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Neutron Sources and Applications in Radiotherapy – A Brief History and Current Trends

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Neutron Sources and Applications in Radiotherapy - A Brief History, and Current Trends

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A brief review of the uses of neutrons in external-beam radiotherapy is presented, with an emphasis on development and testing of epithermal neutron sources for neutron capture therapy applications.

Keywords: *Boron, BNCT, Neutron Source, Accelerators*

The beginnings of nuclear medicine and radiology can be traced to the discovery of x-rays by Roentgen in 1895. Roentgen's announcement of the new phenomenon was closely followed by a flurry of related activity. Many of the most illustrious scientists of the time immediately directed their energies toward a better understanding of radiation. For example, J.J. Thompson and Ernest Rutherford first reported their studies of the ionizing properties of radiation in 1896.

The medical applications of the new x-rays were obvious. The first portable diagnostic machines were deployed for military purposes in 1898. It was also quickly observed that the new rays, at sufficient level of intensity, could have dramatic effects on biological tissue and in particular that they could both cause, as well as eliminate, malignant growths.

In the same time frame, Becquerel made his historic discovery of natural radiation, Pierre and Marie Curie successfully identified and isolated radium and Rutherford, in collaboration with several others, made a series of discoveries including the fundamental demonstration that natural radiation is composed of three distinct components, alpha, beta, and gamma rays – still familiar to us today.

In the United States, Thomas Edison was one of the first to report on new findings concerning x-rays, and in fact he went on to invent the fluoroscope, and the company with which he was associated, General Electric, was an early leader in the manufacture and marketing of x-ray equipment. Edison and, independently, Pierre Curie also suggested the use of internally-deposited radioactive materials for radiotherapy. By 1905 many medical centers were implanting radium tubes in tumors and achieving demonstrable success.

As the new field of radiobiology developed in the 1920's and beyond, a number of improvements in the technology and procedures associated with medical radiological application were developed, continuing to this day with increasingly sophisticated external beam radiotherapy units and internal radionuclide applications with a diverse array of reactor- and accelerator-produced radionuclides and targeting protocols.

Application of neutrons for radiotherapy of cancer has also been a subject of clinical and research interest since the discovery of the neutron by Chadwick, in 1932. For example, fast-neutron radiotherapy, which involves geometric targeting of a well-collimated high energy (15-20 MeV or greater) neutron beam onto the anatomical target region, much as is done with high-energy X-ray beams in photon radiotherapy, was first used by Robert Stone at Lawrence Berkeley Laboratory in 1938[1]. Fast-neutron therapy is now an accepted modality for inoperable salivary gland tumors and it has shown promise for sarcomas, locally-advanced prostate cancer, and certain other malignancies as well[2].

Neutron capture therapy (NCT) is a somewhat different form of neutron-based therapy, first proposed as a general concept by Locher[3]. In NCT, a neutron capture agent, which in current practice is ^{10}B (yielding Boron NCT, or BNCT), is selectively taken into the malignant tissue following the administration of a suitable boron delivery agent. At an appropriate time after boron administration, the treatment volume is exposed to a field of thermal neutrons generated by the application of an external neutron beam produced by a small nuclear reactor or a suitable accelerator-based system. The thermal neutrons interact with the ^{10}B, which has a very high thermal-neutron capture cross section and which, ideally, is present only in the malignant cells. Each boron-neutron interaction produces an alpha particle and a lithium ion. These highly-energetic charged

particles deposit their energy within a volume that is comparable to the size of the malignant cell, leading to a high probability of cell inactivation by direct DNA damage. This process offers the possibility of highly selective destruction of malignant tissue, with cellular-level sparing of neighboring normal tissue. In a sense, BNCT can be viewed as a targeted radionuclide therapy with a mechanism for switching the emissions of the radionuclide on at a selected location in the body and nowhere else.

A third form of neutron therapy that combines the features of fast-neutron therapy and BNCT has also attracted research interest but has yet to be subjected to formal clinical trials. In this modality[4], a boron neutron capture agent is introduced preferentially into the malignant tissue prior to the administration of standard fast-neutron therapy. Because a small fraction of the neutrons in fast-neutron therapy will be thermalized within the irradiation volume, it should be possible to selectively obtain a small incremental absorbed dose in the target volume from neutron capture. In some cases this small incremental dose may be sufficient to produce a significant improvement in tumor control probability.

The first human trials of BNCT for brain tumors were conducted in the United States beginning in the early 1950s using reactor based thermal-neutron beams. These trials were uniformly unsuccessful. Supporting technologies available at the time in the areas of chemistry, physics, and radiation dosimetry were insufficient for the task, the patients experienced no significant benefit, and there were unacceptable side effects. Consequently, these early trials were discontinued. However, researchers in Japan, led by Dr. Hiroshi Hatanaka, to whom this memorial lecture is dedicated, continued to explore the possibilities of NCT[5]. In addition, the required technologies underwent continuous improvement. As a result, NCT experienced a resurgence of interest worldwide in the late 1980's time frame.

In September 1994 BNCT trials resumed in the United States, at the Massachusetts Institute of Technology (MIT)[6] and at Brookhaven National Laboratory (BNL) in New York[7]. These trials used epithermal-neutron beam extraction facilities backfitted to the MIT Research Reactor and the Brookhaven Medical Research Reactor, respectively. Boronated phenylalanine (BPA) was used as the boron delivery agent. The Brookhaven trials were closed in 1999. Clinical irradiations at MIT continued for a somewhat longer period of time, with the last few treatments conducted using a much-improved epithermal beam based on a fission convertor concept[8]. Trials of BNCT, primarily for glioblastoma and melanoma, have also been initiated at various times over the past 15 years in Europe and South America and Clinical work currently is continuing in Japan, Finland, the Netherlands, the Czech Republic, Italy, and Argentina.

Results of the various recent studies of epithermal-neutron BNCT have been encouraging, but do not constitute a significant breakthrough for BNCT as a clinical modality. In general, observations to date indicate that treatment efficacy can be at least comparable to that of the best alternative standard treatments, but normal tissue complications are of concern in some situations and conclusive statistical proof of improved patient survival relative to standard treatments remains to be demonstrated.

A key feature of all of the BNCT clinical trials conducted to date has been the use of research reactor based neutron sources. Until recently in Japan, as well as in the early American trials, thermal neutron beams were used. In the United States and Europe the emphasis since 1987 has been on the use of higher-energy epithermal-neutron beams to produce the required thermal neutron flux at depth. Newer facilities in Japan also feature epithermal as well as hybrid thermal-epithermal neutron beams. Current technology for such beams has reached a high level of development. For a given boron biodistribution, tumor to normal tissue dose ratios that are near the theoretical maximum that can be achieved by optimization of the incident neutron spectrum are routinely possible with this type of neutron source.

However, the supply of research reactors suitable for BNCT applications is limited and not all such reactors are conveniently located near the necessary medical infrastructure. There are also perceived issues with licensing, safety, and operational procedures that might be associated with the use of research reactors in a hospital environment. Thus there has been considerable interest in the development of accelerator neutron sources suitable for BNCT applications. Coupled with advances in boron delivery agents and protocols that would reduce the neutron flux requirements compared to current practice, such neutron sources would

generally be viewed as preferable for clinical implementation of BNCT as a routine modality.

Two types of accelerator neutron sources are of interest for BNCT research and clinical trials. The first group of sources is composed of existing clinical fast-neutron facilities, which can be modified for exploration of NCT-augmented fast-neutron therapy at minimal additional cost. Examples of such facilities where there has been an interest in applications of BNCT augmentation include the proton-cyclotron-based facility at the University of Washington, in Seattle, the proton linear accelerator facility at Fermi National Accelerator Laboratory, in Illinois, the deuteron cyclotron facilities at Harper Hospital in Detroit and in Essen, Germany as well as two accelerator facilities in France. The second group of accelerator neutron sources for BNCT is composed of various developmental facilities designed to produce an epithermal neutron beam for BNCT as the primary therapy.

The Clinical Neutron Therapy Center at the University of Washington (UW) offers an illustrative example of the use of an existing accelerator neutron facility for clinical studies of BNCT-augmented fast-neutron therapy. In the UW facility protons are accelerated in a cyclotron to an energy of 50.5 MeV. The resulting proton beam is directed by a series of magnets and focusing devices onto a 10.5 millimeter thick beryllium target located in the treatment head of an isocentric gantry system. Neutrons produced in the target are subsequently directed through flattening and wedge filters and then through a multileaf collimator to produce the desired shaped neutron field at the isocenter. Methods for optimizing the performance of the UW system for NCT-enhanced fast-neutron therapy applications have been explored[9]. These efforts yielded a design for a new neutron production target capable of producing a neutron beam that yields essentially the same fast-neutron physical depth-dose curve as is the case with the current system, but which also has a significantly-increased low-energy spectral component. In turn, this yields an increased fraction of BNCT enhancement relative to the total therapeutic dose, but with no difference in the physical fast-neutron dose delivered. *In-vivo* clinical testing of BNCT-enhanced fast-neutron therapy for canine lung tumors has been conducted at UW and some limited human applications are described by Bucholtz[4].

Early conceptual work[10] at The Ohio State University and at MIT[11,12] provided much of the initial basis for later development of epithermal-neutron sources for BNCT using low-energy light-ion accelerators. Low-energy protons impinging on a lithium target have been the most popular method for driving accelerator-based systems designed to serve as neutron sources for epithermal-neutron BNCT, although other approaches, such as the deuteron-beryllium interaction, and several others, have also been of interest. The threshold for the $^{7}Li(p,n)^{7}Be$ interaction of interest is approximately 1.88 MeV. The neutrons produced, for example, by 2.5-MeV protons impinging on a lithium target have a maximum energy of approximately 800 keV in the forward direction. Therefore less subsequent filtering and moderation of the neutron source emanating from the target is required to produce the desired epithermal source spectrum, relative to the case with the fission neutrons produced by a reactor, and in fact various studies have shown that the spectral quality of an optimized accelerator neutron source of this type can be nearly ideal, in some aspects better than the best reactor based neutron sources. On the other hand, production of neutrons by a low-energy accelerator can be a rather inefficient process in terms of neutron production per incident charged particle on-target, creating a requirement for rather high particle currents and associated power deposition rates in the target. There are thus many interrelated design factors to consider in connection with the optimization of such systems and there were many lively discussions in various venues during the early years regarding whether a practical and deployable accelerator neutron source could actually be developed for clinical-scale applications.

By 1994 a number of additional research groups had begun to explore the possibilities of accelerator neutron sources for epithermal-neutron BNCT, and an international workshop sponsored by the US Department of Energy was held late in that year[13]. Participants included researchers from the USA, Canada, the United Kingdom, Russia, Japan, Switzerland, Italy, Australia, Germany, Israel and India. Topics covered included extensive discussions of various accelerator types and their advantages and disadvantages, computational studies of various systems, and various experimental studies focused on basic physics as well as practical engineering issues.

The meeting produced a clear (and as it turned out very prescient) consensus that at least one, and probably more than one practical approach to the realization of a clinical-scale epithermal neutron source would in fact emerge from the various development efforts then underway.

In the next few years following the 1994 workshop several research groups did in fact successfully design, construct and demonstrate fully-functional prototypes for accelerator neutron sources that were near-clinical in scale, or that demonstrated scalability to clinical levels. An early demonstration of this type took place at the MIT Laboratory for Accelerator Beam Applications[14]. This system was based on a 4 MeV tandem electrostatic accelerator that produced either a proton or deuteron beam with a maximum rated power level of 10 kW particle currents up to about 4 mA, depending on the desired particle energy. With particle currents in this range, very significant neutron flux levels could be produced using lithium or beryllium as the accelerator target. The charged particle beam passed through an adjustable bending magnet that directed the beam to any of several experiment stations. Each of these stations could have its own target and neutron beam tailoring assembly. Thus, the MIT facility could be used for innovative BNCT-related research in the areas of accelerator target design and moderator-filter design. In addition, this facility provided sufficient neutron flux levels for meaningful BNCT radiobiological research. One such initiative in this latter area involved the exploration of the possible application of BCNT techniques to the treatment of rheumatoid arthritis.

In the same general time frame, researchers at the University of Birmingham, in the United Kingdom, developed a slightly different variation for the design of a low-energy proton-beam-based accelerator epithermal neutron source for BNCT research[15]. This design features a Dynamitron proton accelerator, a lithium target, and a neutron beam extraction arrangement that is at right angles to the axis of the proton beam impinging on a lithium target. In the previous concepts, the axis of the incoming charged particle beam incident on the target was coincident with the outgoing neutron beam axis. The use of the non-coaxial approach stems from certain practical considerations and provides some neutronic advantages. The neutron spectrum emitted from the target in the direction perpendicular to the incident proton beam has a lower average energy than the forward-directed neutron spectrum, with relatively little penalty in total neutron yield. In addition, neutrons emitted in the forward direction can also appear at the irradiation point, but only after losing some energy via at least one scattering interaction. The net result is that less filtering and moderating is required to produce an acceptable epithermal-neutron spectrum. The vertical orientation of the proton beam also permits the target to be operated at liquid or near-liquid conditions, helping to solve a major engineering problem associated with lithium targets, which have a very low melting temperature

In another clinical-scale system design effort during the late 1990s, researchers at the E.O. Lawrence Berkeley National Laboratory and the University of California at San Francisco developed a design and initiated the construction of a significantly higher power accelerator-based epithermal-neutron source[16]. Unfortunately funding shortages prevented completion of this prototype, which featured an electrostatic quadrupole accelerator producing a proton beam that was directed onto a large-area water-cooled lithium target. Several concepts for moderation and filtering of the resulting neutron source were explored and some low-power tests were conducted A distinguishing feature of the neutron spectrum from one of the most promising of these concepts, based on neutron filtering in mixtures of lithium fluoride, aluminum fluoride, and aluminum, is that it is peaked near the high-energy end of the desirable epithermal-neutron range. This yielded an improvement in the therapeutic ratio, compared to what was produced at the time by typical reactor-based epithermal-neutron beams having a flat (per unit lethargy) spectrum over the epithermal energy range[17]. The neutron flux intensity that was anticipated to be achievable with this device was comparable to the intensity of current reactor-based sources.

An additional interesting proton-accelerator-based concept for an epithermal-neutron source useful for BNCT applications has been investigated by researchers in Russia[18], as well as by Idaho State University and MIT[19] and, more recently, in Japan[20]. This idea involves using an incident proton beam that has an energy that is just above the threshold for neutron production in the target. In the case of a lithium target the threshold energy is 1.88 MeV and in the near-threshold concept the incident proton

beam would have an energy of approximately 1.92 MeV. Under these conditions, the angular distribution of the neutrons emitted from the target is highly forward-peaked due to so-called "kinetic collimation", an inherent feature of the kinematics of the neutron production interaction near the threshold, where the outgoing neutron has a velocity in the center of mass system that is smaller than the velocity of the center of mass. In addition, the spectrum of the emitted neutrons is quite soft and may require little or no moderation and filtering to produce an acceptable therapeutic ratio in clinical applications. A difficulty with this concept is the fact that the neutron yield per unit proton current on target is smaller than with accelerator concepts that involve higher energy protons. This is counteracted, however, by the reduced filtering requirements. There are other questions involving stability and target design for this concept, but if it can be realized in a practical and deployable device, it could offer a low-cost system for hospital deployment for some specialized applications.

Finally, during the mid-1990s the Idaho National Laboratory and Idaho State University, investigated the feasibility of an alternate concept for an accelerator-based source of epithermal neutrons for BNCT that features a two-stage photoneutron production process driven by an electron accelerator. In this concept relativistic electron beams impinge upon heavily-shielded tungsten targets located at the outer radius of a small cylindrical tank of circulating heavy water (D_2O). A fraction of the energy of the electrons is converted in the tungsten targets into radially-inward-directed bremsstrahlung radiation. Neutrons subsequently generated by photodisintegration of deuterons in the D_2O within the tank are directed to the patient through a suitable beam tailoring system. Initial proof-of-principal tests using a low-current benchtop prototype of the epithermal photoneutron source concept for BNCT were conducted[21]. The results of these experiments demonstrated that on the basis of neutronic performance, the proposed photoneutron device could offer a promising alternate approach to the production of epithermal neutrons for BNCT. However, control of photon contamination to acceptable levels at the irradiation point would be crucial to the success of the overall concept.

Further details and references relevant to the development of accelerator neutron sources for BNCT are available in the excellent recent review article by Blue and Yanch[22]. Also, as is evident from the proceedings of the most recent three ISCNT meetings, including this one, solid progress in the field has continued, with the ongoing development and testing of the Birmingham facility, the construction of a clinical scale proton accelerator based neutron source by the Institute of Physics and Power Engineering in Obninsk, Russia, expanded efforts in Japan, and various other design studies and experimental tests in Russia, Italy, Korea, China, and Argentina. Perhaps most significantly at this particular juncture, a gantry-mounted neutron delivery system has been designed and is currently being constructed for a commercial customer by Ion Beam Applications Incorporated, in Belgium[23]. This system will be the first gantry mounted neutron delivery system for epithermal-neutron BNCT. It features a 20 mA proton beam incident on a high-performance lithium target, with subsequent moderation and filtering of the resulting neutron source using a high-density MgF_2 beam shaping assembly with a Pb reflector. It arguably represents the current state of the art, based on the accumulated experience of researchers worldwide over the past 20 years.

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References

[1] R.S. Stone, "Neutron therapy and specific ionization", *Am. J. Roentgenol*. **59**:771-785 (1940)

[2] G.E. Laramore , T.E. Griffin, "Fast Neutron Radiotherapy - Where Have We Been and Where Are We Going?", *Int. J. Rad. Onc. Bio. Phys*., **32**:879-882 (1995).

[3] G.L. Locher, "Biological effects and therapeutic possibilities of neutrons", *Am. J. Roentgenol*. **36**:1-13 (1936).
[4] T.A. Buchholtz, G.E. Laramore, K.J. Steltzer, R. Risler, P. Wootton,, T. Griffin, "Boron Neutron Capture Enhanced Fast Neutron Radiotherapy for Malignant Gliomas and Other Tumors", *J. Neuro-Oncology*, **33**:171-178 (1997).
[5] Y. Nakagawa, K. Pooh, T. Kobayashi, T. Kageji, S. Uyama,, A. Matusmura, H. Kumada, "Clinical Review of the Japanese Experience with Boron Neutron Capture Therapy and a Proposed Strategy using Epithermal Neutron Beams, *J. Neuro-Oncolog,* **62**:87-97 (2003).
[6] P.M. Busse, O.K. Harling, M.R. Palmer, W.S. Kiger III, J. Kaplan, I. Kaplan, C.F. Chuang, J.T. Goorley, K.J. Riley, T.H. Newton, G.A. Santa Cruz, X.Q. Lu, R.G. Zamenhof, "A Critical Examination of the results from the Harvard-MIT NCT program phase I clinical trialof neutron capture therapy for intracranial disease", *J. Neuro-Onccology*, **62**:111-121 (2003).
[7] A.Z. Diaz, "Assessment of the results from the phase I/II boron neutron capture therapy trials at the Brookhaven National Laboratory from a clinicians point of view", *J. Neuro-Onccology*, **62**:101-109 (2003).
[8] O.K. Harling, et al., "The Fission Converter-Based Epithermal Neutron Irradiation Facility at the Massachusetts Institute of Technology", *Nuclear Science and Engineering*, **140**: 223-240 (2002)
[9] D.W. Nigg, et al., "Modification of the University of Washington Neutron Radiotherapy Facility for Optimization of Neutron-Capture-Enhanced Fast Neutron Therapy", *Med. Phys.* **27**:359-367 (2000).
[10] C Wang, T.E. Blue, R.Gahbauer, "A Neutronic Study of an Accelerator-Based Neutron irradiation Facility for Boron Neutron Capture Therapy", *Nuclear Technology*, **84**:93-107 (1989).
[11] G.L. Brownell, J.E. Kirsch, J. Kehayas, "Accelerator Production of Epitheral Neutrons for Neutron Capture Therapy", In: H. Hatanaka (Editor), Neutron Capture Therapy – Proceedings of the Second International Symposium on Neutron Capture Therapy, Tokyo, Japan (1985).
[12] J.C. Yanch, X-I Zhou, R.E. Shefer, R.E. Klinkowstein, "Accelerator –based epithermal neutron beam design for neutron capture therapy", *Med. Phys.* **19**:709-721 (1992).
[13] D.W. Nigg (Editor), Proceedings of the First International Workshop on Accelerator-Based Neutron Sources for Boron Neutron Capture Therapy, CONF-940976, Idaho National Engineering Laboratory (1994).
[14] R.E. Klinkowstein, R.E. Shefer, J.C. Yanch, W.B. Howard, H. Song, E. Binello, B.W. Blackburn, J.L. Daigle, S.M. Sears, C.H. Goldie, R.J. Ledoux, "Operation of a High-Current Tandem Electrostatic Accelerator for Boron Neutron Capture Therapy", In: Advances in Neutron Capture Therapy, Volume 1, Elsevier, Amsterdam, Page 522 (1997)
[15] D.A. Allen, T.D. Beynon, "A Design Study for an Accelerator Based Epithermal Neutron Beam for BNCT", *Phys. Med. Biol*., **40**:807-821 (1995).
[16] D.L. Bleuel, R.J. Donahue, B.A. Ludewigt, J. Vujic, "Designing accelerator-based epithermal neutron beams for boron neutron capture therapy", *Med. Phys.* **25**:1725-1734 (1998).
[17] F.J. Wheeler et al., "Boron Neutron Capture Therapy: Implications of neutron beam and compound characteristics", *Med. Phys.* **26**:1237-1244 (1999).
[18] Kononov,V.N, Regushevskiy, N.A, Soloviev, N.A., Leipunskiy, A.I., "Accelerator-Based Intense and Directed Neutron Source for BNCT, In: Advances in Neutron Capture Therapy", Volume 1, Elsevier, Amsterdam, Page 528 (1997)
[19] C.L. Lee, X-L Zhou, R.J. Kudchadker, F. Harmon, Y.D. Harker, Y.D., "A Monte Carlo Dosimetry Based Evaluation of the ^{7}Li(p,n)^{7}Be Reaction Near Threshold for Accelerator BNCT", *Medical Physics* **27**:192-201 (2000).
[20] G. Bengua, T. Kobayashi, K. Tanaka, Y. Nakagawa, "Optimization parameters for BDE in BNCT using near-threshold ^{7}Li(p,n)^{7}Be direct neutrons", *Applied Radiation and Isotopes*, **61**: 1003-1008 (1994).
[21] Nigg, D.W. Mitchell, H.E., Harker, Y.D., Harmon, J.F. "Experimental Investigation of Filtered Epithermal Photoneutron Beams for BNCT", Advances in Neutron Capture Therapy, Volume 1, Elsevier, Amsterdam, Page 477 (1997)
[22] T.E. Blue, J. Yanch, "Accelerator-based epithermal neutron sources for boron neutron capture therapy of brain tumors", J. *Neuro-Oncology*, **62**:19-31 (2003).
[23] F. Stichelbaut, E. Forton, Y. Jongen, "Design of a beam shaping assembly for an accelerator-based BNCT system", These Proceedings (2006).