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Toward a Hospital Based Reactor for Neutron Capture Therapy

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Abstract

The concept of the neutron capture therapy (NCT) is older than 60 years, but a specific tool that is convenient to use in the hospital is not realized yet. The 3 MW Brookhaven Medical Research Reactor (BMRR) has been the only reactor specifically designed for the NCT. Although it was designed in 1950's, it still has the best capability for the NCT in the world. If recent knowledge is applied to design a NCT reactor, its power could be much lower than BMRR with better safety features. While new installation of a reactor in the metropolitan hospital is deemed very hard, accelerators have been installed at many medical centers and the number is increasing. Therefore, research on the use of accelerators as neutron sources of the NCT is active. Since nuclear reactors are already proven neutron sources for the NCT, however, a reactor could be a readily available tool to a medical center in case the efficacy of NCT is proven. It is believed that designing an extremely safe reactor effective for the NCT is technically possible, and it is worthwhile reviewing its basic design concept for the readiness because patients of malignant cancer cannot wait. This paper suggests basic guidelines for the design of a hospital based reactor for the NCT.

1. Introduction

Neutron capture therapy (NCT) is a potentially effective treatment method for radio-resistant and highly invasive tumors such as glioblastoma or melanoma. If a good neutron absorber emitting high LET (linear energy transfer) radiation after neutron absorption is selectively concentrated in cancer cells, selective killing of them is possible by irradiating refined neutrons. The basic idea was born in 1936, immediately after the neutron and the high reaction of slow neutrons with B-10 or Li-6 emitting charged particles, were found. Its application to patients began in 1951 when the neutron beam for NCT was first available at Brookhaven Graphite Reactor (BGR). The BMRR was built specifically for the NCT and began operation in 1959. However, a series of patient treatments for about 10 years using BGR, BMRR and MITR (Massachusetts Institute of Technology Reactor) ended with great disappointment[1]. It was revived in 1980's after a Japanese neurosurgeon Hatanaka reported his astonishing success using small research reactors of HTR (Hitachi Training Reactor, 100 kW) and MuITR (Musashi Institute TRIGA Reactor, 100 kW)[2]. In Japan, four reactors – HTR, MuITR, KUR (Kyoto University Reactor) and JRR-2 (Japan Research Reacor-2) has been employed for patient treatments since 1968 and a new facility in JRR-4 replaced that in JRR-2 recently. At this moment, KUR and JRR-4 are available facilities in Japan.

Patient treatments resumed at BMRR from 1994 after modification of its irradiation facility to get refined neutron beam, and followed by MITR and HFR (High Flux Reactor) in Petten. Many projects are on going all around the world to use already existing research reactors after some modification or to design an optimum reactor for the NCT. Meanwhile, research on the use of accelerators for NCT is active as well.

So far, the reported success is only by reactor thermal neutrons in Japan, but the application has been limited to superficial tumors due to poor penetration of thermal neutrons into the tissue. The trend has been, therefore, to use epithermal neutrons for patient treatments and thermal neutrons as an auxiliary tool for research by small animal or in vitro irradiation. In spite of active research on proper chemical compounds for the NCT, its development has been much slower than expected. Only two compounds of BSH found in 1966 by Soloway and BPA found in 1972 by Mishima, has been used for patient treatments. While B-10 is exclusively used, studies on the use of Gd-157 are under way.

Accelerators are believed as promising epithermal neutron sources for the NCT. More than 4,000 accelerators have been installed at the medical centers and the number is increasing because of the potential to install them in developing countries[3]. If sufficient neutrons can be obtained by some modification of existing accelerators, it will be the best solution.

So far, the only proven neutron source for the NCT is the research reactor. Many efforts to optimize reactors to the NCT, therefore, are found. While majority of them is modifying an existing reactor facility, conceptual designs for new reactors are also made. If a very good chemical compound for the NCT is found, or if the efficacy of the NCT is sufficiently verified by a currently available compound, a neutron source readily installable in a medical center will be in demand because of very limited facilities available. It is not certain which course is shorter between obtaining public acceptance for a small safe reactor and technology development for an accelerator. Nuclear engineers believe that the technology to design an extremely safe low powered reactor is well established, and the public opinion to such reactors is not so bad. From this point of view, summarizing the basic design concept of a research reactor that is optimal to the NCT, is worthwhile.

2. Review on the NCT Neutron Source of Reactors

Neutron Quality

Although the higher energy neutron is the better for deeper penetration into the tissue, its damage to the normal cell should be minimized. The neutron damage to cells is governed by protons – recoiled protons by high energy neutrons and around 0.6 MeV protons produced by $^{14}N(n,p)\,^{14}C$ reactions of which cross-section is 1/v up to 100 keV. Therefore, the curve of kerma/unit fluence of neutron to tissue decreases following $^{14}N(n,p)\,^{14}C$ cross-section as the neutron energy increases up to 40 eV, and then increases following the reaction with hydrogen. The neutron flux-to-dose conversion factor recommended by ANSI/ANS-6.1.1-1977 for the radiation protection activities[4] is depicted in the figure. This curve is not for the dosimetry of radiation therapy but could be used as a reference. It shows almost flat value below 10 keV but rapidly increases at above 10 keV. It agrees with the upper limit 10 keV of design target in epithermal neutron beam found in many NCT facilities. Therefore, it can be said that the ideal one is a 10 keV mono energy neutron beam without any contamination of other energy neutrons or gammas. Since such an ideal neutron source is not found, efforts are focussed to reach close to the ideal beam.

Neutron Flux

The neutron flux should be as high as possible to minimize irradiating time. If the patient moves during the irradiation, other places from the target are irradiated. Therefore, the patient is put under anesthesia during the irradiation. The concentration distribution of a chemical compound for the NCT varies as time goes on, and the time interval for optimum irradiation is limited.

The more dose to cancer cells reduces the possibility or elongate time interval of tumor recurrence, but the dose to normal cells should be below the permitted level. While the BSH or BPA is used, the upper limit of thermal neutron fluence to brain is around 10^{13} n/cm^2. When an epithermal neutron beam irradiates the tissue, the peak thermal neutron flux inside the tissue is about three times of incident epithermal neutron flux. Therefore, the epithermal neutron flux of 10^9 n/cm^2-s needs about 1 hour of irradiation time.

Reactor Neutron Sources

The source of epithermal neutrons is fast neutrons generated by fission in the core. Fission spectrum neutrons are slowed down below 10 keV but not to so low energy until they reach to the irradiation position. For the case of an existing reactor where only a rather narrow and long beam tube is available, a filtering method such as at HFR in Petten is used. Since this kind of facility has very low flux at the irradiation position compared to the reactor power, this concept should be avoided for a new NCT reactor design. A fast core is the better neutron source than a thermal core from the viewpoint of neutron flux-to-power ratio. While the fission power is the same, the fast core has much higher fast neutron flux. Its limitation is that highly enriched uranium fuel is needed. The deficiency of thermal core compared to the fast one could be partly retrieved by using the fission converter at the boundary of the core. The fission plates absorb thermal neutrons leaking from the core and emit fast neutrons, thereby enhance epithermal flux several times and reduce the burden to shield thermal neutrons. The study for the BMRR shows that the epithermal neutron flux at the irradiation position increases 7 times – from 2.7×10^9 to 1.7×10^{10} n/cm^2-s at 3 MW, with better beam quality if the fission converter is employed[5].

The refining method of neutrons in a given reactor core condition, in which spectrum shifting of fast neutrons and shielding of thermal neutrons and gammas are included, is the most important. Spectrum shifters are summarized in reference 6. It should have large scattering cross-section above 10 keV but small cross-section below 10 keV, and not so large mass number but not so small one. From the cross-sectional point of view, Ni-64 is very close to ideal case except a window around 25 keV, but its natural abundance is only 0.926 %, other Ni isotopes have far different cross-section characteristics, and its mass number is rather large to slow down fast neutrons. Therefore, it can be said as a good filter rather than a spectrum shifter. Aluminum and sulfur are actual candidates. Since both have windows at above 10 keV, Al_2O_3 or AlF_3 are usde to block these windows. The use of spectrum shifter in existing facilities is summarized as following;

BMRR	Al + Al_2O_3	
MITR	S + Al	
Finland TRIGA	AlF_3	
KUR, JRR-4	Al + D_2O	D_2O is controlled to choose thermal or epithermal beam

AlF_3 adopted at Finland TRIGA facility which is recently built among the above, will be used at

Georgia Tech. in USA and Studsvik in Sweden, and Cho used it for his conceptual reactor design.

Cadmium is a good shielding material for thermal neutrons, but it emits hard prompt gammas and shields only low energy neutrons. Good 1/*v* absorbers with low prompt gamma such as B-10 and Li-6 may be better but very expensive. Bismuth is the best material for the gamma shielding because of its high atomic number and physical density, very low capture cross-section, no delayed gamma, and low prompt gamma. Its scattering cross-section below 10 keV is not so small but neutron slowing down is almost negligible because of its large mass number.

Since the BMRR is the only reactor in the world built specifically for the NCT, it has the best beam capability among existing facilities. If the beam flux-to-power ratio is compared, however, a TRIGA II in Finland has the highest value, which is 1.3×10^{9} n/cm^{2}-s at 250 kW[7]. The modification study of MuITR which is the same TRIGA II type, shows slightly lower value of 4.1×10^{8} n/cm^{2}-s at 100 kW[8], which may be caused by the use of different spectrum shifter - Al and Al_2O_3 instead of AlF_3 used in Finland. While a conceptual thermal reactor designed by Cho has 3.2×10^{9} n/cm^{2}-s at 300 kW[9], a conceptual fast reactor using fluid fuel designed by Russians has 4.8×10^{9} n/cm^{2}-s at the same power[10]. Since the Russian design is a fast core, its flux could be much higher if the proper spectrum shifter is used. Its design is close to filtering concept by using Ni-64 rather than spectrum shifter. Cho's design also demonstrates that multiple irradiation positions for the NCT – at least four, is possible.

The flux-to-power ratio of Cho's design is about two times of Finland TRIGA, which may be explained that completely new design without any restriction modifying an existing reactor, could enhance the flux-to-power ratio. Furthermore, if the fission converter is employed to Cho's design the flux could be much more enhanced. It is not certain whether the enhancement will be 7 times as in the BMRR, but it can be roughly said that more than 1×10^{10} n/cm^{2}-s of flux could be obtained by 200 – 300 kW reactor power.

3. Hospital Based NCT Reactor

The basic requirements for a hospital based NCT reactor should be considered from the safety especially considering public acceptance, and economics points of view.

The higher flux-to-power ratio is the first priority because it is closely related to both of safety and economics by permitting lower reactor power and shorter irradiation time. The low power and short operation time causes low burnup of fuel, low radiation inventory of the core and surrounding materials, low excess reactivity, low burden in cooling and shielding, little engineered safety features, etc. If it is assumed that the epithermal neutron flux at the irradiation position is 1×10^{10} n/cm^{2}-s at 250 kW, the irradiation time is about 6 min and the power generation is 90 MJ which is approximately equivalent to 3×10^{18} fissions or 2.5×10^{-3} g burnup of U-235. If the reactor has four irradiation positions, and operates three times/day and 300 days/year, up to 3,600 patients could be treated with less than 2.5 g burnup of U-235 in a year.

Its initial fuel in the core could be used for the lifetime of the reactor without any refueling. The core is cooled by natural convection of pool water. A small plate type heat exchanger cools the pool water – in actual situation it is occasionally run. In case of pool failure, the core is safely cooled by natural convection of air. All reactor systems run only limited time - say less than an hour/day, except radiation monitoring and air conditioning systems. The majority of radwaste during the normal operation is very low level filters and ion exchangers of pool water purification system, and filters of air conditioning system.

The reactor should also be safe against abnormal reactivity insertion or failure in the reactivity control. J.K. Kim suggested a subcritical reactor multiplying intense neutron source[11] with the expense of periodic replacement of Cf-252. Even the reactor reaches criticality, however, we can limit its power generation far below safety criteria without any engineered reactivity control. For the cases of power burst reactors, prompt insertion of large reactivity to obtain pulse shaped power behavior, is their normal operation mode. Even a reactor has thousands of safe pulsing records. This fact sufficiently confirms safety against reactivity insertion. For the case of a TRIGA-ACPR with rated power of 300 kW for steady state operation, its peak power reaches more than 20,000 MW with full width half maximum (FWHM) of 4 - 5 ms and the power generation is more than 100 MJ in a pulsing[12]. Air cooled fast burst reactors (FBR) also generate similar pulsing power with shorter FWHM and higher peak power[13]. In these cases the neutron generation in a single pulse is more than that for a NCT treatment discussed in section 2. Therefore, the pulsing operation could directly be utilized for the NCT if very short irradiation time is required, but it is not recommendable because of possible fear of the public to prompt supercriticality. These pulsing operation needs a certain amount of excess reactivity to reach prompt supercritical. Since the prompt temperature defect of the fuel during the pulsing operation is much more than the reactivity worth inserted, the reactor itself turns to subcritical status immediately. As far as the excess reactivity is maintained below a limited value at this kind of reactor, even though all control rods are accidentally withdrawn promptly or slowly and the reactor shutdown mechanism is failed, its power generation cannot exceed the safety limit due to the inherent safety feature. If this small excess reactivity cannot compensate the lifetime fuel burnup, small amount of burnable poison could be mixed in the fuel. Natural erbium is used as a burnable poison in some TRIGA fuels.

The ultimate goal of the epithermal neutron NCT is fractionated irradiation divided by about 4 since it is more effective to control tumors than a single lumped irradiation. Each fractionated irradiation is about 1.5 min if the flux is 1×10^{10} n/cm^2-s. As this is sufficiently short time, the reactor power could be lowered by longer irradiation time. The lower rated power needs the lower excess reactivity in case of a reactor having large power defect, which consequently enlarge the safety margin.

Its operation time should also be limited to keep the radiation inventory in the core as low as possible and to keep the minimum excess reactivity for operation. Operation only during the irradiation is recommended. It reduces shielding requirement for shutter, thereby increases neutron flux at the irradiation position. The square wave operation mode is found in research reactors, and quick and reliable startup is possible by computer control.

Though the reactor power is low and operation time is extremely limited, it can be effectively utilized for both of delayed and prompt gamma neutron activation analysis, neutron radiography, low level radioisotope production, thermal neutron or gamma irradiation of in vivo or in vitro irradiation simultaneously. The neutron activation analyses are very convenient tools to determine cell level boron distribution and its lump concentration in the samples of patients' tissue or blood. These applications need a certain level of thermal neutron flux. A good reflector such as beryllium will provide spaces with good thermal neutron field. Heavy water is not recommendable as a reflector because it causes additional burden in reactor management. The core should be as compact as possible without any irradiation hole causing neutron loss in the core and by using the fuel follower control rods.

So as to judge economics of a reactor mentioned above, the cost of other oncological treatments could be referred. The X-ray conformal radiotherapy (CRT) which uses more than six cross-fired X-ray beams, costs about US$11 million for the accelerator and the first gantry, and about

US$2 million for each added gantry[6]. If it is considered that a reactor could have at least four irradiation positions and its operation cost would be much lower than an accelerator, it is economically competitive as far as the efficacy of the NCT is proven.

4. Conclusions

Designing an extremely safe reactor for the NCT is possible by using already proven technology. An optimized low power reactor could be an effective tool to be used in a medical center. It provides high epithermal neutron flux at multiple positions to finish the irradiation in a few minutes, prompt gamma neutron activation analysis to determine boron concentration in the samples of patients' tissue or blood prior to the irradiation, track analysis for the cell-wise boron distribution, thermal neutron or gamma irradiation for research on the radiation oncology, etc. It is an integrated facility for the NCT and could be used for other medical demands. The reactor itself is safe in any anticipated accident conditions because of low power, limited operation time, low excess reactivity and inherent safety feature of large prompt negative temperature coefficient. Its construction cost could be competitive with medical accelerators, and operation and management cost would be lower than those.

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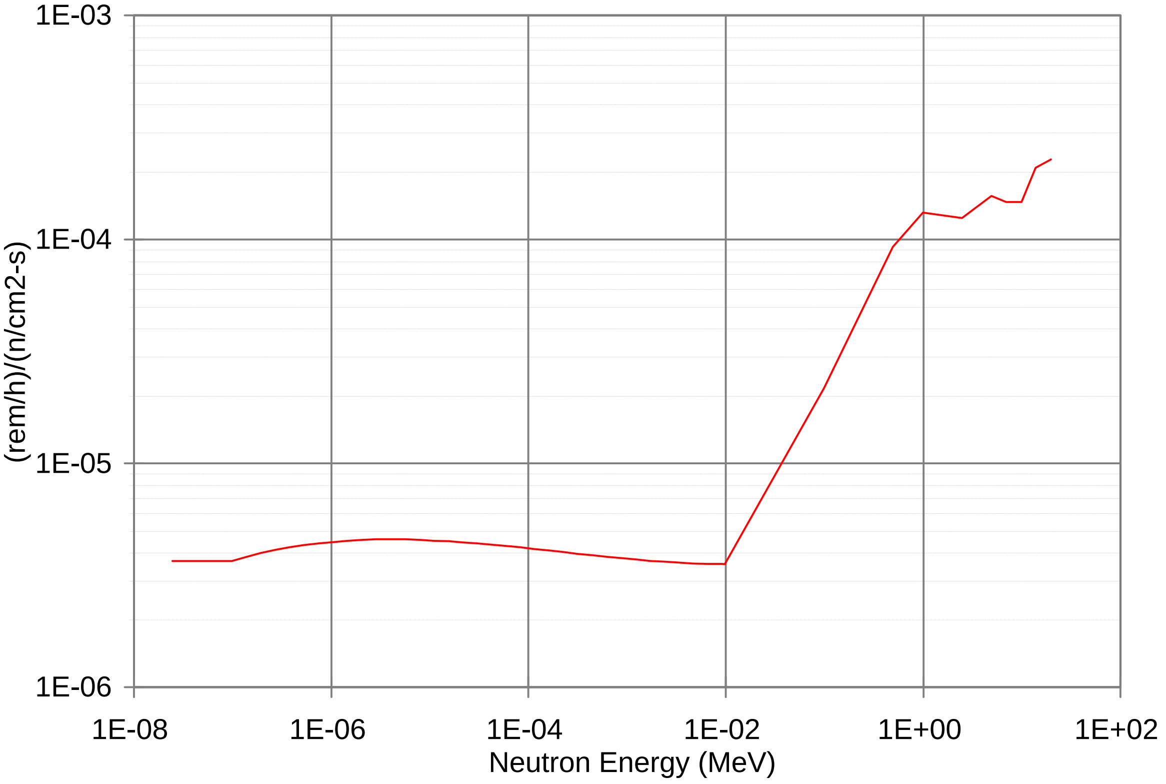

Figure. Flux-to-Dose conversion factor of neutron[4]