REVIEW OF ACCELERATOR-BASED BORON NEUTRON CAPTURE THERAPY MACHINES

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Abstract

Accelerator-based BNCT (Boron Neutron Capture Therapy) facilities are being studied, developed and constructed at many laboratories and hospitals, especially in Japan. In order to provide sufficient neutron flux in the epi-thermal energy region (0.5 ~ 10 keV), an intense proton beam accelerated with a cyclotron, linear accelerator (linac) or DC accelerator up to 2.5 ~ 30 MeV is directed to lithium or beryllium targets to produce neutrons. The neutrons produced have an energy ranging from several hundred keV ~ 28 MeV, depending on the primary proton beam energy and target material, this neutron energy must be degraded to the epithermal region with a moderator system. The boron delivery drug system, patient treatment and radiation exposure planning can be the same as with conventional reactor-based BNCT. In this paper I will review the various possible technology choices being made by current projects in Japan.

INTRODUCTION

BNCT is another modality of radiation therapy for cancer. Unlike other radiation therapies such as X-ray, proton beam or heavy ion beam therapy, which all utilize the injected beam directly as the destroyer of the tumour; BNCT utilizes a neutron beam indirectly. Prior to the treatment, boron is caused to preferential accumulate inside the cancerous cells. Then when exposed to the neutron beam some boron atoms capture a neutron, and a α particle is emitted through the $N + {}^{10}B \rightarrow Li + \alpha + \gamma$. It is this α particle that causes the death of the cancer cell. The advantage of using a α particle over any other charged particle or X-ray is that it has a very short mean radiation length of about 10 μm (assuming an energy of 1.5 MeV as would typically result from the above reaction with an epithermal neutron), this is comparable to the cell size, thus minimizing damage to the surrounding healthy tissue.

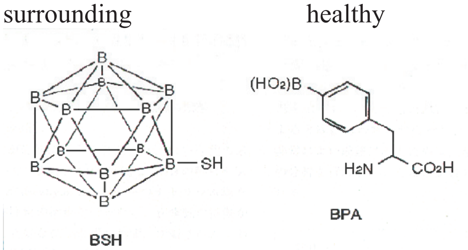

Figure 1: Chemical structure of BSH and BPA.

The choice of boron was made because of the large capture cross section (high capture probability) of the above process, especially for low energy (thermal to epithermal) neutrons. Boron is accumulated in the tumour cells after intravenous injection of chemicals such as BSH or BPA, which have chemical structures as shown in Figure 1. The problem here is that the ratio of boron density accumulated in the cancerous cells is only elevated by a factor of 3 over normal cells after intravenous injection of BSH or BPA, this poor target specificity results in (1) damage to surrounding healthy tissues when they are hit by the neutron beam and (2) the necessity of injecting a large quantity (more than 20g) of the boron compound (which is itself not harmless) into the body before each therapy session. For a long time BNCT researchers have been utilizing neutron beams from nuclear reactors. The problem here is that appropriate nuclear reactors are a scarce resource worldwide, which limits BNCT from becoming a standard of care for cancer therapy. This is in marked contrast with for example X-ray therapy. However, recently another more practical source of neutron beams has been developed, mostly in Japan, based upon a high intensity, low energy proton accelerator. The average proton beam power is 30 to 80 kW, which itself is rather high, but the energy can always be kept under 30 MeV. The required energy depends on which target material is used to produce the neutrons. Beryllium (Be) or lithium (Li) has been considered so far. A Be target requires a proton energy higher than 5 MeV while Li is lower at only 2.5 MeV, but Li has a melting temperature of only 180 °C whereas Be is a solid up to 1287 °C. The cost of the accelerator is estimated to be about 1/10 or less what a heavy ion machine costs and thus presents the potential to become a standard tool for cancer radiotherapy in medium- to large-sized hospitals.

THE ACCELERATOR-BASED BNCT FACILITY

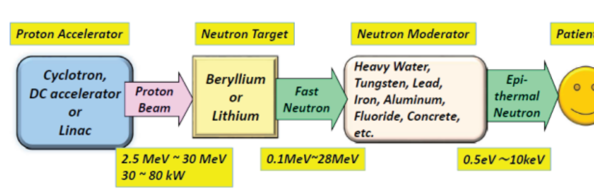

Figure 2: Block diagram of an accelerator-based BNCT facility.

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The role of the accelerator and target system is to produce an intense neutron beam that must be equivalent to that from a reactor. The neutron energy deceleration system (moderator), boron delivery drug system, patient treatment system and irradiation planning methods are almost completely shared with reactor-based BNCT concept. Figure 2 shows a block diagram of an accelerator-based BNCT facility.

The facility consists of the following three subsystems, an accelerator, a target and moderator, and the conventional patient treatment system. In the following, I will discuss mostly the accelerator and target system. There are mainly three choices for the accelerator: a cyclotron, a DC accelerator or a linac, and two choices for target material: Be or Li. In all cases, protons accelerated to have energies between 2.5 and 30 MeV impinge on the target. In thinking through the possible technology choices, we work from the center: (1) what kind of target to use, (2) from that we can estimate the required beam power to provide the design neutron flux, and (3) finally going upstream we can choose an accelerator.

The IAEA Guideline

In all cases, technology choices are based upon the requirements for neutron flux for patient treatment as defined by the IAEA guideline [1].

Neutron energy region: 0.5 eV ~ 10 keV (epi-thermal)
Epi-thermal neutron flux: $> 1 \times 0^{9}$ n/cm^2/s
Harmful fast neutrons: $< 2 \times 10^{-13}$ Gy·cm^2/n
Harmful γ-rays: $< 2 \times 10^{-13}$ Gy·cm^2/n

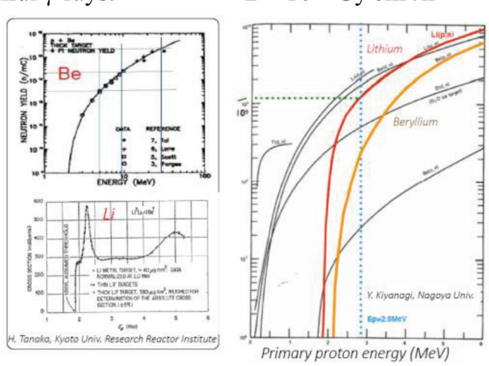

Figure 3: Comparison of neutron production cross-sections for Be and Li as a function of primary proton energy [2].

Target Material, Beryllium or Lithium?

Figures 3 and 4 show neutron production cross-sections and the resulting energy spectrum of the neutrons produced from a Li or Be target. It is clearly seen that from the cross-section viewpoint, Li can produce neutrons with a low energy accelerator (<3 MeV) and the energy spectrum produced is also low (<1 MeV), these are both advantageous for the moderator design. But, the following Li disadvantages also must be considered before choosing it: low melting temperature (180°C); generation of ^{7}Be (which is radioactive with a half-life of 53 days) through the nuclear reaction ^{7}Li(p,n)^{7}Be; generation of tritium through the reaction ^{6}Li(n,t)^{4}He (^{6}Li forms 7.6 % of natural Li); a vigorous exothermic reaction with water and finally easy oxidization. On the other hand, Be is a very stable material with a high melting temperature (1287°C).

Because of lithium's low melting temperature, liquid Li is an attractive choice for target material.

Accelerator

With respect to the possible accelerators, the main characteristics can be summarized as follows:

(1) Cyclotron: CW operation, easy to accelerate to high energy (>13 MeV) but only low current (< 2 mA).
(2) DC accelerator: DC operation, low energy (<3 MeV) but high current (>10 mA) is possible.
(3) Linac: Both DC and pulse operation, expensive to get high energy (> 13 MeV) but high current (> 10 mA) is possible.

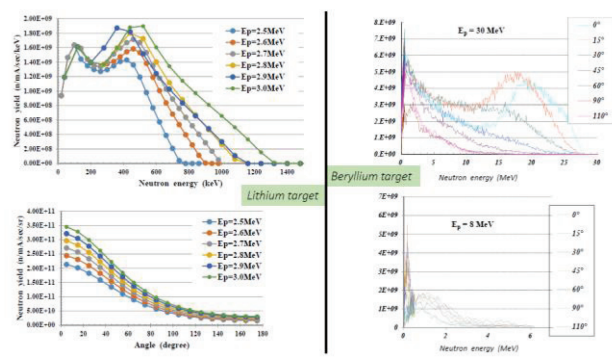

Figure 4: Neutron energy spectrum for various production angles for Li (left) and Be target (right) [2].

VARIOUS TECHNOLOGY CHOICES

As examples of technology choices, actual projects now in progress in Japan will be described in this section, between them almost the full gamut of possibilities are encompassed.

Kyoto University (30 MeV Cyclotron and Thick be Target)

The BNCT facility was designed and constructed through collaboration between Kyoto University and Sumitomo Heavy Industries, Ltd [3]. This project is the most advanced and is now in the clinical trial phase. The main subsystems are a 30 MeV, 1.1 mA (33 kW) cyclotron, a beam transport system including a beam scanning system to reduce the heat density on the target and a Be target and moderator system. The principle feature of the facility is that there were no serious technical challenges in the design. The cyclotron is a mature technology and the target manufacturing process is simple. Since the incident proton beam on the target is stopped in the cooling water layer, the target is free from the blistering problem [4]. On the other hand, we should be prepared to handle a high residual radiation level after long term beam operation, which could be up to 100 mSv/h or more. Stray high-energy neutrons cause this, as shown in Figure 4. For the same reason, the moderator design must be carried out carefully to keep the contamination of the epi-thermal neutrons by unwanted fast neutrons to within the allowed range (see Fig. 5).

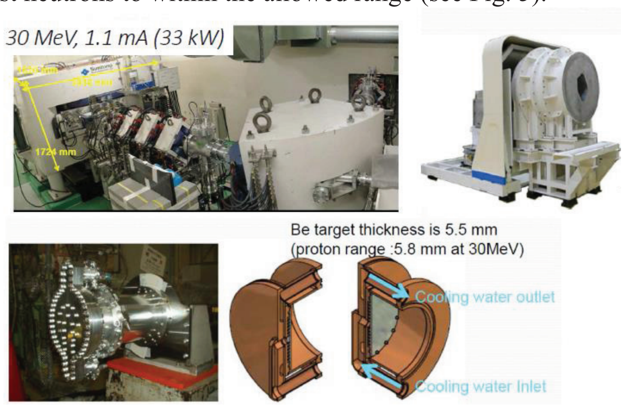

Figure 5: Photos of the cyclotron (upper left), moderator (upper right) and target system (lower) [3]. The Be is 5.5 mm in thickness, which is slightly thinner than the Bragg peak depth of the beam. The beam is stopped in the cooling water layer which resolves the blistering problem.

National Cancer Center (RFQ Linac and Solid Li Target)

The National Cancer Center is collaborating with CICS, Inc. to develop a facility based on a solid Li target technology. The average beam current is 20 mA and is accelerated with a CW RFQ linac up to 2.5 MeV (50 kW). Since there are only a few technical problems with the linac it has already passed the radiation facility inspection by the government authorities. The major feature of interest is in the target design.

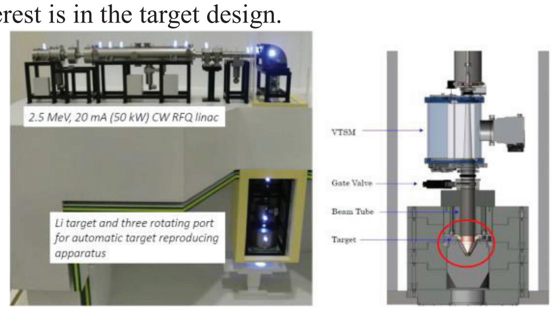

Figure 6: Schematic drawing of the NCC facility configuration (left) and target system with automatic Li layer reproducing apparatus (right) [5].

As summarized previously, the thorniest issue in the choice of a Li target is how to avoid the accumulation of radioactive elements, such as ^{7}Be and tritium, after long-term beam operation. This group has come up with an excellent idea to solve this problem. As is shown in Figure 6, three rotating port mechanism is used to make possible an automatic reforming Li layer. The first port is used for the irradiation as normal. A second port is used to strip off the Li layer with water, here taking advantage of the 'problem' that Li reacts strongly with water. The residual is drained off and stored in a holding tank on the hospital premises. A third port is used for creating a fresh Li layer by vapor deposition. This target mechanism is in the final development stage and is waiting for clinical trials.

Nagoya University (2.8 MeV DC accelerator and hermetic sealed liquid Li target)

The accelerator is a conventional Dynamitron as is shown in Figure 7, which accelerates a DC beam (15 mA) up to 2.8 MeV (42 kW).

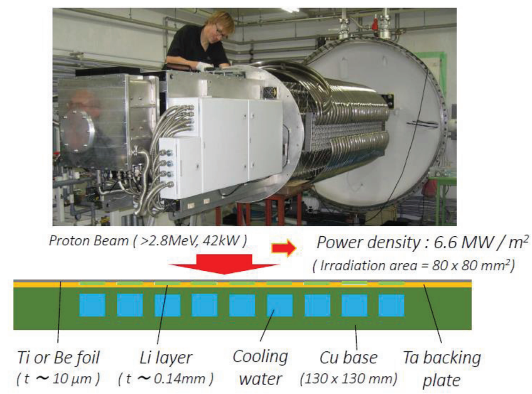

Figure 7: Picture of the Dynamitron (upper) and cross sectional drawing of the target (lower) [2].

Its major feature of interest is the Li target development. Figure 7 (lower) shows the cross section view of the target structure [2].

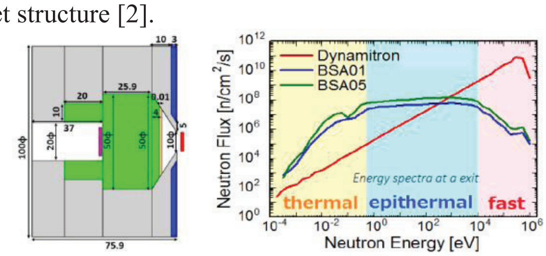

Figure 8: A cross sectional drawing of the moderator and estimated neutron spectrum at the exit of the dynamitron (red), original moderator design (blue) and improved design (green).

Step-1: A Ta backing plate is attached to a Cu cooling base by the HIP (Hot Isostatic Press) process. An embossed-structure is formed on the surface of Ta plate. Ta has a high threshold for blistering (H^{+} fluence > 1.6 x 10^{21} H^{+}/cm^{2}) and is highly corrosion resistance and has good wettability for liquid Lithium.

Step-2: A thin Ti foil is next attached to the Ta plate by HIP. Ti also has a high corrosion resistance and good wettability for liquid Lithium

Step-3: Li is introduced into the thin spaces in the Ta embossed structure. This process is still under development.

Unwanted ^{7}Be products could be confined in the target and the Ti covering prevents oxidization of Li and allows for long term operation.

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Information on the moderator design and neutron spectrum was provided by Yoshiaki Kiyanagi [2] and is shown in Figure 8. Since the neutron energy is low (see Figure 4), the dimension of the moderator can be compact (a cylindrical shape 1 m in diameter and 75.9 cm long).

Tokyo Institute of Technology (Liquid Li Target Development Only)

This group carried out a liquid Li target development and successfully demonstrated a stable liquid Li flow [6] as shown in Figure 9. Parameters are listed below:

Temperature	220 º C
Flow speed	30 m/s
Vacuum pressure	10^{-4} Pa
Layer width	45 ~ 50 mm
Length	50 mm
Liq. Li circulation	electromagnetic pump

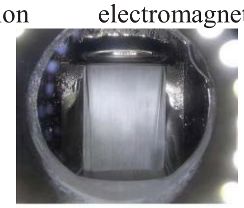

Figure 9: Liquid Li flow in the circulating loop (from top to bottom) [6].

This achievement opens the desirable possibility of using a liquid Li target-based BNCT facility. However, before any wide spread adoption by hospitals, remaining problems that must be solved would be in how to maintain a stable flow at 220°C over long time periods and how to separate and sequester the ^{7}Be from the circulating loop for safe storage on-site.

Tsukuba University (8 MeV Linac and Thin Be Target)

The first stage of this project was to think about choices of energy and target material with the goal of wide spread use in hospitals. Based on nuclear reaction data as shown in part in Figure 10, an 8 MeV linac and a thin Be target were adopted. Figure 4 shows that the upper limit of the neutron energy with an 8 MeV primary proton beam on the Be target is 6.1 MeV and is mostly concentrated below 3 MeV, note that that is below the threshold energy of many nuclear reaction channels participated in by fast neutrons [7].

The next stage was the technology choice for the accelerator. Only a linac can provide the high beam current required to get a high enough beam power to generate sufficient neutron flux, because the possible acceleration current from a cyclotron is limited. Almost inevitably, the linac consists of a 3 MeV RFQ and DTL driven by a klystron. Figure 11 shows a schematic layout of the facility, which was installed in an existing building after renovation [8].

Since most of the group members of this project came from J-PARC, the basic design is based on the well-established technology of the front end of the J-PARC injector linac. The differences with J-PARC are to increase (1) the duty factor from 2.5 % of J-PARC to 20 % and (2) the RFQ and DTL are driven by a single klystron. This change (2) was required by the limited space available in the existing building.

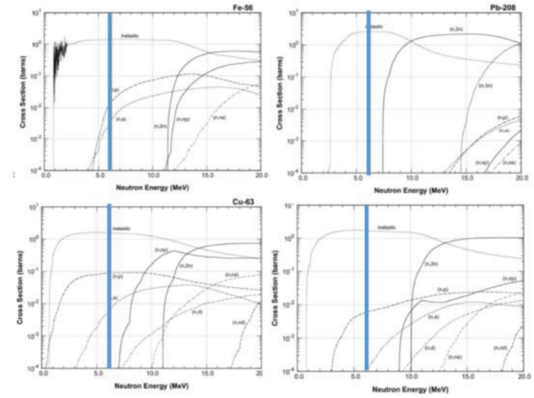

Figure 10: Nuclear reaction cross sections (barns) for ^{56}Fe (upper left), ^{208}Pb (upper right), ^{63}Cu (lower left) and ^{65}Cu (lower right) as a function of neutron energy [8]. Blue vertical lines are at 6.1 MeV.

Main beam parameters are summarized below:

Beam energy	8 MeV
Peak beam current	50 mA
Maximum pulse width	1 ms
Maximum repetition rate	200 Hz
Maximum duty factor	20 %
Maximum average current	10 mA
Maximum beam power	80 kW

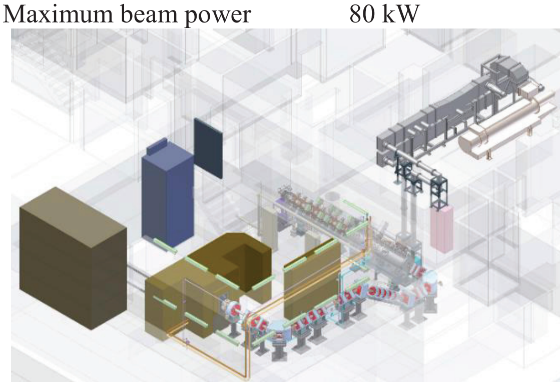

Figure 11: A schematic drawing of the facility layout.

Changes from the J-PARC design (1) and (2) in turn bring as a result the following technical problems:

(1) Difficult temperature control of the RFQ and DTL and developing long pulse klystron modulator power supply.
(2) Difficult beam loading compensation for the two different nature cavities.

The first problem can be solved by developing an advanced cooling water design and control system and a new klystron modulator power supply design utilizing a droop compensation circuit by DAWONSYS, Inc.

In order to solve the second problem, a sophisticated control of at the RF low level is essential.

The essentially challenge of this technology choice is the development of a target system consisting of a thin Be plate capable of withstanding the heavy heat load and the blistering problem. The solutions are as follows:

The beam spot size on the target is expanded to reduce the heat load density; this is accomplished by using a beam optics design consisting of two quadrupole and octapole magnets.

A three layer target consisting of Be / blistering mitigation metal / copper heat sink was developed with a HIP technology. The thickness of the Be is slightly thinner than the 8 MeV proton Bragg peak depth in order to stop the beam at the edge of the middle layer.

All construction of the hardware systems has been completed and the preliminary epi-thermal neutron spectrum was measured in December 2015. The estimated and expected epi-thermal neutron flux with 80 kW beam power was $4.3 \times 10^9/cm^2/s$.

Okinawa Institute of Science and Technology Graduate University, OIST (3 MeV RFQ Linac and Solid Li Target)

This group is a newcomer to the accelerator-based BNCT development world and therefore could profit from the experiences of the preceding groups. Progress is still in the design phase, but has made a critical decision to use a newly developed solid Li target technology. As is discussed in the previous section, the enemy of any Li target is ^{7}Be accumulation and lithium's low melting temperature and high reactivity with water and oxygen. The lesson from the National Cancer Center project is that to avoid this problem: "do not use the same target for long periods".

Recently, ULVAC, Inc. and SANKI INDUSTRY, Inc. have developed a stable and tractable solid Li target which can be exposed to air [9] maintaining good thermal conductivity between the solid Li layer and a copper heat sink. The size of the target is still limited to only 50 mm in diameter, but has already passed a severe DC accelerator beam life test with the following conditions:

Beam energy	3 MeV
Beam current	60 μA (DC, 180 W)
Beam spot size	50 mm
Power density	9.2 MW/m^2

Based on this experimentally proven technology and building on the Tsukuba University experience, the OIST-design parameters are summarized as:

Beam energy	3 MeV
Peak beam current	50 mA
Maximum pulse width	1 ms
Maximum repetition rate	200 Hz
Maximum duty factor	20 %
Maximum average current	10 mA
Maximum beam power	30 kW
Target size	120 × 120 mm
Heat density on the target	2.1 MW/m^2
RFQ	352 MHz
Klystron	600 kW multi beam
Klystron modulator	DRC (Tsukuba type)
Ion source	ECR (Tsukuba type)

SUMMARY AND CONCLUSION

All combinations of the individual technologies show up in the activities of Japanese projects for developing accelerator-based BNCT facilities. It should be mentioned that of these projects, the most advanced one is the Kyoto University group. Southern TOHOKU General Hospital in Fukushima, Japan has already constructed one of the same type and is ready for clinical trials. A few more hospitals are going to introduce the same type.

However, in order to establish a mature BNCT technology, we should not forget that we still need more studies and experience to understand what could be developed into a real mass production type. Also at the same time, we should not forget that the accelerator and target are the only frontend of the facility. Even more important development items needed are for a better drug delivery system, and improved methods for clinical treatment planning. We should also work to improve our imaging technology and of course into understanding of mechanisms of cancer.

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