Description/Abstract DEFG02-89ER60874

Summary:

The DOE-funded accelerator BNCT program at the Massachusetts Institute of Technology has resulted in the only operating accelerator-based epithermal neutron beam facility capable of generating significant dose rates in the world. With five separate beamlines and two different epithermal neutron beam assemblies installed, we are currently capable of treating patients with rheumatoid arthritis in less than 15 minutes (knee joints) or 4 minutes (finger joints) or irradiating patients with shallow brain tumors to a healthy tissue dose of 12.6 Gy in 3.6 hours. The accelerator, designed by Newton Scientific Incorporated, is located in dedicated laboratory space that MIT renovated specifically for this project. The Laboratory for Accelerator Beam Applications consists of an accelerator room, a control room, a shielded radiation vault, and additional laboratory space nearby.

In addition to the design, construction and characterization of the tandem electrostatic accelerator, this program also resulted in other significant accomplishments. Assemblies for generating epithermal neutron beams were designed, constructed and experimentally evaluated using mixed-field dosimetry techniques. Strategies for target construction and target cooling were implemented and tested. We demonstrated that the method of submerged jet impingement using water as the coolant is capable of handling power densities of up to 6 x 10^7 W/m^2 with heat transfer coefficients of 10^6W/m^2-K. Experiments with the liquid metal gallium demonstrated its superiority compared with water with little effect on the neutronic properties of the epithermal beam. Monoenergetic proton beams generated using the accelerator were used to evaluate proton RBE as a function of LET and demonstrated a maximum RBE at approximately 30-40 keV/μm, a finding consistent with results published by other researchers. We also developed an experimental approach to biological intercomparison of epithermal beams and compared the RBE characteristics of the MIT Reactor M67 clinical beam, the Brookhaven Medical Research Reactor clinical beam (both of which were used in Phase I/II clinical trials of BNCT) and the MIT LABA BNCS beam. Additional research initiated under this program involved an investigation of the potential of BNCT for the prevention of restenosis and the development of accelerator-based fast neutron brachytherapy. A total of 10 student research theses (2 Undergraduate, 4 Masters, and 4 Doctoral) were completed as part of this research program.

DOE Patent Clearance Granted
for Mark Doorsaak
14 May 2003

DISCLAIMER

Accelerator Based Neutron Beams for Neutron Capture Therapy

DE-FG02-89ER60874 Final Report

Jacquelyn C. Yanch, Principal Investigator

Introduction:

The DOE-funded accelerator boron neutron capture therapy (BNCT) program at the Massachusetts Institute of Technology has resulted in the only operating accelerator-based epithermal neutron beam facility capable of generating significant dose rates in the world. With five separate beamlines and two different epithermal neutron beam assemblies installed, we are currently capable of treating patients with rheumatoid arthritis in less than 15 minutes (knee joints) or 4 minutes (finger joints) or irradiating patients with shallow brain tumors to a healthy tissue dose of 12.6 Gy in 3.6 hours. The accelerator, designed by Newton Scientific Incorporated, is located in dedicated laboratory space that MIT renovated specifically for this project. The Laboratory for Accelerator Beam Applications consists of an accelerator room, a control room, a shielded radiation vault, and additional laboratory space nearby.

In addition to the design, construction and characterization of the tandem electrostatic accelerator, this program also resulted in other significant accomplishments. A number of epithermal beam configurations based on various charged particle reactions were designed, constructed, installed, and experimentally evaluated in tissue-equivalent phantoms using mixed-field dosimetry techniques. Target cooling strategies for high current applications have been developed, implemented and tested during both phantom experiments and animal and cell irradiations. We demonstrated that the method of submerged jet impingement using water as the coolant is capable of handling power densities of up to 6×10^7 W/m^2 with heat transfer coefficients of 10^6W/m^2-K. Experiments with the liquid metal gallium demonstrated its superiority compared with water with little effect on the neutronic properties of the epithermal beam. Monoenergetic proton beams generated using the accelerator were used to evaluate proton RBE as a function of LET and demonstrated a maximum RBE at approximately 30-40 keV/μm, a finding consistent with results published by other researchers. We also developed an experimental approach to biological intercomparison of epithermal beams and compared the RBE characteristics of the MIT Reactor M67 clinical beam, the Brookhaven Medical Research Reactor clinical beam (both of which were used in Phase I/II clinical trials of BNCT) and the MIT LABA boron neutron capture synovectomy beam. Additional research initiated under this program involved an investigation of the potential of BNCT for the prevention of restenosis and the development of accelerator-based fast neutron brachytherapy. A total of 10 student research theses (2 undergraduate, 4 masters, and 4 doctoral) were completed as part of this research program and over 40 conference and journal articles were published (see attached listing).

1. The MIT Laboratory for Accelerator Beam Applications (LABA)

The Laboratory for Accelerator Beam Applications consists of 3300 sf of laboratory space renovated specifically for this project by MIT. This space contains an accelerator room, a control room, and a shielded vault in which experiments are carried out. A schematic illustration of the layout of these areas is shown in Figure 1. The facility also includes additional laboratory space used for cell culture facilities and experimental preparation (not shown in Figure 1).

The tandem electrostatic accelerator is located in the 26'x10'accelerator room. Charged particles leaving the accelerator pass through a steering magnet and then through a 4 ft thick concrete wall into the radiation vault. In the vault, a switching magnet directs the ion beam into one of five independent experimental beamlines. The versatility of this set-up made possible the operation of several concurrent experimental programs ranging from radiobiology studies, to high power target testing, to in-phantom neutron dosimetry and animal irradiation studies.

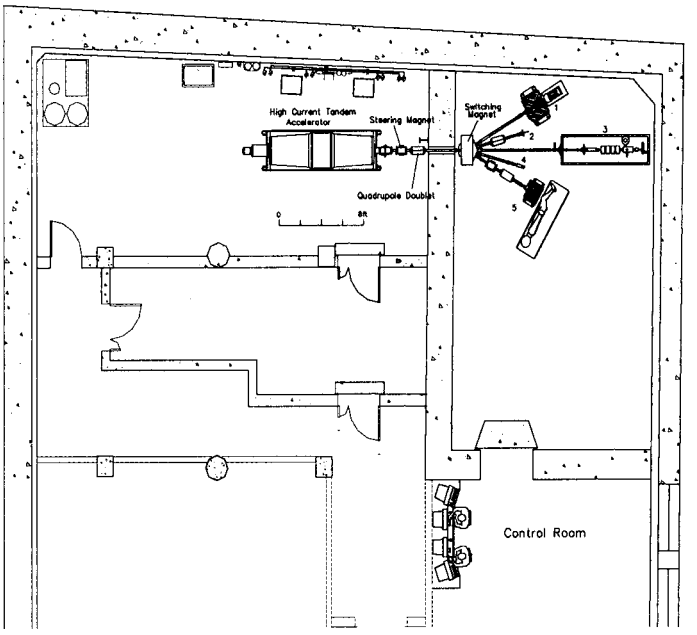

Figure 1: Layout of the accelerator facility at MIT LABA, showing the accelerator room, control room, and radiation vault.

2. Accelerator Development and Testing:

Figure 2 shows a photograph of the high current tandem accelerator developed and assembled under this program and installed at MIT LABA. The accelerator, designed by NSI, is roughly 3 meters long and weighs approximately 2,000 lb. High currents are made possible by a unique power supply and accelerating column design, as described in the next section. Cooling and electrical requirements are modest and include only standard chilled water service and 3-phase 208 V electrical supply, making this device very suitable for hospital installation. In addition, the use of specially designed accelerating tubes allows the acceleration of high ion currents with minimal X-ray generation, eliminating the need to shield the accelerator itself. Considerable attention has been given to the development of an easy-to-use PC-based accelerator control system. The mouse-driven control interface, which was designed and implemented by Pyramid Technical Consultants, allows system functions to be controlled and monitored from a remote computer. While providing full freedom to set all operating parameters, the user interface also provides the option for automatic feedback stabilization of ion source and accelerated current.

This accelerator has been operational since 1996. It has been used for a variety of experimental investigations ranging from dosimetric evaluation of epithermal neutron beams via mixed field dosimetry, to radiobiological and animal irradiation studies, to hardware design evaluation. Throughout this period, accelerator operation served two purposes. First, the generation of significant particle currents has allowed us to investigate many aspects of BNCT.

Second, we have been able to continually evaluate the performance of this hardware design to determine its suitability for eventual installation in a hospital or medical centre. Further details can be found in the attached paper:

> Klinkowstein R.E., 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 and R.J. Ledoux, "Operation of a High Current Tandem Electrostatic Accelerator for Boron Neutron Capture Therapy," (B. Larson, J. Crawford and R. Weinreich, Eds.) Advances in Neutron Capture Therapy, Elsevier Science B.V., Amsterdam, Volume I, 522-527, 1997.

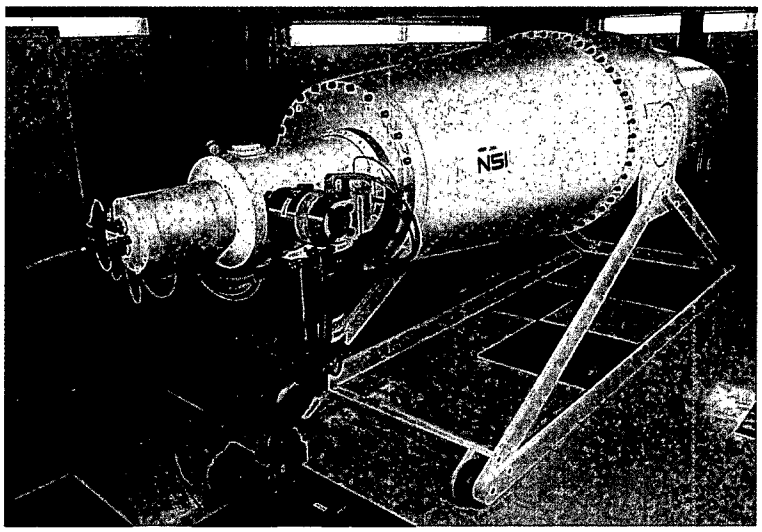

Figure 2: The NSI high current tandem accelerator showing the ion source, pressure vessel, and exit beamline entering the radiation vault wall.

Accelerator Testing and Operating Experience: Accelerator testing and operation proceeded on two fronts. First, the accelerator operating parameters most relevant to future clinical use for BNCT were evaluated. Concurrently, accelerator operating parameters relevant to radiobiology and in-phantom dosimetry studies were established and extensive operating experience was gained. Highlights of the operating regimes studied during this program are given below:

- The high current negative ion injector has been operated at proton beam currents of up to 6 mA, verifying that the NSI multi-cusp negative hydrogen ion source meets the beam current requirements for clinical BNCT.
- Proton beam currents of over 1 mA have been accelerated and delivered to a target located in the radiation vault.
- Extremely low X-ray radiation levels were measured at the wall of the accelerator pressure vessel during high current operation. Measured levels were in the range 40-100 μrem/hour. Low radiation levels means that no additional shielding around the accelerator is required.
- Accelerator voltage stability has been directly measured during high voltage operation. The measured voltage regulation is very high, approximately one part in 10^4.
- Accelerator operation over a very wide range of terminal voltages has been established. The accelerator has been successfully operated with beams of energies varying by more than a factor of 30.

The results summarized above indicate that the high current tandem accelerator technology developed in this program is potentially useful for clinical BNCT as well as radiobiology and in-phantom dosimetry studies. Particularly important to the latter applications is the excellent voltage stability that allows single particle effects and narrow-band neutron energy spectra near reaction thresholds to be studied. Additionally, the wide range of tunability of the accelerator terminal voltage, and hence the final particle energy, makes this accelerator technology ideal for the evaluation of a number of different charged particle reactions over a range of bombarding energies.

3. Development of High Power Targets and Cooling Strategies:

Accelerator-based production of intense neutron beams requires the fabrication of appropriate targets and the development of cooling strategies capable of removing large heat loads efficiently and safely. In this program we demonstrated that the method of submerged jet impingement using water as the coolant is capable of handling power densities of up to 6×10^7 W/m^2 with heat transfer coefficients of 10^6 $W/m^2 - K$. From the coupling of calculations, simulation and experimental measurements we confirmed that submerged jet impingement is a successful approach to heat removal from the neutron-producing targets used in accelerator-based BNCT for both clinical and research applications. Details can be found in the attached paper:

Blackburn B.W., J.C. Yanch and R.E. Klinkowstein, "Development of a High-Power Water Cooled Beryllium Target for Use in Accelerator-based Boron Neutron Capture Therapy (ABNCT)," *Medical Physics,* **25**(10): 1967-1974, 1998.

We subsequently turned our attention to the potential of using a liquid metal coolant to further improve cooling capability and to make cooling of lithium targets a practical option.

Liquid Gallium Cooling

Gallium is a rare metal with many properties that make it attractive as a cooling fluid. Liquid gallium possesses thermo-physical properties which make it ideal for applications with heat fluences as high as 20 MW/m^2. Although it is solid at room temperature gallium melts at a temperature of 29.8 C and remains liquid over a range of almost 2200 degrees. Only tin has a longer liquid range. In addition to its long liquid range, gallium has an extremely low vapor pressure even at high temperatures. Gallium can be pumped relatively easily as long as it is maintained as a liquid. It has a viscosity only slightly higher than water, but its kinematic viscosity is lower than water thereby increasing its convective heat removal. Like water, gallium expands upon freezing so it must be kept from freezing in metal or glass containers. Gallium toxicity has been compared to that of aluminum, and it has no known acute effects even at high doses. Unlike most liquid metals, gallium wets most materials making it attractive for heat transfer. Unfortunately, gallium has limited compatibility with most materials. In the liquid state it cannot be brought in contact with materials such as copper, aluminum, iron, nickel, etc. It can be contained in organic polymers or certain grades of stainless steel. The price of gallium fluctuates dramatically, but the current cost is around $600 per kg. Table 1 lists the pertinent properties of liquid gallium and water.

Table 1 Thermophysical Properties of Liquid Gallium and Water

	Gallium	Water
Density (kg/m^3)	6100	1000
Melting point (°C)	29.8	0.0
Boiling point (°C)	2205	100
Thermal conductivity (W/mK)	40	0.6
Specific heat (kJ/kg)	0.396	4.2
Viscosity (kg m/s)	0.00196	0.000855
Kinematic viscosity (m^2/s)	3.2e-7	8.55e-7

Our initial tests using water coolant illustrated that heat fluences of 15 MW/m^2 could be removed from a 0.254 cm thick beryllium target with high velocities in a submerged jet impingement configuration. These tests found that heat removal was due to forced convective boiling and required jet velocities of 24 m/s and flow rates of 87 GPM which were provided by a 15hp centrifugal pump. Because the target relied on boiling for the heat transfer, critical heat flux (CHF) was a major concern at high heat fluences. During tests with water, in fact, CHF failure of the target was witnessed (at a heat flux of approximately 5×10^7 W/m^2). However, liquid gallium can be melted and pumped near room temperature and, because of its low kinematic viscosity, Reynolds numbers (Re) are generated which are over a factor of 2 higher than water at similar flow velocities. Being a liquid metal, gallium possesses a thermal conduction coefficient which is over 50 times higher than water. With a boiling point of over 2000 °C critical heat flux is not a limiting factor with gallium. Standard Nusselt number correlations which can be used to predict heat transfer coefficients for many fluids cannot be used for liquid metals, however, because of their high conductivity which competes with convection in heat transfer.

Preliminary experiments to illustrate the effectiveness of gallium cooling were conducted using LABA's tandem accelerator to heat a 0.254 cm thick beryllium target which was cooled with either water or liquid gallium at 50 °C at flow rates of approximately 1 L/min. Temperatures were measured at various target locations and at power loadings from 0-500 Watts. Temperature measurements were then used with the finite element code ADINA to estimate the average heat transfer coefficient. Results of the temperature measurements indicated that for equal flow rates, gallium significantly lowers the temperature at the interface between the fluid and the target. For example, at a flow rate of 1 L/min gallium was able remove 490 Watts with a temperature increase of 25 °C compared to a 40 °C increase with water. The magnitude of the temperature difference will increase as power on target increases. Even at low flowrates gallium generates a convective heat transfer coefficient of up to 6.0×10^4 W/m^2K. Unlike water which would boil at 100 °C, heat transfer from gallium would be linear over a large range of powers. With water, CHF begins to be a problem when the target surface temperature is higher than the saturation temperature by about 30 °C. This is not the case with gallium, however, since it has a low vapor pressure and a boiling point of 2200 °C.

Experiments using an array of submerged jets were conducted to determine area-averaged Nusselt number correlations for water and gallium over a Reynolds number range of $7000<Re<38000$. The spreading factor β_{max} was introduced into the gallium correlation to account for surface wetting effects. Area-averaged heat transfer coefficients, $\underline{h}$, produced by an array of gallium jets were found to exceed those of water for $Re > 13500$. At a Reynolds number of 35000 an $\underline{h}$ of 10^5 W/m^2K was measured with the gallium array compared to 5.5×10^4 W/m^2K for water. Simulations of the thermal and mechanical stresses found that a gallium-cooled beryllium target could withstand beam powers of up to 20.2 kW. Because of its low melting point, lithium targets were able to achieve 10 kW only if the beam power density was kept below 11.6 MW/m^2. No significant difference in figures of merit used to characterize epithermal neutron beams for BNCT were found when water was replaced by liquid gallium as the cooling fluid.

4. Determination of the RBE of Protons of Various Energies:

Energetic neutrons deliver dose to tissue primarily via elastic collisions with light hydrogen, creating energetic "proton recoils". The energy transferred to the proton depends on the angle of scatter and ranges, with equal probability, from zero up to the entire kinetic energy of the incident neutron. Since it is difficult to generate monoenergetic neutron beams, experimental determination of neutron RBEs as a function of energy can be approached by evaluation of the biological effect of monoenergetic protons of various energies. The RBE for neutrons of a given energy can thus be evaluated by integrating over the RBEs of the proton energies expected in the

recoil proton spectrum of that neutron energy. This is the approach developed at LABA under this program. The neutron energy range we investigated, several keV to 1-2 MeV, is that encountered in neutron capture therapies. Experimentally determined neutron RBE in this energy range are particularly scarce.

The protons energies we examined are 94 keV, 250 keV, 390 keV, 700 keV, 1.2 MeV, and 1.8 MeV. These energies were selected because the protons vary widely in their LETs and ranges in a cell. The 94 and 250 keV protons do not pass completely through a V79 cell, with the 94 keV proton probably not even reaching the cell nucleus. Assuming an average cell thickness of 6.4 μm, the 390 keV protons just pass through the entire cell, while the 700 keV, 1.2 MeV, and 1.8 MeV protons easily traverse the entire cell thickness[19-21]. The three highest energies were also chosen so that their RBEs can be compared to those reported by Belli et al. and Folkard et al. Details of the experimental design of these experiments and of our results can be found in the attached preprint:

M.A.Sitek, J.C.Yanch, K.D.Held, "Determination of the Relative Biological Effectiveness of 94 keV to 1.8 keV Protons," (under revision).

5. Biological Dosimetry of Epithermal Neutron Beams:

The beams used in BNCT are designed to consist primarily of epithermal neutrons in the energy range of 4 eV - 40 keV. However, the beams at the various institutions are by no means identical in their energy spectra, and inter-beam comparisons will be required in order to combine or compare clinical data obtained at the different locales. Beams can be compared in several ways, including by in-air dosimetry, in-phantom physical and radiobiological dosimetry, as well as with clinical endpoints. In-air and in-phantom dosimetry use ionization chambers to determine the fast neutron dose rate. However, the neutron sensitivity of the tissue equivalent ionization chamber used in calculating the fast neutron dose rate is typically averaged over a large neutron energy range and is not beam specific. This leads to uncertainty in determining the neutron dose rates and neutron energy spectra that will be present in any beam cross-calibrations using ionization chamber data. Since the linear energy transfer (LET) varies with neutron energy, the biological properties of the beams could be quite different even though the neutron dose rates are similar. Radiobiological inter-beam comparisons of cell survival would eliminate these uncertainties by providing a direct measure of the radiobiological effect. In addition, radiobiological inter-beam comparisons would be useful in determining whether data from various clinical trials, with their low patient numbers, can be combined.

As part of this DOE program we developed an experimental technique used to determine cell survival and relative biological effectiveness (RBE) as a function of depth in a water-filled phantom irradiated with an epithermal neutron beam. Using this method of "biological beam characterization" we compared three existing epithermal neutron beams: the MIT Reactor M67 clinical beam, the Brookhaven Medical Research Reactor clinical beam (both of which were used in Phase I/II clinical trails of BNCT), and the Boron Neutron Capture Synovectomy beam at MIT LABA (developed under a separate program for use in the treatment of Rheumatoid Arthritis using the $^{10}B(n,\alpha)$ reaction).

The recent clinical trials in the United States used healthy tissue response as one of the clinical end points. Since the concentration of boron in the healthy tissue was seen clinically to be approximately a factor of four lower than the concentration of boron in the tumor tissue, the radiation dose to healthy tissue is primarily due to the mixed field beam which consists of fast neutrons, thermal neutrons, and photons. Therefore, since the objective of our study is to use cell survival as a means of considering damage to healthy tissue, no boron is was included in the samples.

The dose components of each epithermal beam being used for BNCT are known at the beamport exit. However, once the beam interacts with material, the dose components will change due to moderation and attenuation of the neutrons and photons present. The average neutron

energy will decrease due to moderation of the neutrons, and the overall neutron spectrum will shift toward lower energies with increasing depth in the material. Therefore, during a BNCT treatment, the dose components change with depth in the patient. Correspondingly, when looking at surviving fraction in a water-filled phantom, each depth must be considered independently, since the neutron spectrum is different at each depth. To account for the changing spectrum in these experiments, cells are positioned at multiple depths, and several irradiations were carried out, each of varying duration. Survival curves are generated for each depth, and comparisons of RBE were made. Full details of the methodology we developed can be found in the attached paper:

White, S.M., K. Held, M.R. Palmer and J.C. Yanch,, "Biological Dosimetry for Epithermal Neutron Beams," *Radiation Research*, **155**(6): 778-784, 2001.

This paper presents results of RBE determination at the MITR M67 beam. Comparison of RBE data obtained in the three beams listed above can be found in the preprint:

White, S.M., K. Held, J.A.Coderre, and J.C. Yanch,, "Biological Dosimetry of Epithermal Neutron Beams for Neutron Capture Therapies," *submitted to Radiation Research.*

6. Accelerator Based Fast Neutron Brachytherapy:

The installation of a switching magnet at LABA allows us to direct the charged particle beam to any one of 5 separate beamlines. This has facilitated the investigation of a number of experimental projects simultaneously since apparatus does not have to be removed from the beamline following each experiment. One such experimental investigation has been accelerator-based fast neutron brachytherapy (ABFNB).

ABFNB involves the interstitial or intracavity insertion of a narrow, evacuated accelerator tube ("needle tube") with a beryllium target at the tip which generates neutrons within the tumor when hit by a deuteron (or proton) beam. Extensive computer simulation and heat removal calculations predicted that 1) treatment of even large tumors could be carried out in 8-30 min, depending on reaction and charged particle energy, 2) significant dose enhancement via BNCT is possible, and 3) removal of heat from the tube tip can be carried out via simple convection using chilled water. These design and calculational studies were followed by the construction and testing of two prototype devices, one of which is shown in Figure 3. At this point further development of ABFNB was supported by a grant from the National Science Foundation. Full details of the development of this approach can be found in the attached paper:

Song H., J.C. Yanch and R.E. Klinkowstein, "Accelerator-Based Neutron Brachytherapy," *Medical Physics*, (**29**)1: 15-25, 2002.

Figure 3. Photograph of the prototype brachytherapy source showing the outer tube and two flange base pieces. Two thermocouple leads are led out through the coolant inlet and outlet.

7. BNCT for the Prevention of Restenosis:

The potential of Boron Neutron Capture Therapy for the prevention of restenosis following balloon angioplasty was investigated at MIT LABA as part of this DOE program.

Angioplasty is a treatment for atherosclerosis, a progressive vascular disease characterized by 'plaque' within the intima of large and medium sized arteries. Plaque is a result of (i) smooth muscle cell proliferation, (ii) extensive connective tissue including collagen and elastic fibers, and (iii) accumulation of lipid in the form of cholesterol. Plaque build-up results in occlusion of the artery and reduced oxygen delivery to the heart muscle. If untreated, this will be followed by reduced ejection fraction, muscle atrophy and eventual myocardial infarction.

One treatment for atherosclerosis involves the insertion of a balloon dilation catheter into the stenotic region of the occluded artery. The balloon is then inflated to dilate the catheter. This technique, called angioplasty, is safe and effective in improving blood flow. Unfortunately, 30-60% of angioplasty patients exhibit restenosis within six months. Radiation delivered to the vessel wall during or immediately after angioplasty has been shown to reduce or inhibit the restenosis. We investigated the potential for delivering a therapeutic dose to a stenotic lesion via BNCT while maintaining acceptably low doses to adjacent healthy tissue (skin, heart and lungs).

Method: Lesion and healthy tissue doses were evaluated via Monte Carlo simulation. The MCNP code was used to model the dosimetric effects of three accelerator-based neutron beams in an anthropomorphic phantom. This phantom was developed in the Principal Investigator's laboratory for Nuclear Medicine imaging investigations and has a particularly detailed model of the heart (patterned after the MCAT phantom by B. Tsui et al). A 0.31 cm diameter lesion on the left anterior descending coronary artery was modeled on the surface of the heart closest to the skin of the chest.

Three beryllium-based neutron beams moderated by a 9 cm diameter D_2O moderator and 18 cm think graphite reflector were modeled as described in Table 3. The skin is the dose limiting tissue for this therapeutic application. Therefore results were analyzed as follows. First, the time required to deliver a skin dose of 800 RBE-cGy was determined. This is the dose threshold at which a mild but temporary skin erythema occurs. Next, the concentration of boron needed to result in the delivery of 2000 RBE-cGy to the lesion was calculated for the therapy time determined above. Finally, the heart and lung doses were calculated based on therapy time, boron uptake and assumed uptake ratios.

Results: Results using three different accelerator-based epithermal beams demonstrate that maximum therapy times range from 25.5 to 91 minutes (depending on the charged-particle reaction used to generate neutrons) to deliver a 2000 RBE-cGy does to the lesion without exceeding an 800 RBE-cGy tolerance dose to the skin of the chest. This skin dose could certainly be lowered with a corresponding increase in boron concentration in the lesion. All three epithermal neutron beams result in healthy tissue doses that are below threshold for acute or late radiation effects. Heart and lung doses are especially low given the tolerance doses for these tissues of 3000 cGy and 4500 cGy respectively.

Conclusions: Although our calculations demonstrate that delivery of radiation dose to stenotic lesions is dosimetrically possible with BNCT, a number of issues must be considered. These include the feasibility of developing appropriate boron delivery agents, and the fact that irradiation of the vessel epithelium can actually create new stenotic lesions (the boron compound must therefore have a high specificity for the target lesion and rapid clearance from the blood pool). In addition, a number of other approaches to irradiating stenotic lesions during or following balloon angioplasty are under investigation and these appear to hold considerable more practical promise for clinical application than BNCT. For these reasons, this pursuit of this application of BNCT was not continued under this program.

Publications Related to DE-FG02-89ER60874

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