Small accelerators for the next generation of BNCT irradiation systems

T. Kobayashi[1], K. Tanaka[2], G. Bengua[1], M. Hoshi[2] and Y. Nakagawa[3]

kobato@rri.kyoto-u.ac.jp tanakake@hiroshima-u.ac.jp gbb@post3.rri.kyoto-u.ac.jp
mhoshi@hiroshima-u.ac.jp ynakagawa@kagawasyoni.hosp.go.jp

[1] *Research Reactor Institute, Kyoto University, Osaka 590-0494, Japan*
[2] *RIRBM, Hiroshima University, Hiroshima 734-8553, Japan*
[3] *National Kagawa Children's Hospital, Kagawa 765-8501, Japan*

The neutron irradiation system for boron neutron capture therapy (BNCT) using compact accelerators installed at hospitals was mainly investigated for the usage of direct neutrons from near-threshold $^7Li(p,n)^7Be$, and moderated neutrons from 2.5 MeV $^7Li(p,n)^7Be$ reactions and other reactions. This kind of system can supply the medical doctors and patients with convenience to carry out BNCT in hospitals. The accelerator system would be regarded as the next-generation of BNCT in the near future.

I. Introduction

Research reactors have been the neutron source for neutron capture therapy due to its stability and the neutron intensity it can generate. However, recent developments in accelerator technology have brought considerable attention to accelerators as neutron sources. Investigations on the use of accelerator systems for BNCT were started in the early 1980's, the use of $^7Li(p,n)^7Be$ (Q-value: -1.644MeV, threshold: 1.881 MeV) reaction has also been considered based on its neutron yield and neutron energy spectrum while recent research efforts are looking into practical accelerator configurations[1]. This reaction has mainly been used for (1) the production of neutrons from 2.5 MeV protons moderated in thick Li targets and (2) the production of low energy neutrons from near threshold proton energies. Other reactions similar to (1) can also produce high neutron yields, for instance, $^2D(d,n)^3T$, $^2D(t,n)^4He$, $^9Be(p,n)^9B$, $^9Be(d,n)^{10}B$ and spallation reactions. Moderation of these neutrons are always needed to fit the energys for BNCT, but many accelerator systems would be available [2,3].

The advantage of (2) lies in the fact that direct neutrons from the $^7Li(p,n)^7Be$ reaction which makes the scaling down in terms of the size of the system possible. Additionally, the neutrons produced with (2) are mostly forward directed which means that collimation of the neutron beam may no longer be necessary. In other words, the structure surrounding the target can be simplified and this will allow more freedom in the movement of the target assembly allowing a bigger range of directions for beam delivery. Our investigation of the use of small accelerators for neutron production using near threshold $^7Li(p,n)^7Be$ reaction in a hospital-based neutron irradiation system is anchored on these aforementioned merits [4-7].

II. Principle, characteristics and history of BNCT

Neutron capture therapy destroys cancer cells by selectively by irradiating them with neutrons which produces radiation with short range and high LET (Linear Energy Transfer) from heavy charged particles which are products of the reaction between the neutrons and a stable isotope that have been uptaken by the cancer cells. Low energy neutrons have a large reaction cross-section with the isotopes used for NCT which results in the production of high LET particles. At present, large neutron flux of thermal and epithermal neutron beams from research reactors are being used together with a couple of boron compounds. This kind of therapy is therefore aptly called Boron

Neutron Capture therapy or BNCT. The reactions between ^{10}B and thermal neutrons result in the emission of alpha particle and ^{7}Li nuclei whose ranges in tissue are around 10 μm and 5 μm, respectively. Gamma rays with an energy of 478 keV are also produced via the $^{10}B(n,\alpha\gamma)^{7}Li$ reaction. The selective nature of the cell killing effect of this reaction is shown in figure 1.

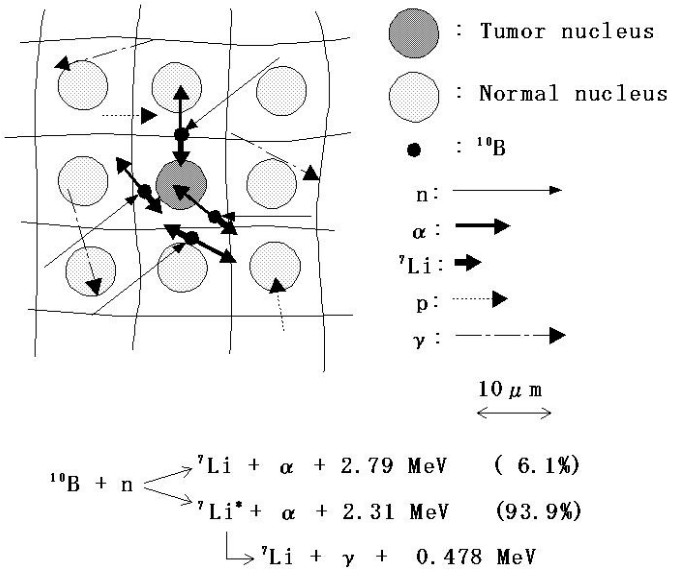

Fig.1. Principle of BNCT

BPA BSH

Fig.2 Currently used boron compounds

In actual treatment situations, controlling the dose in deeper regions, order of a few centimeters, of the irradiated body becomes more difficult because the thermal neutron flux distribution varies considerably in these deeper parts while the boron concentration in the tumor and its neighboring healthy tissues remain fixed. The boron compounds which are used in present clinical trials are BSH and BPA, the chemical structure of both compounds are shown in figure 2.

Neutron capture therapy was first proposed by an American physicist named G. Locher. BNCT was carried out from 1951 to 1961 using the BNL and MIT reactors. In spite of the insufficient results from the early experiments, only fundamental researches were allowed to continue while treatment irradiations were suspended from 1962 until September 1994 when treatment irradiations were again conducted. Epithermal neutron irradiation in Europe was initially carried out in 1997 at the Petten Reactor in The Netherlands and then was followed by Finland (1999), Russia and Czech Republic (2000), Sweden (2001), Italy (2002). Argentina followed suit in 2003.

The encouraging results of Japanese clinical trials from 1968 became an impetus for the renewed interest in BNCT worldwide which gained momentum around the early 1980's, with the first ISNCT being held in Boston in October of 1983. This was followed by biennial meetings which were held in Tokyo, Bremen, Sydney, Ohio, Kobe, Zurich, San Diego, Osaka and Essen

(2002). In October of 2004, the conference will again be held in Boston and two years after Japan is hosting the ISNCT. At present, BNCT clinical trials are being performed in Japan for malignant brain tumor (since 1968), malignant skin cancer (melanoma; since 1987) and parotid cancer (since 2001).

III. Requirements for the next generation BNCT

Intra-operative BNCT has been widely used in the Japan clinical trials for the treatment of brain tumors. In this treatment regimen, bulk tumor in the brain is first removed surgically and then the affected portion of the brain is exposed directly to a neutron beam without the scalp and skull. The merit of this method lies in its ability to deliver of the maximum dose in deeper parts of the brain. However, in open skull BNCT irradiation, the patient bears the load of two surgeries during the treatment, one to debulk the tumor and the other during neutron irradiation where the portion of the skull and scalp has to be removed again to directly expose the brain. Recently, the use of epithermal neutron beams in Europe, America and Japan has opened the possibility of BNCT irradiations one or two weeks after tumor removal which do not require a second surgery for removing the scalp and skull. Moreover, it will be advantageous to have the neutron irradiation facility in a hospital because BNCT irradiation can be carried out immediately after the surgical removal of the tumor. Both the surgery and the BNCT irradiation are therefore carried out in a single medical procedure. This procedure would have small risks of tumor metastasis etc. This procedure is theoretically feasible and can easily be performed in current research reactor irradiation facilities.

However, an accelerator based irradiation system is preferred for intra-operative BNCT since it provides a greater freedom and precision in choosing irradiation locations and positioning

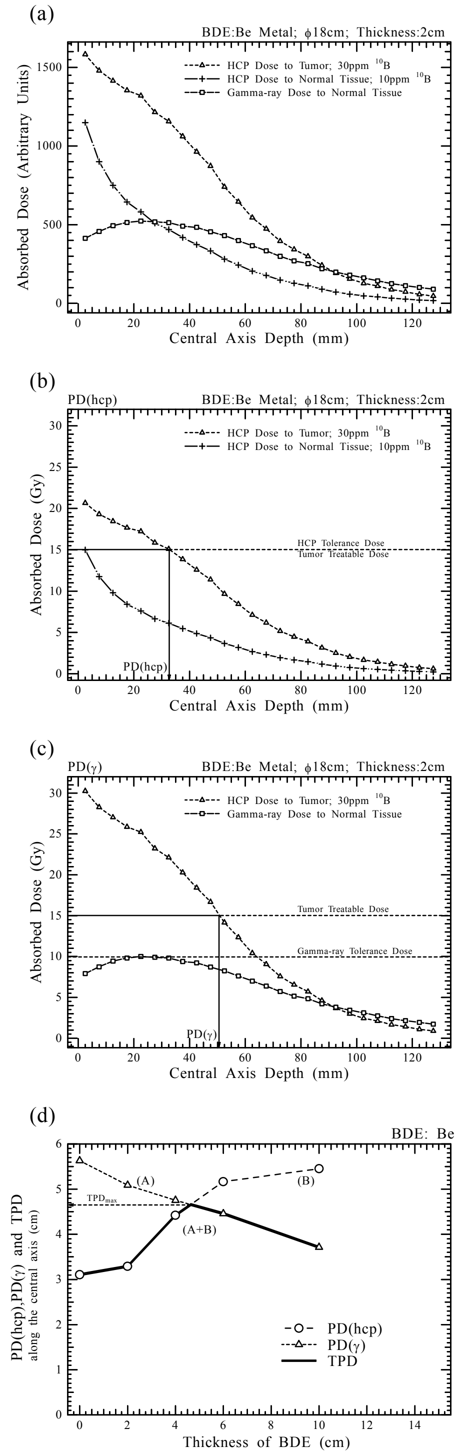

Fig.4. The relationship between the heavy charged particle (HCP) protocol depth (PD(hcp)), gamma protocol depth (PD(γ)), TPD and BDE when a Beryllium Metal BDE is used. Figure (a) shows the dose distribution for the three dose components in terms of arbitrary absorbed dose units. Figures (b) and (c) illustrate the definition for HCP protocol depth PD(hcp) and gamma protocol depth PD(γ), respectively. In Figure (d), line (A) shows the relationship between the BDE thickness and PD(hcp), line (B) shows PD(γ) and the solid line (A+B) shows the TPD.

patients. This is especially useful because a change of the position and direction of irradiation has a big influence on the change in irradiation dose to the tumor. At this point, a neutron irradiation system suitable for intra-operative BNCT using small hospital-based accelerators for the near threshold $^{7}Li(p,n)^{7}Be$ reaction is being designed and planned. Moreover, Europe and American irradiation facilities, which previously did not perform intra-operative BNCT, may now be considering carrying out this procedure. It is possible that in the future, intra-operative BNCT would become one of the standard BNCT irradiation procedures. Of course, non-surgical BNCT using hospital based neutron sources using accelerators will have its own outstanding merits.

IV. Components of an accelerator-based neutron irradiation system

An accelerator-based neutron irradiation system is made up of roughly 3 main elements. These are (1) the particle accelerator (designs of which varies), (2) the neutron producing target and (3) the moderator assembly which adjusts the energy of the neutrons produced in the target so that they will be within the usable range for BNCT. Figure 3 illustrates the Russian designed irradiation system which uses a tandem type electrostatic accelerator and the $^{7}Li(p,n)^{7}Be$ reaction for neutron production. The use of direct neutrons from the $^{7}Li(p,n)^{7}Be$ reaction is still limited at present. On the other hand, irradiation systems employing neutron moderation can be implemented by means of various accelerator systems, for example electrostatic type, RF type and fusion type, in either circular or linear accelerating structures.

With the boron compound (BPA) used in current BNCT clinical trials, Positron Emission Tomography (PET) can be integrated into the irradiation system where its main roles are 1) to previously judge whether the patient has suitable boron distribution for BNCT and 2) to determine the accumulation of boron in order to accurately decide when the neutron irradiation can be carried out. The boron concentration can likewise be measured from the boron concentration in the blood by prompt gamma ray analysis during irradiation. Generally, an accelerator for preparing PET pharmaceuticals can also provide neutrons for the boron concentration measurement by prompt gamma-ray analysis method.

Fig.3. A tandem type electrostatic accelerator (Russian) [9].

V. Evaluating neutron beams from accelerator

One way of evaluating the neutron beam characteristics would be in terms of the treatable protocol depth (TPD). TPD indicates the maximum depth in the irradiated body wherein the dose to tumor is equal to the prescribed treatment dose and at the same time the healthy tissue dose is less than or equal to the tolerance dose of healthy tissues for gamma and heavy charged particle doses as prescribed by the dose protocol being used in the treatment. Although the TPD is expressed in terms of central axis depths, it offers a comprehensive evaluation of the dose distribution in an irradiated body by considering the absorbed doses along both the central axis and off-axis locations. Any changes in the irradiation parameters (i.e., target system configuration, incident proton energy) that could affect the absorbed dose in the irradiated body are reflected in computing the TPD. The TPD concept was used for evaluating the characteristics of direct neutrons from near threshold $^{7}Li(p,n)^{7}Be$ reaction [8].

Additionally, the TPD can be adjusted by using materials called boron dose enhancers (BDE) which are intended to increase the boron dose in the irradiated body by moderating and scattering fast neutrons before. Figure 4 shows an example of how the TPD is computed for a beryllium metal BDE. BDEs are external to the target assembly and therefore do not add bulk and maintains the mobility of the irradiation system. They are placed between the body being irradiated and the target assembly [7].

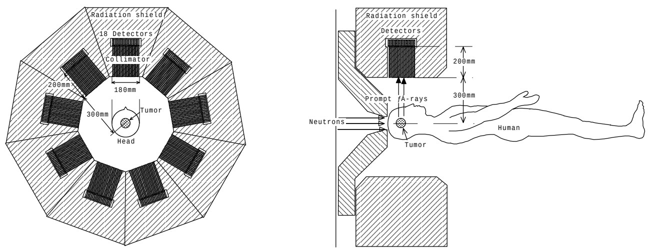

Fig 5. Non-invasive online dose measurement system for BNCT principle used in SPECT

VI. Conclusions

Nuclear reactors will be the main source of neutrons for BNCT until such time that an accelerator which will provide enough neutron intensity is finally constructed. It is very likely that in the near future nuclear reactors will be replaced by accelerators, provided that the latter satisfies the necessary conditions for irradiation, because of the practicality of its use. However, before this happens, problems like heat removal in the target material, stability of control for large current accelerators, and the technical confirmation of the various components of an accelerator based neutron source needs to be done in order to establish its reliability for actual use.

One desirable feature of future accelerator based system will be its ability to perform non-invasive online dose measurement during neutron irradiation. The general idea on how this can be implemented is shown in figure 5 where the prompt gamma ray measurement principle used in SPECT is employed [10]. With this method, precise dose estimation and the evaluation of the change boron concentration can be performed. A small accelerator system can also be used together with various diagnostic equipment.

Because this treatment is the only radiation therapy done for brain tumors, the big expectation for this treatment is understood from the fact that it can be practically used anywhere in the world. Expanding the applications of BNCT, which has the ability of selective treatment of tumor in the cellular level, to other tumors besides brain tumor and melanoma will open up a field of radiation therapy that assumes surgical operation and its combination with other radiation therapy. In order to further promote this in the future, research and development of a neutron irradiation system for exclusive use of neutron capture therapy with accelerators and the development of a dose measurement evaluation system is desired.

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