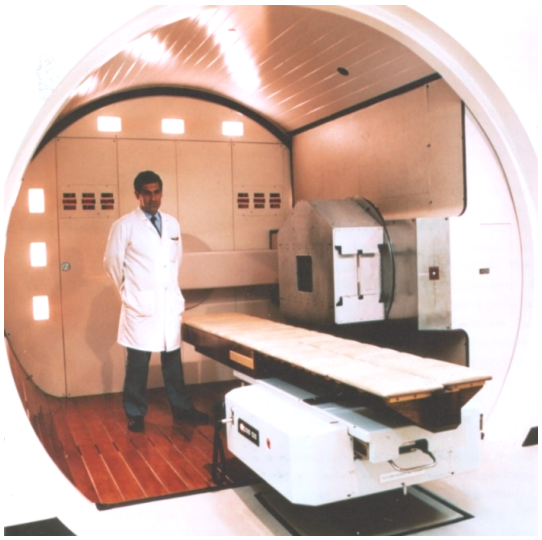


Fig. 13 Dr. Mark Yudelev in the treatment bore of the WSU/KCC unit. (Photo courtesy of the author.)

The development of these facilities ushered in a new phase in the history of FNT, the beginning of clinical trials using high energy, hospital-based neutron facilities. The majority of worldwide FNT treatments from the 1990s to the present day have been delivered by the four previously described facilities, with nearly 11,000 patients treated between them and counting.

Even before the development of advanced hospital-based facilities, a number of successes were observed from FNT treatments in the 1970s and 80s. Griffin summarized a number of studies showing favorable outcome for neutrons, most notably successes for unresectable salivary gland tumors and prostate cancer [7]. The RTOG-MRC study of FNT vs photon therapy for inoperable, recurrent or unresectable malignant salivary gland tumors was closed early due to the far superior local control provided by the neutron arm [8]. Two prostate cancer trials, RTOG 77-04 and NTCWG 85-23, both showed a statistically significant improvement in local control and RTOG 77-04 demonstrated a significant improvement in overall survival at 10 years [9,10]. It was anticipated that deployment of these new, more advanced, facilities would result in additional clinical success. Unfortunately, many subsequent studies yielded disappointing results.

While FNT has always enjoyed radiobiological advantages over low-LET photon and electron radiotherapy, the technological aspects of FNT have had difficulty keeping pace with those of conventional radiotherapy, thus sacrificing some of its potential advantage. The NTCWG 85-23 study provides an excellent example of the value of such technological advancements in radiotherapy delivery. While the neutron arm resulted in an overall increase in severe (Grade 3 and above) complications, all of these complications occurred at the two facilities without an MLC [10]. The CNTS treated 51 patients on this trial without a single Grade 3 complication. The WSU/KCC facility would later treat over 800 prostate cancer patients with a Grade 3 toxicity incidence of < 2% [11]. Even with a radiobiological advantage, accurate and precise delivery is of paramount importance.

While a number of favorable clinical outcomes for FNT have been observed, one may argue whether the results from these trials contain any true clinical "home runs." Positive clinical results have been obtained for salivary gland, advanced prostate cancer, soft tissue sarcoma, osteosarcoma, paranasal sinus, breast, and melanoma. However, many of these tumors are rare, and while local control has been demonstrated statistically in many trials, few trials have shown a survival benefit. Indeed, despite significant differences in local control, there was no statistically significant long term survival benefit for patients in the neutron arm of either the RTOG-MRC salivary gland trial or the NTCWG 85-23 prostate study. The mixed neutron and photon results presented by Forman for high-risk prostate cancer patients are exceptional [11] but there are many successful options available for patients with this disease. As of the turn of the millennium, FNT was still in search of something more to solidify its niche in radiotherapy.

Most clinical publications in the 2000s were based on results from studies performed in the 1980s and 90s as few trials have been initiated since then. Not only did these pre-2000s treatments suffer from relatively poor delivery capabilities in comparison to current technology, many were delivered without the aid of robust treatment planning systems which would allow visualization of the quality of the delivered dose distributions. The dawn of the new millennium saw a number of technological advancements including, but not limited to, improved beam shaping facilitated by advanced MLCs, improved treatment planning and dose calculations facilitated by advanced treatment planning systems, improved dosimetry and prediction of biological effects facilitated by advanced dosimetry techniques, and advances in radiobiological modeling methods and available data.

Advanced microdosimetry techniques were developed for high flux, high LET applications which would provide comprehensive mixed field dosimetry and facilitate accurate prediction of RBE for these beams [12]. An example from the WSU/KCC facility is shown in figure 14. These techniques would also provide the ability to evaluate

contributions from neutron capture reactions and were used not only to evaluate the characteristics of FNT and Cf-252 neutron brachytherapy, but also the potential of boron neutron capture enhancement of these two neutron treatment modalities. In addition, they were used to evaluate the dosimetric characteristics of the two BNCT facilities in the US, the reactor facilities at the Massachusetts Institute of Technology and Brookhaven National Laboratory [13-15].

Cf-252, discovered in 1950 at Berkeley, using the same cyclotron used to deliver most of the early FNT treatments, spontaneously emits neutrons with a mean energy of 2.1 MeV and half-life of 2.65 years. The first human treatments with Cf-252 were carried out in 1968 and since then, a number of treatment sites have been studied for which neutron brachytherapy may be potentially advantageous, including cervical, esophageal, and rectal cancer. Figure 15 depicts the lineal energy (microdosimetry) spectrum from Cf-252 at 5 cm in water for several simulated site diameters. The main impediment has been the availability and cost of developing Cf-252 sources and this has resulted in a relatively limited amount of clinical data for fast neutron brachytherapy.

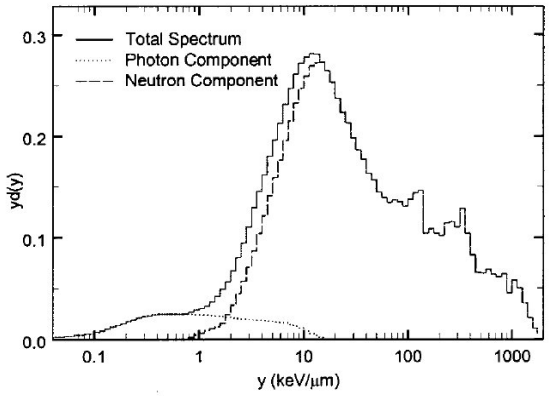


Fig. 14 Lineal energy spectrum for a 1μm site measured in the WSU/KCC FNT beam along with individual neutron and photon components. (Reproduced from ref. 12.)

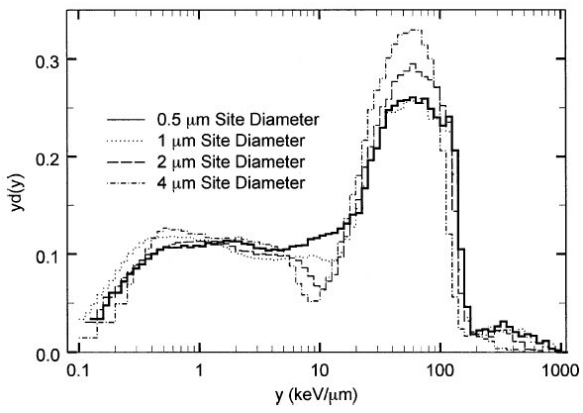


Fig. 15 Cf-252 lineal energy spectrums measured at 5 cm in water for multiple site diameters. (Reproduced from ref. 13.)

In 2004, a state of the art MLC was designed and implemented at the KCC/WSU FNT, enhancing treatment field resolution and facilitating rapid, automated treatment beam shaping [16]. This new MLC used 30 cm thick steel leaves projecting a 5 mm leaf width at isocenter and featured a robust computer control system which included both a primary motor drive mechanism and secondary automated visual leaf position validation system. The singly focused leaves had a blocking step to reduce interleaf transmission and an end-leaf step to allow opposing leaves to close within the primary beam. Figures 16 and 17 illustrate the design of this device while figure 18 shows the control system interface. The development of this beam shaping device would pave the way for the delivery of intensity modulated neutron radiotherapy (IMNRT).

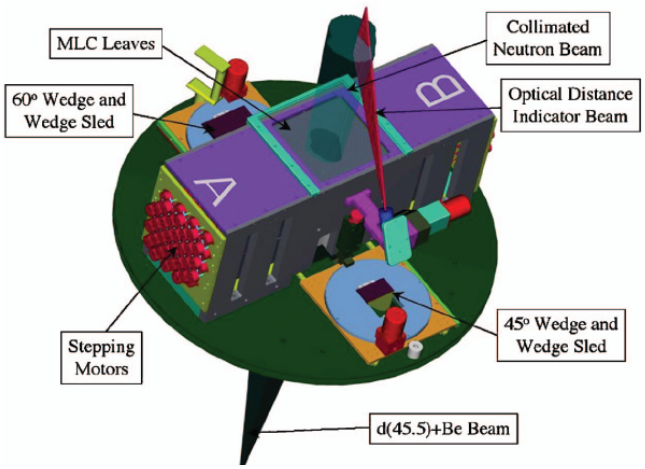


Fig. 16 Rendering of the high-resolution, computer-controlled MLC developed for the WSU/KCC FNT facility. (Reproduced from ref. 16.)

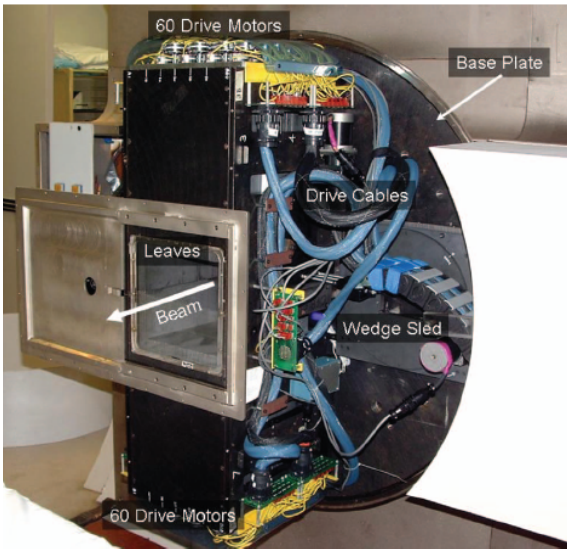


Fig. 17 The WSU/KCC MLC mounted on the gantry, shown here without the cover. (Reproduced from ref. 16.)

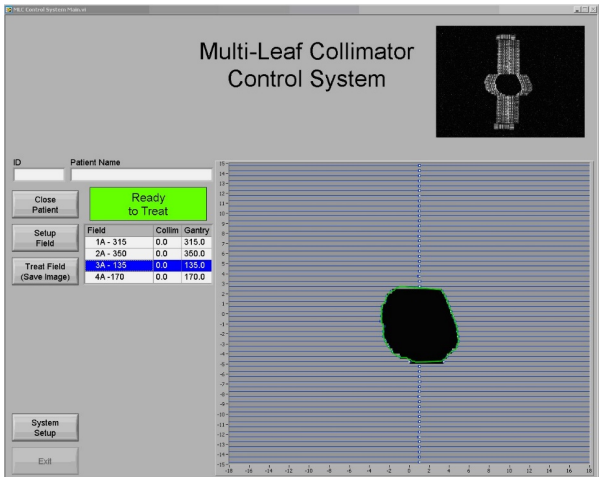
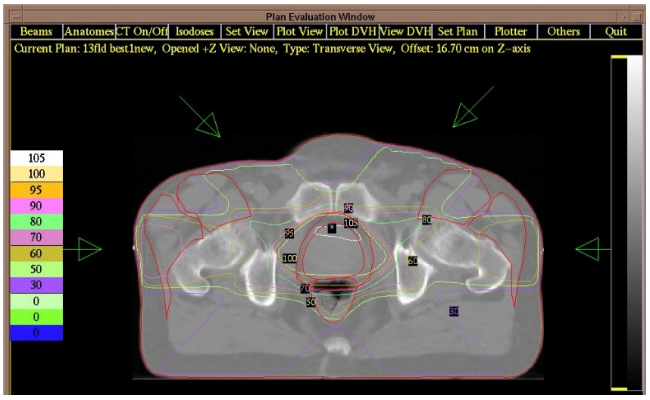


Fig. 18 WSU/KCC computer-controlled MLC system interface. (Image courtesy of the author.)

Concurrent development of advanced treatment planning capabilities at WSU/KCC allowed the creation of IMNRT plans and the first such plans were developed in 2004 [17,18]. An example IMNRT plan is shown in figure 19.



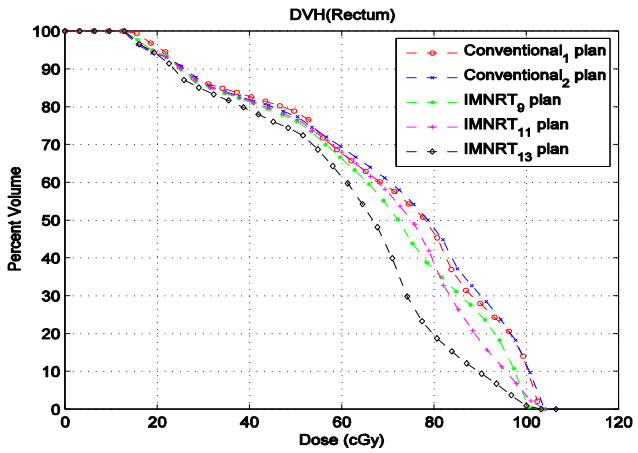


Fig. 19 Calculated dose distribution for an IMNRT plan created for a prostate cancer case (top) along with a comparison of rectal DVHs between conventional and IMNRT plans (bottom). (Reproduced from ref. 18.)

An associated set of biologically effective dose calculations and radiobiological dose escalation evaluations were performed for prostate cancer treatment as the first target site [19]. An example is illustrated in figure 20. Delivery accuracy was further improved with the implementation of modern image guidance techniques using the gantry-mounted x-ray tubes. An automated six degree of freedom correction method using implanted fiducial markers was developed for the treatment of prostate cancer [20,21]. The development of IMNRT capabilities greatly improved the dose distribution characteristics of FNT while the concurrent development of image guided FNT allowed the reduction of treatment margins. Both of these enhancements would provide the capability to significantly reduce out of target doses which had long been an area of difficulty for FNT given its proclivity for significant normal tissue complications.

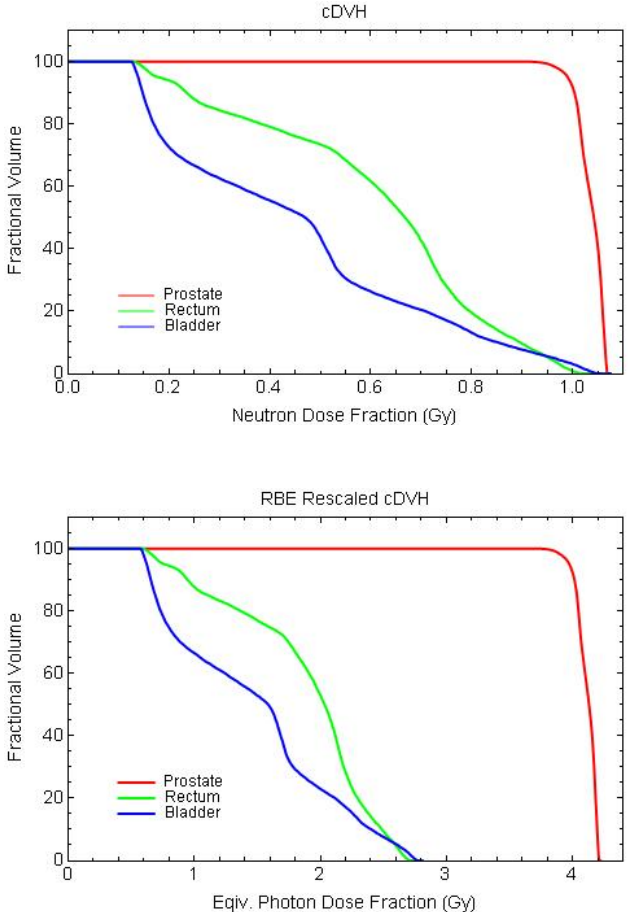


Fig. 20 Cumulative neutron DVHs for prostate, rectum and bladder for a representative prostate cancer case (top) along with corresponding equivalent photon DVHs scaled by RBEs for each organ modeled as a function of dose per fraction (bottom). (Images courtesy of the author.)

Unfortunately, the world would have to wait for the clinical implementation of IMNRT as the KCC/WSU facility was closed in 2007. The cost of operation of such a facility far exceeds that of conventional radiotherapy treatment units and no specific reimbursement codes were available for FNT. However, the unique nature and technological capabilities of this facility made it exceptionally well positioned to deliver state of the art image guided IMNRT treatment. And due to the belief that the clinical potential of FNT had yet to be fully unlocked and that it still had an important role to play in radiotherapy, the KCC/WSU facility was re-opened in 2010 and work commenced on IMNRT.

A new method was developed for IMNRT planning using a commercial TPS for inverse plan optimization and leaf sequencing and an in-house TPS for dose calculation [22]. New techniques were developed for dosimetry, evaluation of biologically effective dose, and delivery quality assurance. Commissioning culminated in 2011 with the planning, delivery, and evaluation of the AAPM TG-119 test suite for IMNRT [23]. Figure 21 shows calculated dose distributions for the TG-119 mock prostate and head and neck cases and figure 22 shows the first use of an ion chamber array filled with tissue-equivalent gas for planar dosimetry for IMNRT QA.

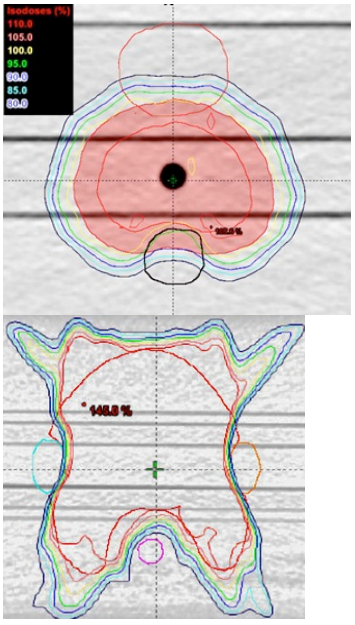


Fig. 21 Calculated dose distributions for the TG-119 mock prostate and head and neck cases during IMNRT commissioning at the WSU/KCC FNT facility. (Images courtesy of the author.)

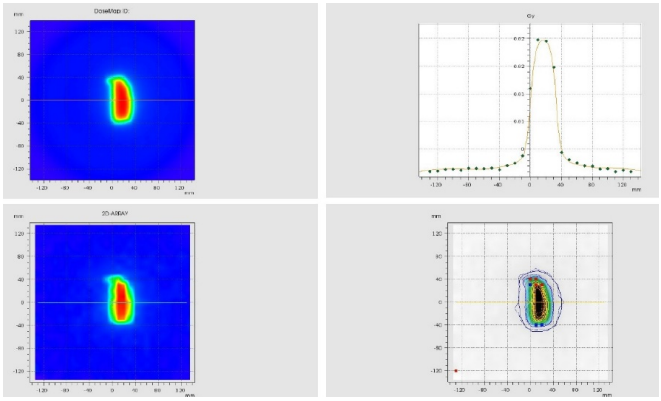


Fig. 22 Representative MLC shape from segmental IMNRT delivery evaluated using a tissue-equivalent gas filled ion chamber array for IMNRT quality assurance at WSU/KCC. (Reproduced from ref. 23.)

Despite the relatively poor penetration of the WSU/KCC FNT beam and practical limitations in the number of segments, these IMNRT plans were similar to those generated for photon IMRT, with the exception of very complex cases. Delivery accuracy was similar to photon IMRT at the time, as measured and calculated doses for > 90% of measurement points were within TG-119 derived confidence intervals. Unfortunately, during pre-treatment QA measurements for the first IMNRT patient, failure of the superconducting magnet caused another shut down of the facility, this time permanently. While WSU/KCC would be the first to commission IMNRT, it would never deliver it to a patient and the world would have to wait again for IMNRT.

Meanwhile, the University of Washington CNTS also developed numerous advances in technical capability, first showing that the MLC dramatically reduced treatment toxicity to local normal tissue structures [24]. Figure 23 illustrates the improved dose distributions achievable using the MLC to deliver 3DCNT for a prostate treatment. Improvements in the accuracy of neutron dosimetry and beam characterization [25] and development of a custom built commercial TPS with neutron-specific scattering kernels allowed more accurate dose calculations and the ability to perform inverse planning for the creation of IMNRT plans [26].

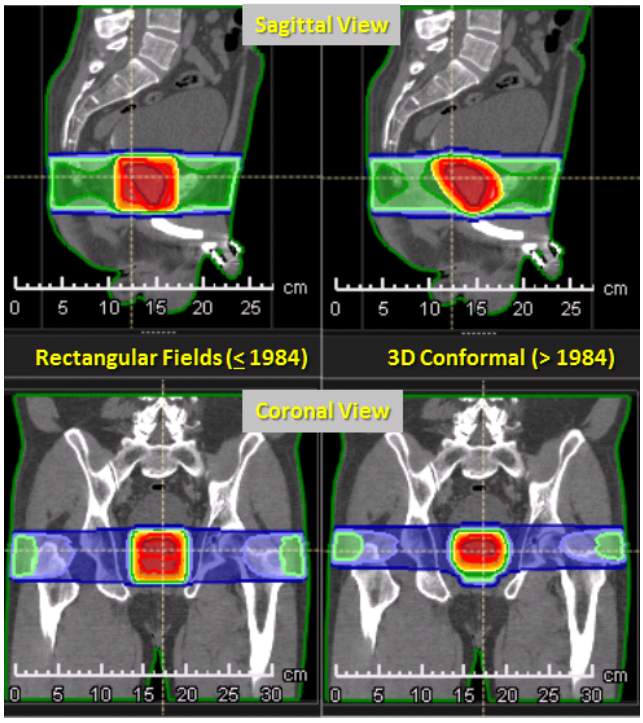


Fig. 23 Comparison of pre-MLC neutron dose distributions (left panels) with 3DCNT plans shaped with the UW CNTS MLC (right panels). (Images courtesy of Landon Wootton and Robert Stewart.)

In 2022, the CNTS ultimately became the first (and thus far only) facility to deliver IMNRT [27]. Figure 24 illustrates an example of the improved dose distributions achievable with IMNRT for a head and neck cancer treatment. For the initial cohort of plans created for comparative dosimetry for head and neck cancer treatment, IMNRT improved the therapeutic ratio by an average of >50% compared to 3DCNT. To date, over 100 patients have been treated with this improved delivery technique and a new imaging system has been developed to facilitate efficient patient specific QA for IMNRT [28]. Figure 25 provides an illustrative example of this technique which compares Monte Carlo calculated ^{11}C decay maps with induced ^{11}C activity measured using neutron positron emission portal imaging. The CNTS is also currently investigating flattening filter free delivery for IMNRT and exploring additional ways to capitalize on the biological advantages of FNT, including expanded use of hypofractionation, and more advanced RBE modeling techniques [29,30]. Figure 26 illustrates the distribution of various particle types in the CNTS beam while figure 27 presents RBE for DNA double strand breaks as a function of energy for recoil protons and other ions.

A substantial portion of our published clinical data from FNT trials has come from the UW CNTS group and developments at this facility continue to push the field of FNT forward. It is, to the author's knowledge, the only remaining clinical FNT facility still in operation.

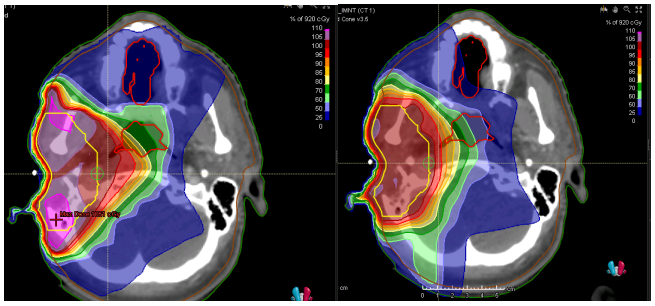


Fig. 24 Comparison of dose distributions created for head and neck cancer treatment using 3DCNT (left panel) and 5 field IMNRT (right panel) at the UW CNTS. (Images courtesy of Landon Wootton and Robert Stewart.)

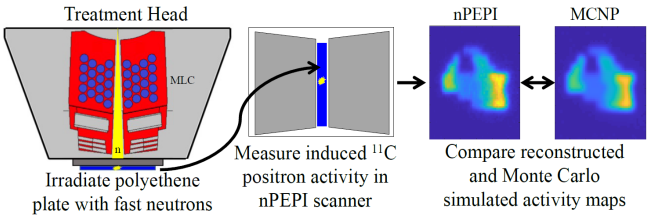


Fig. 25 Patient specific QA tool comparing MC calculated ^{11}C decay maps with measured induced ^{11}C activity using neutron positron emission portal imaging. (Image courtesy of Robert Stewart.)

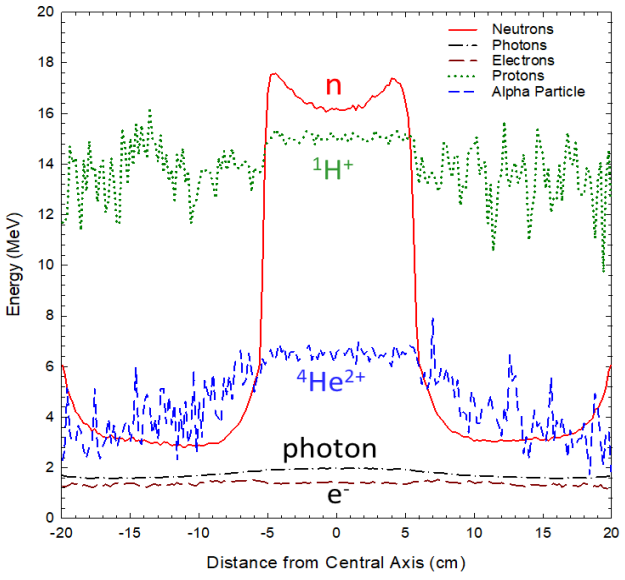


Fig. 26 Distribution of neutrons and secondary particles in the UW CNTS beam. (Reproduced from ref. 30.)

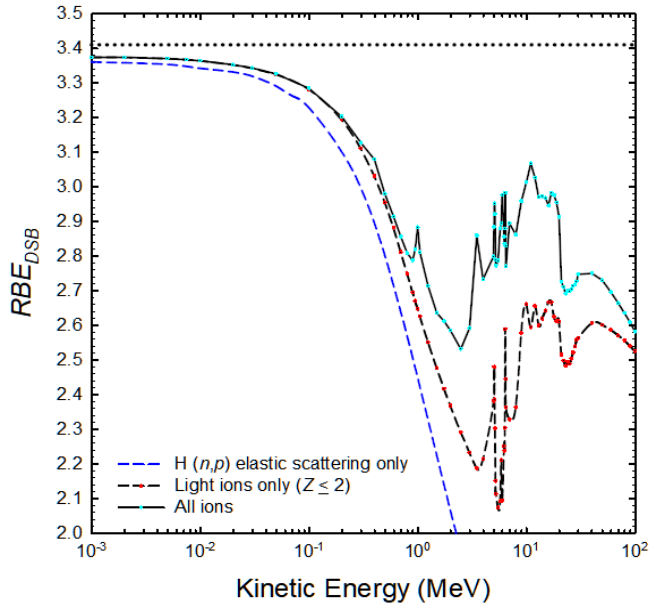


Fig. 27 RBE for DNA double strand break induction in normoxic cells as a function of kinetic energy for recoil protons, light ions and all ions. (Reproduced from ref. 29.)

One elusive target that would certainly represent a clinical "home run" for FNT is Glioblastoma Multiforme (GBM). FNT is currently the only treatment modality which has demonstrated the capability to consistently sterilize a GBM [31,32]. Unfortunately, no therapeutic window was observed in the early FNT trials for GBM as normal brain tolerance doses are substantially lower than doses required for local control. In 2007, a modern PET-guided conformal FNT study for GBM patients also unfortunately yielded disappointing results [33]. A mechanism for providing a tumor-specific boost to FNT for GBM could potentially yield a solution to this problem and such a treatment, referred to as Boron Neutron Capture Enhanced Fast Neutron Therapy (BNCEFNT), was originally proposed in 1978 [34]. Estimates of its radiobiological effects and clinical potential were further explored in 1994 [35], and a clinical feasibility investigation was performed for the WSU/KCC facility in the late 1990s [14,36]. Figure 28 shows lineal energy spectrums measured in the WSU/KCC FNT beam (unmoderated beam) and a beam moderated with 25 cm of steel (moderated beam) to increase the thermal neutron fluence in order to facilitate the boron neutron capture (BNC) boost. Also shown is a biological weighting function correlating LET with RBE which demonstrates a small predicted increase in RBE in the moderated beam. Figure 29 shows microdosimetry results using paired dosimeters, one of which contains ^{10}B and thus illustrates the enhancement from the BNC reaction. This relative dose enhancement is shown in both the moderated FNT beam and at 5 cm from a ^{252}Cf neutron brachytherapy source.

Figure 30 illustrates the relative shapes of the FNT dose distribution in the WSU/KCC moderated FNT beam and the associated thermal neutron distribution which is representative of the potential BNC dose given an appropriate ^{10}B distribution. This illustrates that the FNT beam can be accurately collimated around the gross disease while the BNC boost can potentially eliminate microscopic disease even at significant distances from the collimated field edge. Figure 31 shows the thermal neutron fluence as a function of depth suggesting that peak BNC enhancements are achievable at depths appropriate to treat a GBM.

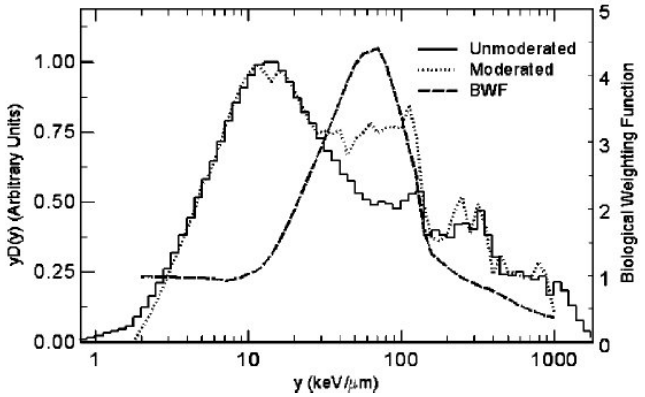
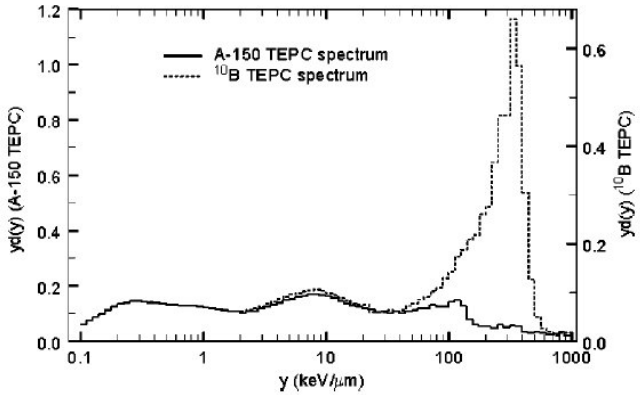


Fig. 28 Neutron lineal energy spectrums for a 1μm site diameter in moderated and unmoderated WSU/KCC FNT beams along with a biological weighting function. (Reproduced from ref. 14.)



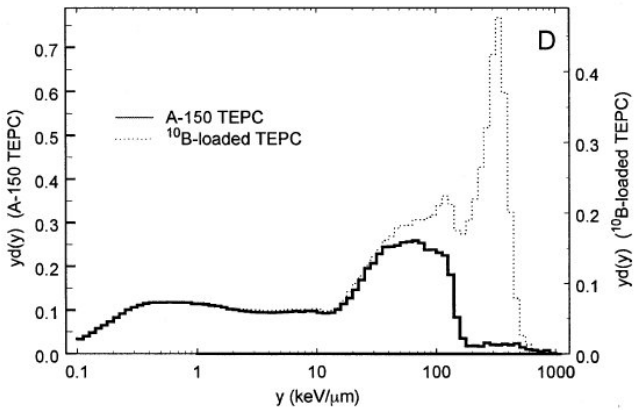


Fig. 29 Lineal energy spectrums measured for a 1μm site diameter in the moderated WSU/KCC FNT beam (top panel) and at 5 cm from a ^{252}Cf neutron brachytherapy source (bottom panel) with and without BNC enhancement. (Reproduced from ref. 14 (top) and 13 (bottom).)

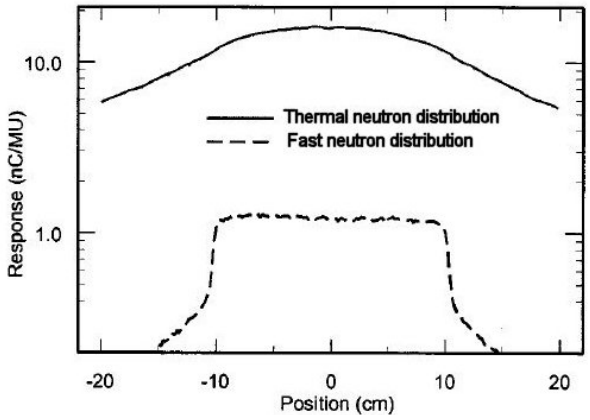


Fig. 30 Measured thermal neutron and fast neutron profiles in the WSU/KCC BNCEFNT beam measured using ionization chambers with (thermal neutron) and without (fast neutron) ^{10}B loading. (Image courtesy of the author.)

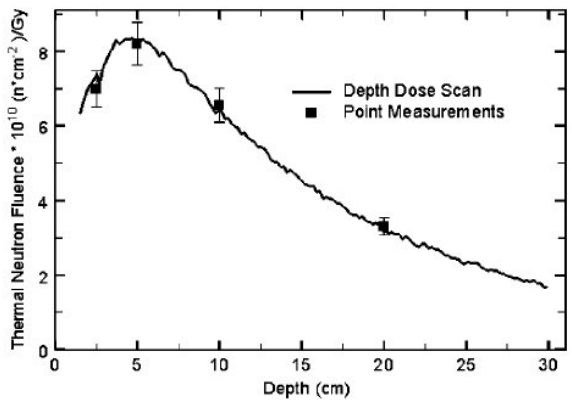


Fig. 31 Thermal neutron fluence as a function of depth in water measured in the WSU/KCC BNCEFNT beam. (Reproduced from ref. 14.)

In the BNCEFNT feasibility study using the WSU/KCC moderated FNT beam, an estimated therapeutic gain of nearly 60% was achieved using this BNCEFNT beam and boron concentrations already achievable in boron neutron capture therapy patients at that time [14]. This gain appears sufficient to open a substantial therapeutic window for the treatment of GBM but requires a significant investment of resources for dosimetric characterization, plan creation and evaluation, and drug delivery and evaluation, and a variety of other aspects necessary for the development of a clinical program. Such applications represent the kinds of opportunities that may still be available with FNT and remain largely unexplored.

III. Summary

While FNT is no longer a major weapon in our radiotherapy arsenal, its story remains an important chapter in the history of radiation oncology. The history of FNT includes many important lessons about the biological effectiveness of different particle types, energies, beam delivery capabilities, mixed treatment regimens, and fractionation schemes, to name a few. These lessons should reinforce our efforts to understand fundamental radiobiological characteristics of radiation therapy and should continue to be taught to future practitioners of radiotherapy including radiation oncologists, medical physicists, and radiobiologists. FNT has provided conclusive evidence for improved local control compared to photon treatment in a variety of disease sites, specifically those that are known to be resistant to conventional radiotherapy. It remains an important potential option in the treatment of rare radioresistant tumors, particularly given new advances in our delivery and treatment planning capabilities. Better control of the dose delivery and better understanding of its radiobiological effects could further enhance the ability of FNT to eliminate radioresistant tumors for which there are limited therapeutic options. FNT still thrives at the CNTS who "continue to find fast neutron therapy clinically more useful and effective in the treatment of patients at high risk for local recurrences in both curative and palliative settings." [25]

And what of the future? Interest in FNT has diminished greatly since the excitement of previous decades but one may question whether there remains a reimagined role in precision oncology. While neutrons earned a poor early reputation from significant normal tissue toxicities, its advantages have often been underestimated. Ideally, FNT should remain a primary option for rare, radioresistant cancers. Along with its utility for the treatment of radioresistant tumors, it also has the potential to provide significant financial and logistical advantages in shortening treatment courses. Neutrons have comparable clinical RBE and similar clinical results for some tumor types in comparison to heavy ions such as ^{12}C. Heavy ion therapy is

prohibitively expensive in many countries, thus supporting the potential development of new neutron therapy installations, particularly in developing countries where patients often present with large, advanced tumors. Shorter treatment time is also advantageous in these circumstances for clinical, logistical, and financial reasons. Compared to heavy ion facilities, FNT offers a cost-effective high-LET option for low- and middle-income countries. The future of FNT may thus lie partly in its potential for wider availability.

Regardless of whether new FNT facilities are created, clinical data from FNT will continue to guide other high LET therapy techniques. As noted by Suit in his review of heavy particle therapy, "fast neutron therapy was the first high LET radiation therapy." [37] It is difficult to overstate the contributions of FNT to our understanding of the radiobiology of radiation therapy. This experience has proven invaluable for the development of contemporary particle therapy protocols. The development of RBE modeling frameworks, many of which were first validated using clinical data from FNT trials, have informed the development of treatment protocols and the prediction of the biological effectiveness of proton and carbon ion therapy [38-41]. Results from FNT treatment of hypoxic tumors laid the groundwork for many trials in carbon ion therapy. Indeed, FNT trials helped delineate the therapeutic window for high-LET radiation, balancing increased tumor control probability against the risk of severe normal tissue complications.

We have learned much from our experience with FNT, however, as it continues to seek clinical "home runs" which would solidify its role in radiotherapy, we must ask whether it might strike out first. Our lack of understanding of the radiobiology of FNT and the subsequent profound normal tissue toxicities of the first phase of its history could be considered strike one. The failure of the majority of clinical trials in the second phase of FNT to demonstrate a survival advantage over conventional treatments could be considered strike two. Could strike three become the closure of the final remaining FNT facility, or will FNT make a dramatic comeback? Consider the trajectories of major areas of current clinical radiation oncology research as well as the current comprehensiveness of our understanding of radiation biology. Most studies of proton therapy thus far have demonstrated little or no difference in outcomes from photon therapy [42-44]. Most current photon therapy efforts are based on the "belief that optimal doses to the tumor and normal tissue have already been determined with near complete accuracy, and the only challenge remaining is to ensure that these idealized doses are reproduced in the clinic with the utmost rigor." [45] "Such approaches treat our wildly inadequate understanding of cancer biology and radiation effects in tissue as settled science." [45] Indeed, how much have we yet to learn about radiobiology? Maybe FNT still has more to teach us and more to offer to our patients.

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