Neutron Capture Therapy (NCT) & In-Hospital Neutron Irradiator (IHNI)—a new technology on binary targeting radiation therapy of cancer

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Abstract: BNCT is finally becoming "a new option against cancer". The difficulties for its development progress of that firstly is to improve the performance of boron compounds, secondly, it is the requirements of quantification and accuracy upon radiation dosimetry evaluation in clinical trials. Furthermore, that is long anticipation on hospital base neutron sources. It includes dedicated new NCT reactor, accelerator based neutron sources, and isotope source facilities. In addition to reactors, so far, the technology of other types of sources for clinical trials is not yet completely proven. The In-Hospital Neutron Irradiator specially designed for NCT, based on the MNSR successfully developed by China, can be installed inside or near the hospital and operated directly by doctors. The Irradiator has two neutron beams for respective treatment of the shallow and deep tumors. It is expected to initiate operation in the end of this year. It would provide a safe, low cost, and effective treatment tool for the NCT routine application in near future.

Key words: Neutron Capture Therapy; boron compound; radiation dosimetry; neutron beam; in-hospital neutron irradiator

1 The latest international positioning of the NCT

The NCT is a new technology on binary targeting radiation therapy of cancer, and its basic principle was initially put forward by the American biophysicist G. L. Locher in 1936[1], however, the first NCT clinical trail on human was done by Assistant Professor and neurosurgeon of Harvard Medical Collage Dr. W. H. Sweet[2]. In the research work to radioisotopes e. g. $^{32}PO_4$, which were presented by the end of 1940s, Dr. Sweet sharply noticed the phenomenon of Blood-Brain Barrier (BBB) i. e. instead of in the healthy brain tissues, many normal ions dramatically concentrated and deposited on brain tumor focus. Based on this discovery, Dr. Sweet developed his idea that β-emitter of ^{32}P nuclide in normal phosphate ions might be an effective and ideal radiopharmaceutical, which would destroy brain tumor cells but protect the normal brain tissues. His in-depth study further indicated the phenomenon of BBB caused by $^{32}PO_4$, although the radiopharmaceuticals were able to protect the normal brain tissues, it failed to protect such organs and tissues like liver and marrow in human body for fast metabolism, and compared with brain tumor, these organs and tissues would absorb more ^{32}P. Evidently, the effective use of BBB was subject to successfully restraining the destructive effect of nuclear decay to each individual brain tumor cell. The other significant inspiration of Dr. Sweet sourced from the treatise of Conger and Giles published in 1950, they described the experiment of radiating lily bulb with thermal neutrons and reached to the conclusion that micro containing ^{10}B accounted for the tissues of plant where were killed by big radiation dose. All these experiments inspired a neurosurgeon's career responsibility in conquering malignant brain tumors. Dr. Sweet and his colleagues then became the trail blazers in introducing BNCT to the USA for cancer treatment and utilizing boron compound easily obtained at that time in the USA and thermal neutron beam from research reactor.

1.1 The first decade of the NCT clinical trials from 1951 to 1961 was a disappointed outcome

Dr. Sweet and his colleagues infused ^{10}B of sodium borate, sodium pentaborate, etc. to 61 malignant brain tumor patients, and utilized BGRR in BNL Nuclear Research Center and research reactor in Massachusetts Institute of Technology to irradiate the brain tumor focus with the maximum neutron flux of 10^{10} $n/cm^2 \cdot s$ in 30 to 90 minutes. The experiment result was to our great disappointment. The mean survival

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time of the 61 patients was 5.7 months, none of the patients survived one year after operation, and the NCT's treatment effect were same as that of conventional treatment. As no advantage could be seen from the NCT, the NCT clinical treatment of malignant brain tumor patients seemed to be a failure. From then, the NCT clinical practice switched to the basic research of the BNCT, and in the wake of considerable amount of lawsuits, the President Bill Clinton was forced on to specially deal with cases through President Consultation Committee.

1.2 Dr. H. Hatanaka's achievement astonished the world

Dr. H. Hatanaka, a neurosurgeon from Tokyo University, was studied in Harvard Medical College from mid of the 1960s to early 1970s. Under the guidance of Dr. Sweet, Dr. H. Hatanaka was engaged in relevant research of BNCT. Dr. H. Hatanaka was young but an excellent learner at that time. He analyzed information of Dr. Sweet's study, and verified quite same data and processes where he had queries. When he came back to Japan, after a full preparation of one year, he started brain tumor BNCT clinical trail in 1968. Different from the Americans' initial experiment, Dr. H. Hatanaka made a full innovation in clinical technique in the following aspects:

1) Instead of having a conventional craniotomy bone window, Dr. H. Hatanaka removed the whole skull of his patients to let the entire brain tumor focus under the exposure of neutron field. In this way, the irradiation neutron flux at the depth of 8 cm to 10 cm under the cerebral surface would be more than 10-fold higher as compared to the delivery of neutrons through a conventional craniotomy bone window.

2) Dr. H. Hatanaka adopted a new boron compound polyhedral borane anion, sodium mercaptounde cahydro dodecaborate (BSH) of low toxicity, which entered into bond easily with specificity of glioma cells and had no sediment in blood vessels.

3) Instead of intravenous infusion, Dr. H. Hatanaka infused boron compound in carotid artery and vertebral artery of his patients to increase the ^{10}B concentration in cells. Moreover, Dr. H. Hatanaka did not start neutron irradiation until fractional ^{10}B could be traced in blood vessels.

4) Dr. H. Hatanaka adopted big dose of steroid hormone in modulation for the purpose of protecting epithelial cells of brain capillary vessels against BBB destroy as the method had been proved out an ideal effect of radiation protection.

Neutron source was provided by a HTR of 100 kW.

From 1968 to 1985, Dr. H. Hatanaka treated 77 patients of various brain tumors with his modified BNCT, and out of them, 40 were of grade III to IV gliomas patients. According to the calculation of international Kaplan-Meier statistics, 5-year survival rate of patients with brain tumor at the depth of 6 cm under the cerebral surface was 58 %, and 10-year survival rate 29 %[3]. Compared with the poor 5-year survival rate of 5.7 % recorded for conventional treatment, Dr. H. Hatanaka's small reactor really made a significant achievement and astonished the entire world. On the international medical arena especially in neurosurgeon circles, he had become "A Shining Star in the East".

1.3 NCT development in the Europe

Although Japan's technology had touched off some kinds of disputes, censures and sneer from various quarters, people started to look at BNCT with new eyes. After years of stoppage in BNCT clinical trial, MIT and Harvard Medical College had organized a joint team and adopted the following achievements collaboratively developed in the USA:

1) The second generation boron compound [(L)-4-dihydroxy-borylphenylalanine] (BPA)

2) Epithermal beam with better features

3) Quantitative measurement of specimen ^{10}B concentration with nuclear reaction of ^{10}B (n, α) Prompt γ-ray Activation Analysis (PGRAA)

4) 3D treatment program software of radiation dose pre-estimate, etc.

The Americans restarted brain glioma clinical trial of phase I/II in the 1990s, and in the same time, United States Department of Energy provided financial support to the relevant eight research centers in the USA (TSU, INEL, BNL, OSU, SUNY, MGH, MIT and T-NEMC). As the available facilities in Japan could not meet treatment requirements of patients at home and abroad, Japan built MUITR in the 1970s, and KURR, JRR-2, JRR-3, etc. in the 1980s. JRR-4 added with NCT irradiation neutron beam was designed and built in the 1990s.

The Europe paid special attention to clinical trials. Under the framework of Medical Science & Healthy Research Program published by the European Union, BNCT was regarded as a nuclear application field friendly to human being, and based on the high neutron flux research reactor HFR in Netherlands, research topic of "BNCT Clinical Trial of Gliomas" was carried out by cooperation of many countries. In summer of 1990, an epithermal neutron beam was designed and installed on HFR in Petten, which realized full power operation in 1991. In 1992, after conducting extensive measurements and studies to nuclear and radia-

tion biological features of Petten HFR beam facility, systematic studies to radiation tolerance of healthy brain tissues of dogs and preclinical treatment to grade III/IV glioma patients, the BNCT glioma patients clinical trial of phase I/II started[4]. While the anti-nuclear drive hit its high tide in the Europe, such a development speed was really worthy of admiring as it reflected the determination and persistence of the Europe in developing BNCT. Up to now, out of eight BNCT clinical centers in the world, five are located in the European countries (Netherlands, Finland, Italy, Czech and Sweden), and the latest development and achievement in BNCT studies are reported by these countries frequently.

1.4 Chances and risks accompanied with NCT development

Although the Americans had taken command of the modern BNCT technology, and the research results obtained by MIT/Harvard joint team might represent the top level of BNCT clinical trial in the 1990s, there was still no breakthrough in BNCT application. The mean survival of 13 months after irradiation achieved by MIT/Harvard joint team was similar to survival statistics reported by other BNCT centers as well as hospital treatment by means of surgical operation plus conventional external beam photontherapy. Efforts of generations are required to find solutions for difficult problems of science and technology, especially in case of brain glioblastoma multiforma, a cancer developed in brain, the most complicated organ of human body. Moreover, BNCT remains as such an inter-discipline involved with nuclear physics, nuclear radiation dosimetry, radiation biology, pharmacologic chemistry, neurosurgery, etc. The risk of BNCT is not only due to objective factors, the impact of other factors like perplexity of lawsuits in the consequence of the initial BNCT clinical trial in the USA, queries to continuity of BNCT principle put forward by radiotherapy community in the USA, insufficient financial support to the high BNCT clinical trial expenses, etc. were making things even worse. Impacted by such extremely difficult conditions sourced from political and economic reasons, the Americans were forced to once again stop all its BNCT clinical trials at the beginning of the new century. In Japan, no obvious progress had been made in BNCT trial survival of brain tumors after the period of Dr. H. Hatanaka. With respect to AA and GMB, which adopted the practice of combination of surgery plus BNCT, the reported 5-year survival attained 10.4 %, however, such a percentage was on selective basis of patients. Quite a few active clinical centers in Japan adopted innovations of various multi-combinations like mixed beam irradiation of epithermal neutron combined with thermal neutron, boron compounds infusion of BPA combined with BSH, BNCT combined with fractional photontherapy, etc. All the efforts made by Japan indicated the treatment benefits i.e. life of certain patients had been extended.

In the transition from the 20th century to 21st century, the important features of booming BNCT research and clinical trial activities in the world are all due to encouragement and inspiration from Dr. H. Hatanaka's success. Nowadays, 22 research reactors of different types seated in 17 countries and regions are engaged in BNCT research and experiment activities, and eight reactors in seven countries use BNCT in clinical trials. Treatment of cancer types have been expended from various brain malignant tumors to cancers in the other organs and tissues of human body. The third generation of boron compounds, which shows better features in compliance with BNCT requirement are being synthesized and tested by different methods. In order to let the BNCT be accepted as a routine therapy in an extensive application field, technology of in-hospital installed neutron source is developing in its mature stage and certain prototypes have been installed or are in their last stage of installation. My summary to the development history of BNCT is that people's dream has come true, research work results have changed to clinical application and the experimental treatment is turning to routine therapy.

1.5 BNCT, a new option against cancer

Started from 1983, the International Society for Cancer Neutron Capture Therapy (ISNCT) has organized its academic conference in every two years. In its 13th Florence Conference held in Italy in November 2008, Prof. Aris Zonta of Pavia University and President of the Conference, declared in his opening ceremony speech that "BNCT has reached to a new stage, and BNCT was becoming a new option in cancer treatment ultimately[5]." He also expressed his viewpoint that the BNCT seemed to be the exclusive method for treatment of recurrent head and neck cancers, skin malignant melanoma, diffusive liver cancers, etc. at present time. The long development process of the BNCT in 72 years, from the BNCT basic principle establishment to the ICNCT Florence Conference 2008, witnessed the BNCT standing on cancer treatment arena at last. Just as descriptions in his treatise titled "What is the Future for BNCT" addressed by our venerable senior in the BNCT, Prof. R. Barth of Ohio University, "It probably lies in filling a nitch for those malignances, whether primary or recurrent, for which there is no effective therapy." Such a positioning for BNCT

spurs our scientific researchers, doctors and engineers engaged in relevant fields of BNCT studies to establish their ambitious confidence and maintain constant efforts in their works, and moreover, brings soul comforts to those utterly pain-stricken cancer patients and reignites their extinguished instinct in seeking survival.

2 Clinical trial achievements of the NCT

2.1 Malignant brain tumors treatment

BNCT clinical trial of brain tumors includes glioblastoma (GBM), astrocytoma (AA, OA), medulloblastoma, meningion, primitive neuroectodermal tumor (PNET), arteriovenous malformation (AVM) and metastatic tumors.

2.1.1 Case report 1

A 50-year-old Japanese man developed severe headache and lowered mental activity accompanied with speech disturbance and right hemiparesis, he had difficulty in stepping car brake paddle with his right foot. Cerebral angiography demonstrated tumor stain in the left front-parietal area (Fig. 1(a)). Histological diagnosis was glioblastoma (GMB) (Fig. 1(b)).

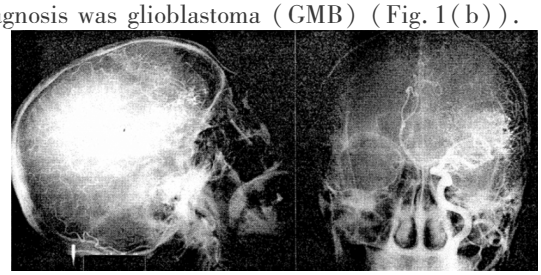
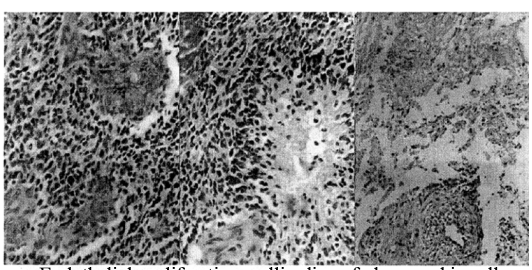


Fig. 1(a) Angiograms demonstrating a 6.5 cm × 5.5 cm × 4.5 cm vascularized tumor in the postero-inferior portion of the left frontal lobe

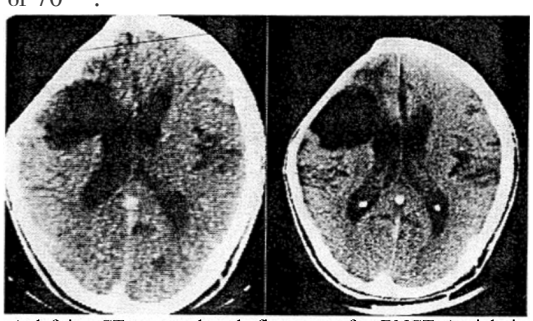


Endothelial proliferation, pallisading of pleomorphic cells, large area of necrosis etc.

Fig. 1(b) Glioblastoma

Using BSH and thermal neutron beam, he received BNCT at HTR in June 1972. After craniotomy under general anaesthesia, a ping pong ball 3.5 cm in diameter was inserted into the cavity to improve the neutron penetration. Neutron flux was measured on the surface of ping pong ball and on the bottom of the cavity using gold foils. The neutron fluence was 8.8×10^{12} n/ cm^2 and 5.3×10^{12} n/ cm^2 respectively. Boron concentration in the tumor tissue was 15.3 ppm and 27.3 ppm (1 ppm = 10^{-6}) in the blood. Retrospective analysis of the radiation dose of boron n-alpha reaction was 7.5 ~ 16.8 Gy (physical dose).

A follow-up CT scan studied five years, nine years and seven months and 15 years after BNCT (Fig. 1(c) & Fig. 1(d)) demonstrated that with the exception of porencephalic cyst found after 11 years, there was no recurrence of the tumor, and all the patient's speech disturbance and right hemiparesis eliminated after the BNCT, After 20 years, the man was still alive as a farmer and hold driving license at the age of 70[6].



At left is a CT-scan made only five years after BNCT. At right is a CT-scan made nine years and seven months after BNCT.

Fig. 1(c) A 50-year-old male with glioblastoma in the left posterior frontal lobe

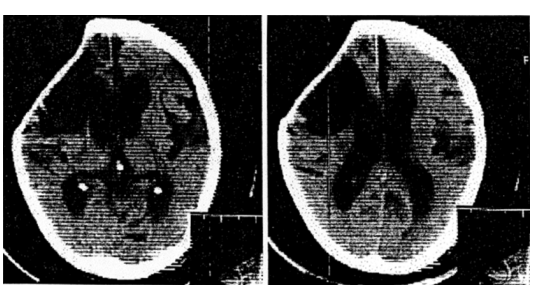
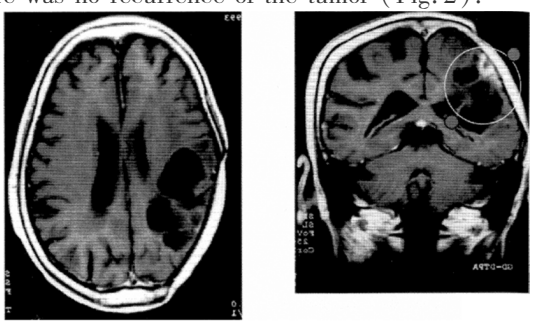


Fig. 1(d) Follow up CT scan 15 years after BNCT. The patient had good QOL for more than 20 years

2.1.2 Case report 2

A 60-year-old woman with glioblastoma diagnosed as grade II-III astrocytoma in the right frontal lobe underwent BNCT at MUITR in July 1977. Using BSH and thermal neutron beam, her tumor was removed after craniotomy, a ping pong ball was inserted into the cavity and neutron flux was measured on the surface of ping pong ball and on the bottom of the cavity using gold foils. The neutron fluence was 1.45×10^{13} n/ cm^2 and 7.5×10^{12} n/ cm^2 respectively. According to the retrospective analysis of the radiation dose of boron n-

alpha reaction, tumor volume dose was 15.9 Gy (physical dose). Follow-up MRI studied 16 years after BNCT demonstrated multi-cystic lesion, however, there was no recurrence of the tumor (Fig.2).



Boron concentration:14.0 ppm in tumor tissue, 13.3 ppm on blood.
Radiation time: 140 min. Radiation dose: 15.9 Gy (B-10 n-a)

Fig.2 Follow up MRA after 16 years after BNCT

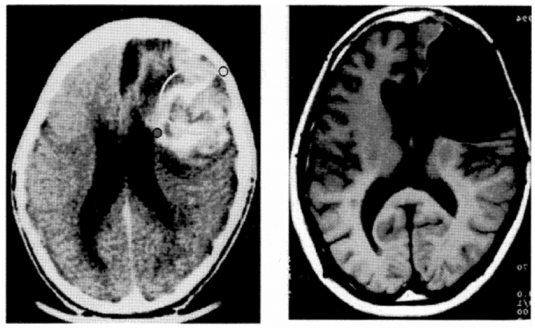
In October 1985, eight years after her BNCT operation, the woman attended the International NCT Symposium in Tokyo as a volunteer and served coffee to the meeting participants, who thought highly of her good service in the conference at the age of 68![7]

2.1.3 Case report 3

An 11-year-old Japanese girl with grade II-III oligo-astrocytoma started her anti-epilepsy treatment in 1974. The patient's headache had taken a turn for the worse and kept vomiting from August 1981, and her right hand became week in early September 1981. CT scanning demonstrated a huge tumor in the right frontal lobe. The patient underwent craniotomy on August 18, 1981, and after removing cyst liquid, the patient was shifted to MUITR for BNCT on October 19, 1981. After treatment, the symptom of the girl's tumor contrast enhancement disappeared gradually, i.e. CT scan image indicated the disappearance of tumor enhanced tissues one year after BNCT treatment. The girl had no deficiency accounting for neuropathy, received a good response for her behavior in school and proved to be normal in her physical growth. As a guest, the girl was introduced to all the meeting participants of the International NCT Symposium[8].

The follow-up MRI studies of 14 years after BNCT are given in Fig.3.

The above three cases demonstrate patients who enjoy over 10-year survival and quality of life (QOL) after BNCT, although the achievements are on selective basis of patients in clinical trial. According to the available reference literature in the world, the recorded over 10-year survival patients with IV glioblastoma or III-IV glioma after current standard treatment is ten cases only[9], when making comparison with BNCT records made in clinical trial in such a short time, we do see the potentiality of BNCT's future.



Planning (left) Oct. 1981 at MUITR. Follow up MRI (right) in 1994.
Radiation dose at target point (sic) was 23 Gy

Fig.3 Oligo-astrocytoma (G3)

2.2 Recurrent head and neck malignancies (HNM) treatment

At present time, scope of recurrent HNM BNCT clinical trial is including: cancer in oral-squamous cell cancer, parotid gland cancer, mucoepidermoid carcinoma, acinic cell carcinoma and adenoid cystic carcinoma; muco melanoma in nose and lacrimal sac; undifferentiated thyroid carcinoma in oropharynx; lymph node metastases in neck, etc.

2.2.1 Case report 1

A 67-year-old woman was diagnosed with mucoepidermoid carcinoma of parotid gland in 1998 and underwent a parotidectomy, followed by radiotherapy. In March 1999, the tumor recurred. In October 2001, the ulcerated tumor had grown to 13.5 cm × 12.5 cm × 8 cm and caused pain, bleeding and mucous exudates. On December 18, 2001, the patients had her first BNCT and her tumor shrunk by 63 %, the second BNCT was performed with gelatin-sheet on January 23, 2002 due to insufficient radiation dose at the tumor surface had resulted in re-growth. The second BNCT caused great effect on the patient such as tumor reduction, relief of pain and exudates-secretion from the ulceration. With the third BNCT performed on December 17, 2002, one year after the first BNCT, the size of tumor had a remarkable reduction (94 %) and disappearance of tumor were ulceration achieved with normal skin cover and continuing improvement in facial palsy[10] (Fig.4).

2.2.2 Case report 2

A 61-year-old man with recurrent maxillary sarcoma (Fibroblastic osteosarcoma) after neo-adjuvant and adjuvant chemotherapy and operation was treated with 68 Gy of radiation in vain. With the purpose of improvement of quality of life (QOL), the BNCT was performed for the patient at the terminal stage. In this case, tumor/normal tissue (T/N) boron concentration ratio attained 3.5 to 4.0. A peak of the total dose

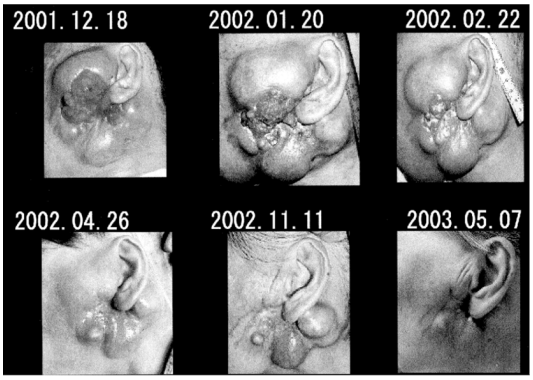


Fig 4 Recurrent parotid gland cancer BNCT 3 times (01. 12. 18, 02. 1. 23, 02. 12. 17)

equivalent at the tumor was 28. 4 Gy-Eq (3 cm depth) and the deepest tumor (9. 5 cm depth) was 4. 4 Gy-Eq. Performance status (PS) of the patient remarkably improved: before BNCT (PS:4) and after BNCT (PS: 2). Before BNCT, the patient was bed-ridden all days due to severe headache, bleeding, nausea and vomiting, and after BNCT, he could walk to the hospital for two months on his own foot without those symptoms[11].

The above cases are BNCT curative results of recurrent HNM with epithermal neutron beam irradiation on Kyoto University Research Reactor (KURR) in Japan by adopting boron compound infusion of BPA combined with BSH after conducting ^{18}F-BPA-PET study.

It is well known that recurrent HNM resists radiotherapy and chemotherapy and shows extensive growth, and necessitates a wide resection including surrounding tissues. To avoid severe impairment of oro-facial structures and functions, exploration of new treatment is of top urgency.

Japan initialed BNCT clinical trial on 21 recurrent HNM patients in 2001 and achieved a therapeutic response rate of 81 %. QOL of patients had been improved significantly and 4-year survival rate reached to 39 %, in spite of slight side effects such as transient mucositis and alopecia (less than Grade-2 by NCI-CTC).

BNCT clinical trial results in Japan and Finland indicated that BNCT represented a new and promising treatment approach even for a huge or far advanced HNM.

2.3 Treatment of liver metastases

2.3.1 Case report

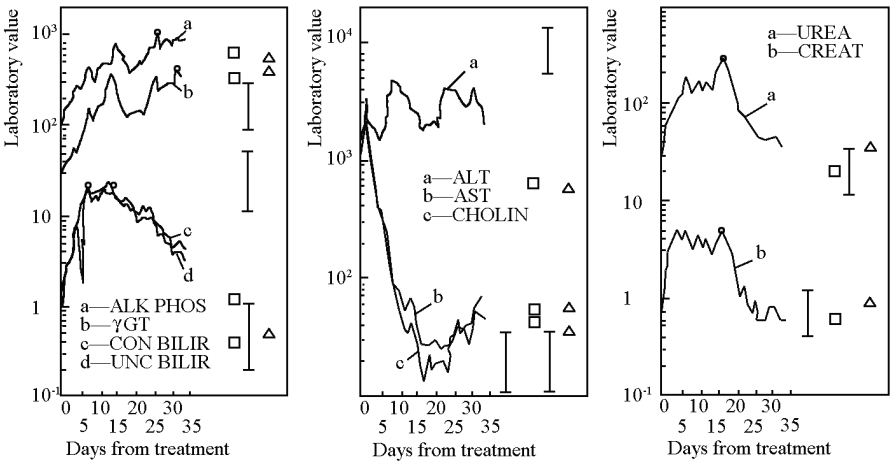
A 48-year-old Italian man with synchronous diffuse liver metastases from a sigmoid adenocarcinoma received surgery resection seven months before in a hospital, where the patient underwent a complete course of standard chemotherapy, however, the hepatic situation and clinical conditions appeared worsened. An external US scan showed six metastases in both liver lobes, confirmed by spiral CT. GEC was 63 %. At the beginning of the operation an intraoperative US scan revealed the presence of 14 metastases in the liver. Before removing the liver, the BNCT clinical medical team of Pavia University infused 750 mL of 0. 14 M solution of BPA-fructose complex (300 mg/kg body weight) through the patient's colic vain during a period of two hours. After one hour from the start and at the end of perfusion, tumor and liver samples were collected for boron concentration measurement, and then treatment plan with prescribed radiation dose was formulated. At this point, the hepatectomy was completed. On the bench the isolated liver was washed with chilled UV solution and then carried to the Reactor Laboratory of Pavia University. Here, following the treatment plan, the explanted liver was submitted to thermal neutron irradiation up to the fluence of 4×10^{12} cm^{-2} (11 min). Taken back to the operation theatre, the liver was washed again with chilled UV solution and then reconnected to the vascular and biliary stumps of the patient. The procedure required 21 hours altogether. The patient was maintained in a no-liver status for six hours. The BNCT postoperative period presented the some complications in sequence like thrombotic occlusion of the left femoral vein, renal and hepatic insufficiency, left foot drop, etc. however, the patient was in general good conditions seven months after the operation: laboratory values were good (Fig. 5), neoplastic markers were negative, GEC was 73 %, spiral CT and PET showed absence of metastatic nodules in the liver[12].

Italy has started a long term research program of BNCT clinical trail of liver metastases transplantation since 1987. The great creation of the Italians has proved that BNCT remains as an exclusive option in treatment of diffuse live cancer, for which surgery operation, radiotherapy and chemotherapy used to do nothing helpful. The success of Italians has further expanded curative types of cancers with BNCT application and updated BNCT clinical trail to a new level. Nowadays, Japan, Finland, Argentina as well as the European Union have all actively engaged in BNCT pre-clinical researches of liver cancer.

2.4 Malignant melanoma

Melanoma is a cancer highly destructive locally and highly metastatic distally with different types e. g. nodular melanoma (NM), the most malignant tumor with early vertical invasion and ability to metastasize to distant organs through lymph- and blood-vessels. Acral lentiginous melanoma (ALM), the most common type among Japanese and in other Asians, such as Indone-

sians, is also treated surgically, quite often with amputation, although prognosis is not necessarily good. The other choices of treatment including conventional radiotherapy often fail.



Preoperative values are indicated at t=1. Operation day is at t=0. Squares and triangles give values at 90 and 180 days after treatment. The vertical segments are, in the given scale, the ranges of normal values. Circles show the worst values.

Fig. 5 Behavior of some laboratory values vs. time

2.4.1 BNCT clinical trail of melanoma in Japan

Japan started its first BNCT clinical trail of melanoma in 1987 and received an encouraging treatment result. All the 12 patients with primary melanoma were free from lymph node metastasis and were evaluated by 5-year survival after BNCT. Out of six cases of ALM, four survived over five years. With respect to three NM cases, one survived longer than five years and two less than one year. Three cases of lentio maligna melanomas (LMM) and one lentio maligna (LM) were cured successfully without any local recurrence and distant metastasis and LMMs have survived more than five years and LM over two years, respectively[13].

2.4.2 BNCT clinical trail of melanoma in Argentina

Argentina started project of phase I/II multiple subcutaneous melanoma BNCT clinical trail in 2003. From October 2003 to June 2006, seven patients at the mean age of 64 years (51 to 74 years) received epithermal beam irradiation at RA-6 reactor after being infused with BPA compound of 14 g/m^2 (eight irradiation procedures covering ten anatomical areas). The normal skin maximum tolerable dose (MTD) is 16.5 ~ 24 Gy-Eq, and whereas the infused BPA compound administrated dose in normal tissue varied from 15.8 to 27.5 Gy-Eq. According to analysis to evaluable nodules, the Argentines reached to the conclusion that the toxicity could be maintained at an acceptable level when the overall response was observed in 69.2 % of the modules defined as a target, with 30.7 % of additional nochanged tumors. Out of 10 evaluate anatomical areas, analysis of three anatomical areas demonstrated ulceration (30 % of grade III toxicity approximately)[14].

The researches of the Japanese and the Argentines indicated that if improvement on boron-containing compounds could induce a T/N boron concentration ratio of >4.0, if boron concentration of tumor and its surrounding tissues could be measured prior to irradiation and in the course of irradiation, if the total radiation dose of each patient could be calculated without histological sampling, and if the hospital based neutron source accepted by the public could be available, the outpatient service of BNCT melanoma in communities with high population density would possibly come true.

2.5 Application expansion of BNC principle

2.5.1 In addition to the above mentioned clinical trials, BNCT preclinical researches have been expended to cerebral metastatic of melanoma, lung cancer, pancreas cancer, mammary gland cancer, cervix cancer, prostate cancer, chordoma and even leukaemia.

2.5.2 Application of BNCT in non-cancer diseases treatment

In the USA, Switzerland, Argentina, etc., Boron Neutron Capture Synovectomy (BNCS) has been developed by taking reference of BNCT principle for non-cancer diseases treatment especially the patients with rheumatoid arthritis (RA) (Fig. 6).

The research work is in basic experimental stage at present time. Scientists of MIT in the USA have taken relevant samples of synovium and cartilage from the patient's focus and incubated the samples in test tubes. It was discovered that the average RA synovium uptake of ^{10}B concentration was 30 ~ 50 folds higher

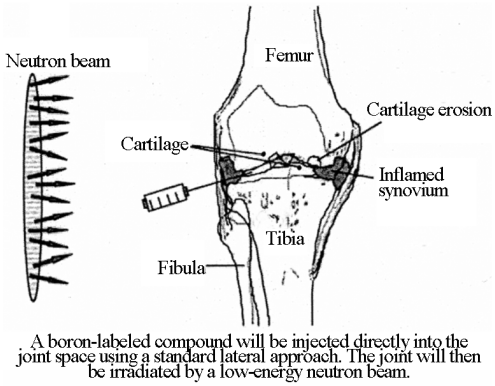


Fig. 6 Schematic illustration of Boron Neutron Capture Synovectomy

than that in BNCT case, whereas the uptake ^{10}B concentration of cartilage remained at a very low level. In spite of quick flow-out rate of ^{10}B concentration from articulations was 50 ppm/h in average, the uptake ^{10}B concentration of optimized retention of 15 minutes in articulations was maintained at an even much higher level of 490 ppm, that was to say, in the neutron irradiation duration of eight minutes, a curative dose of 100RBE Gy would be generated to synovium[15]. After animal experiment, BNCS is expecting to reach to stage of patient's clinical trial. We are all looking forward to hearing the successful feedback of BNCS, as this new clinical therapy with advantages of non-surgery operation, painlessness, low cost and short time of outpatient treatment will bring benefit to patients especially those aged ones who have been tortured by rheumatoid arthritis for years.

2.5.3 BNC, an immunologic tool

In order to mitigate the high death rate of arteriosclerosis in consequence of heart transplantation operation, scientists of MIT in the USA are developing a CD_3 antibody, i.e. boron-containing nucleoside, which is able to maintain ^{10}B concentration in T cells at an adequate high level, and passivate over 90 % of T cells penetrated to the heart of heteroplastic transportation so as to prevent occurrence of arteriosclerosis caused by parenchymal rejection and extend the patient's life. In guinea pig test, the extremely high intake ^{10}B concentration was observe[16]. With the further development of this technology, Boron Neutron Capture principle application in the filed of human immunologic research will have a vast range of prospects.

3 Bottleneck in development process of the NCT

The past 73 years witnessed a long and difficult process of BNCT application in consequence of its elaborate basic rationale. To date, the BNCT clinical trial on patients has been sustaining for 59 years. There are still many obstacles on the way of transferring BNCT to a routine therapy. Bottlenecks are mainly summarized in the three points as below:

3.1 Improvement on specificity and functionality of boron-containing compounds for BNCT tumors treatment are urgently required

As one unitary form of binary targeting radiation therapy of cancer, boron compounds delivery agents development process started from the 1950s can be divided into the following three generations.

3.1.1 the first generation boron compounds

Boric acid and its certain derivatives e.g. sodium borate, sodium pentaborate, paracarboxy-phenyl boronic acid, sodium perhydrodecarborate, etc. of water soluble compounds[17] were adopted in the early stage of failed BNCT clinical trial. As these boron compounds were in compliance with phenomenon of BBB and did not enter into normal brain tissue, the objective of selectivity could be met. Nevertheless, the clinical trials had proved that these boron compounds demonstrated a poor selectivity to tumors and short retention in tumors. Due to ^{10}B concentration ratio of 0.5 ~ 0.8 in tumor and normal tissues blood, blood vessel walls of normal brain tissues around tumor focus were apt to be destroyed by high LET α radiation dose of neutron field, and patients used to die in the consequence of being over-radiated or their tumors recurred when tumor cells were not killed thoroughly.

3.1.2 The second generation boron compounds

The second generation boron compounds are extensively adopted in the current BNCT clinical trials. Boron compounds approved by Federal Drugs Administration (FDA) are mainly including [(L)-4-dihydroxy-borylphenylalanine] called BPA[18] and polyhedral borane anion, sodium mercaptounde cahydro dodecaborate called BSH[19]. Although the two boron compounds have such advantages of low toxicity and longer retention in tumor tissues, ^{10}B concentration ratio of >1 in tumor/brain and tumor/blood, and confirmed safety of intravenous infusion, they are still not able to meet the following fundamental requirements to the boron compounds for BNCT.

1) Low toxicity to whole body and low intake boron concentration of normal tissues. ^{10}B concentration ratio of >(3 ~ 4):1 in tumor and normal tissues is required in BNCT.

2) Each tumor cell is required to have 10^9 ^{10}B atoms in one tumor cell i.e. around 20 μg ^{10}B in unit gram tumor.

3) In the course of BNCT clinical trial, the boron

compound is required to be of rapid clearance from patient's blood and normal tissues but persistence in tumor.

All the above mentioned requirements to boron compounds for BNCT account for indistinct curative effect of available BNCT, especially the brain glioblastoma (GMB). Keeping in view of the strong metastatic trend of tumor cells to normal tissues, the complex of tumor cell histology and the heterogeneity of tumor cell constitution, the available BPA and BSH are not the ideal boron delivery agent for BNCT, and development of new delivery agents is a must.

3.1.3 The third generation boron compounds

So-called the third generation boron compounds mainly consist of a stable boron group or cluster attracted via a hydrolytically stable linkage to a tumor targeting moiety, such as low molecular weight biomolecules or monoclonal antibodies (mAb). For example, the targeting of the epidermal growth factor (EGF) receptor (EGFR) and its mutant isoform (EGFRvIII), which are over-expressed in gliomas as well as in squamous cell carcinomas of the head and neck, and allow large amount of boron entering the tumor tissues (Fig. 7).

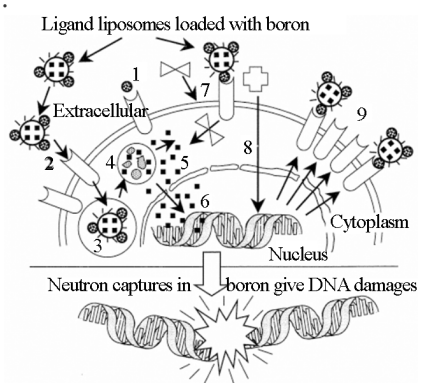


Fig. 7 Principles for uptake of ligand liposomes in tumor cells when receptors are targeted

The tumor cell nucleus and DNA are especially attractive targets because the amount of boron required to produce a lethal effect may be substantially reduced if it is localized within or near the nucleus. Other potential subcellular targets are mitochonadria, lysosomes, endoplasmic reticulum, and Golgi apparatus. Amphiphilic compound is also the required character for the third generation delivery agent. Water solubility is an important factor for a boron agent that is to be administrated systematically whereas lipophilicity is necessary for it to cross the Blood-Brain-Barrier (BBB) and diffuse within the brain and the tumor. Therefore, amphiphilic compounds processing a suitable balance between hydrophilicity and lipophilicity have been of primary interest because they should provide the most favorable differential boron concentration between tumor and normal brain, thereby, enhancing tumor specificity. With the exception of the amphiphilicity, the molecular weight of the boron compound is an important factor for the third generation delivery agent, because it determines the rate of diffusion within both brain and the tumor.

It is indeed a great challenge in application of the third generation boron compound delivery agents in patient's clinical trial, for example, the high molecular weight EGFR tumor targeting monoclonal antibodies[20] developed by Dr. Gong Wu and his colleagues in the USA has set up its curative effect in animal test, however, the effective delivery of boron compound to patient's brain remained as a big problem, although the agent was directly delivered to brain by circulation enhanced delivery (CED) method. In additional to this, there are variables in EGFR expressing from one tumor to the other, and even in the same tumor, EGFR expression are not the identical. Moreover, the deliver agent will not be effective unless it targets to both wild-type EGFR $^{(+)}$ and its EGFRvIII $^{(-)}$.

How can the third generation boron compound delivery agents be developed with the compliance of BNCT routine treatment? There is still a long way to go, the extensive and systemic studies in this aspect are required to fill up the gap.

3.2 Quantification and accuracy in radiation dose evaluation are required

Due to lack of experience in quantification and fineness control to radiation dose in BNCT clinical trials on brain tumors and other tumors, tumor recurrences as well as phenomena of edema and necrosis in the consequence of inaccurate radiation dose administration have been observed in all related case reports. Neutron radiation dose for BNCT clinical trials is mainly subject to the consolidated consideration of three factors, i. e. ^{10}B concentration in tumor, neutron flux in collimating to tumor volume and irradiation time on the reactor. Relatively to say, it is not difficult to give real-time accurate evaluation of irradiation flux and irradiation time i. e. neutron fluence being delivered to tumor volume, however ^{10}B concentration in tumor and normal brain tissues can only be indirectly calculated by comparing the measured ^{10}B concentration data of instant blood samples respectively collected before radiation, in the course of irradiation and after irradiation to the corresponding time-wised brain tumor ^{10}B concentration-time relational curve. Such a curve is prepared on the basis of the relevant animal experiments,

autopsy analysis and the accumulated histological information. As all the calculation data is to be programmed by the computer qualified in simulation experiments. The treatment plan computer software is to work out the prescribed radiation dose or evaluate the treatment radiation dose. Although the available treatment plan computer software is most perfect, although its calculation time meets the clinical requirement of neurosurgeons, real-time tumor radiation dose, the artificially assumed similarity data of T/N ^{10}B concentration ratio of 3∶1, etc. remain ambiguous. In these years, the NCT team of MIT in the USA has led an International Dosimetry Exchange with participants from eight clinical trial research centers in seven countries. This team has published a series of reports, evaluated differences in dose specification between centers in the Europe and the USA[21]. Individual dose components calculated from treatment plans formulated by the participating centers were compared to the MIT measurements and differences ranging from 4 % ~370 %. Among centers using BPA, the maximum dose to brain determined for the same nominal specification of 10 Gy (w) is significantly higher than 1 of the assumption at US-BNL:

1) US-Harvard/MIT 1.32
2) Finland-VTT 1.43
3) Netherlands-JRC 1.49
4) Sweden-Studswik 1.74

The great difference indicated that in clinical trials, ambiguity in radiation dose evaluation significantly accounted for the uncertainty of BNCT clinical trials. In the transition from the 20th century to 21st century, the international medical circles have developed a PET-CT image diagnosis technique. PET is able to sensitively and woundlessly indicate physiological metabolism and pathological transformation of human organs at early stage, whereas CT is able to accurately indicate the anatomical structure of human organs. The combination of PET and CT enables us to know the organ anatomical structure of with lesion, and in the same time, obtain the fine description of biological metabolism process of the organ. The PET-CT has updated diagnosis of neurological diseases, cardiovascular system diseases, tumor diseases, etc. to a new level. At the beginning of the new century, the Japanese scientists have infused delivery agent BPA mixed with the PET tracer isotope ^{18}F to patient in BNCT clinical trials for real-time indication of the quantitative biological process and dynamic transformation capability of BPA in patient's tumor focus and its surrounding anatomical tissues. The clinical trial case report of a thyroid cancer patient indicated that T/N boron concentration of BPA ratio measured by ^{18}F-BPA-PET technique was 2.9, cases of the primary and recurrent oral cavity cancer patients 1.9 ~4.0, cases of malignant meningioma patients 2.0 ~5.0 and case of newly diagnosed and recurrent glioblastoma patients 7.8 and 3.8 ~4.3 respectively. Compared with the semi-quantitative evaluation of radiation dose calculated on the basis of measurement of the patient's blood boron concentration plus certain similarity data, such an individual-patient-based quantitative data collection is undoubtedly a more advanced methodology for accurate measurement and control of radiation dose in BNCT clinical trial application. The improvement on BNCT curative effect will eventually quicken the process pace of BNCT routinization, however, we think with such ^{18}F-BPA-PET/CT/MRI technical systems there will be some unmeasured factors, which request for further improvement and updating. For BNCT itself, the real-time evaluation of radiation dose within the scope of cells still remains as a bottleneck in radiation dosimetry development process, and the problem solution is subject to long term and in-depth researches.

3.3 Development of hospital based BNCT neutron source are urgently required

Descriptions of one unitary form of binary targeting radiation therapy i.e. boron compounds have been given in the above Items **3.1.1** to **3.1.2**, the other unitary form is neutron source. So far, all the BNCT preclinical research results and BNCT clinical trials achievements are subject to utilization of neutron sourced generated by nuclear research reactors. The reliable and sustainable supply of adequate neutron flux with energy field of less than 0.4 eV can be used for cell culture, small animal experiments and clinical trial tumors developed in the shallow tissues of human body, whereas the more advanced epithermal neutron beam with energy field of 0.4 eV $< E_n <$ 10 keV can be used for tumors developed at deep tissues of human body. A set of fission convert beam (FCB) facilities has been installed in research reactor MITR of the USA, the facilities enable patients to be exposed in a position in air epithermal neutron flux of (3.2 ~4.6) $\times 10^9$ n/ cm^2 · s when the beam port is of aperture of 16 ~8 cm in diameter. The measured specific absorptive dose data within the aperture scope are all the constants with values smaller than the intrinsic background value of 2.8×10^{-12} RBE Gy· cm^2/n induced by epithermal neutron in human body tissues. The dose distribution obtained from FCB facilities approaches to the theoretical optimum for BNCT[22].

In the past few decades, BNCT application had been developed on the basis of research reactor, however, scientists had gradually realized that the research

reactor really could not be regarded as a friendly environment for complicated medical treatment[23] due to the following reasons:

1) The patient had to be sent to the research reactor accompanied neurosurgeons and nurses after a long journey, as almost all the large and medium sized research reactors were located at the remote sites far from the populated areas.

2) The patient was apt to develop psychological fear in a surrounding of nuclear setups with high level of security e. g. multiple physical barrier, armed soldiers and patrol police dogs, barbed wires fencing walls, etc.

3) The patients emergency rescue facilities, hospital diagnosis databank, special liquid penetration pump operation procedure, etc. are not available in nuclear setups, it is almost impossible to perform a complete neurosurgical operation especially in case of clinical trial incorporating with new technology e. g. human brain boron compound direct delivery via circulation enhanced delivery (CED).

4) These research reactors have been designed with power ranging from 100 to 45 000 kW for providing neutron source to shared use of comprehensive nuclear technology applications. In the operation period of reactors, priority is always given to the scheduled irradiation activities like radioisotopes production, materials and nuclear fuels experiments and tests, monocrystalline silicon neutron transmutation doping (Si-NTD) production, neutron activation analysis (NAA) and neutron radiography (NR), etc. BNCT clinical trial irradiation program is all subject to the reactor operation schedule allocated in the fixed days and time durations at high price.

5) Most of available large and medium sized research reactors are in the edge of decommissioning, the aging and outmoded systems and components require a prolonged outage for maintenance.

6) Poor availability of research reactors for BNCT. Nowadays, only Japan IRR-4 and Finland Fir-1 research reactors[24] are in operation for extensive BNCT clinical trials.

Keeping in view of the above mentioned deficiencies of research reactors in BNCT clinical trials, the requirement voicing for new hospital based neutron source designated for BNCT clinical trials or available neutron source in the vicinity of hospitals is becoming stronger and stronger with each passing day. Different approaches with possibility have been studied and summarized as below:

3.3.1 ^{252}Cf spontaneous fission radioisotope source

^{252}Cf spontaneous fission radioisotope source is a compact-designed BNCT radiation facility suitable for hospital installation. The disadvantage of the facility is caused by short half life of ^{252}Cf radioisotope (2.6 years), that is to say, the facility has to meet its refueling operation frequently, which will affect the availability, and in addition, violent to regulatory requirements for operation of nuclear facilities. The source fuel loading of the facility is 1 g approximately, keeping in view that production of ^{252}Cf radioisotope is very difficult and such a strategic resource is very expensive, practical value and promotional application value of ^{252}Cf radioisotope have been restrained.

3.3.2 Accelerator based neutron source (ABNS)

People have been engaged in development of ABNS, quite a proper option for BNCT, for 30-odd years. ABNS will not form long-live radionuclides on the facility installation site. Site selection, surveillance procedures related to facility construction and operation will be easily evaluated and approved by the concerned authorities and accepted by the public. Nevertheless, in respect of BNCT clinical trials, the technology of ABNS is not yet proven, especially in the aspects of large yield neutron targeting material selection and cooling technology, and issues related to beam facility neutron activation. Of course, developments in feasibility of ABNS construction cost, routinization of ABNS operation, rationality of ABNS operation cost, etc. are subject to further in-depth analysis and comparative results.

After long time of research and development, some prototypes of the ABNS facilities installed in following countries have proved out their general maturity:

1) Right Angle BOA Type Facility in Birmingham University of the UK

2) Tandem Static Electric Quadrupole TESQ Type Facility in the Argentina Institute of Atomic Energy

3) Proton Cyclotron PCA Type Facility at Kyoto University Reactor Research Institute (KURRI) of Japan

4) Dynamitron IBA Type Facility in Ion Beam Application Co. of Belgium

With the exception of principled description, feasibility evaluation to ABNS can not be given until the most important clinical trial experience feedback is available.

3.3.3 Small sized reactor specially designed for BNCT

Safety in application, stability in operation, reliability in irradiation administration, and availability in clinical trials for reactor based neutron source have been fully verified, the results strongly recommended

the facility to be an exclusive neutron source not only for the present BNCT clinical trials, but also an indispensable neutron source for the future BNCT development. Specially designed hospital based BNCT reactor neutron source is the most realistic option. Although the facility still shows certain deficiencies and inconveniences, the available technology can surely solve them all by incorporating proper modifications. Technically to say, giving the first priority to miniature nuclear reactor and extremely high safety in selecting neutron source for BNCT application is our design guide line, for which the International Atomic Energy Agency (IAEA) gave overall description to this topical subject in its special publication of "Current Status of NCT" as early as in 2001[25]. In this book, the significance of building new type of reactor specially for BNCT (miniature reactor with extremely high safety) was confirmed by the descriptions of "Compared with the existing reactor facilities, it can be located near a hospital, in a large population center where the therapy is needed. In addition, patient's treatment consideration can be incorporated from the beginning, therapy providing the highest level of care and comfort." In respect of the facility performance, the book gave a description for requirements to such facility as follows:

1) The most advanced design and the extremely high efficiency i.e. low power and extremely high safety.

2) Capability in delivering adequate neutron flux to multiple irradiation positions.

3) A thermal neutron beam for cell culture in test tube and small animal experimental research as well as treatment of tumors developed at shallow tissues of human body.

4) An epithermal beam based on the spectrum shifting concept for effective treatment of tumors developed at deep tissues of human body.

5) A set of on-the-spot real-time detection device for blood boron concentration prompt gamma NAA and micro-measurement of boron distribution for accurate evaluation of radiation dose.

According to estimate of experts, construction cost of specially designed reactor for BNCT is five to seven million Euros. This book also emphasized that the facility would be completely feasibility in technical consideration, but the important factor worthy of noticing was the public's acceptance to it, in a word, the outstanding issue was related to human consciousness and safe surveillance only. Issues related to BNCT neutron source can be summarized by citing the relevant description given by Prof. Otto K. Harling in his opening ceremony speech of the 13th ICNIC as below:

"The demand for more epithermal irradiation facilities would increase significantly if BNCT achieves general acceptance as a routine radiation oncology modality. Additional modifications of existing reactors, new reactors designed specially for BNCT and accelerator based sources would all have to be very desirable to locate these new neutron sources in or close to hospitals, as is being done with the new hospital based reactor source near Beijing, China"[26].

4 Development of IHNI in China

4.1 Development background

4.1.1 Inspiration of the new century

Biomedical era that people are waiting for long finally comes. Science and technology are bound to extend the helping hands to the quality improvement of the life of human being especially in the aspect of disease treatment, which remains as one of important substances being pursued by the New China for six decades in the economic development and society progress as well as the great target for building a harmonious society.

4.1.2 Man is bound to overcome cancers

According to statistics of recent years, population of cancer victims, which account for the major reason of death in China, is around 1.6 million each year equal to 24 % of urban and rural population death toll. The economic losses caused by cancer exceeded hundred billions of RMB each year. Nevertheless, medical protection and control to certain malignant tumors and cancers of high incidence produce little effect. For benefit of human being, various new technologies in treatment of cancers are a must.

4.1.3 Break bottlenecks in the development process of NCT

Great efforts have been made by China in finding suitable reactor neutron source for civil application. China has a very good background for technical development of miniature neutron source reactor. In 1980s, China's prototype reactor[27] with features of intrinsic safety, low power output, small sized design, low cost investment and unattended operation were successfully developed and installed in cities for the purpose of NAA. Such miniature neutron sources reactors can serve as the special BNCT neutron source facilities after being properly modified and optimized, and make contribute to the problem solving for finding suitable BNCT neutron sources.

4.1.4 Private financing support

At present stage, the government has no sufficient budget to support certain frontier and inter-disciplines application projects, which have no immediate econom-

ic return but does have long term prospects, but thanks to the in-depth implementation of policy of reform and open pursued by China in developing its economy, certain privates are aiming at making investment to these hi-tech and low investment amount projects. Encouraged by the government policy and supported by the authorities concerned, the IHNI facilities in China have become a project mainly invested by privates.

4.2 Prototype of IHNI facilities

4.2.1 Functions of prototype of IHNI facilities

The full name of first IHNI facilities is In-Hospital Neutron Irradiator Type I, which aims at BNCT clinical treatment of brain cancers with craniotomy and non-craniotomy cases. The prototype facility is composed of three modules i. e. miniature nuclear reactor neutron resource facility, neutron beam facility and conventional medical setups. For full verification of the design rationality, BNCT adaptability and overall layout effectiveness of the facilities, the site of first prototype facilities (IHNI-I) was selected at a place of 2 km away from the supporting hospital. It is the exposure of certain unpredictable factors and deficiencies, especially problems related to radiation dose distribution and level that lays a firm foundation for the safety and effective consideration of designing the facilities right in the hospital building or the independent structure in close vicinity of the hospital.

4.2.2 Site and scope of prototype facilities

The site of prototype facilities is on the northwest of Xinzheng in the vicinity of China Institute of Atomic Energy (CIAE), Fangshan District, Beijing and 2 km away from the supporting hospital (No. 401 Hospital affiliated to CNNC). The distance between the site and hub of Beijing is about 40 km. the prototype facilities cover an area of 1 860 m^2, and the main building (including neutron source facility, neutron beam facility, medical facility, relevant process rooms and labs, medical preparation room, offices, etc.) has a floor space of 477 m^2. The underground structure part for installation of reactor core components, neutron beam facility and measurement room is a frame work of 4 m (depth) × 10 m (width) × 18 m (length) with a building area of 175 m^2. The structure above the ground is of 10.5 m (height) × 10 m (width) × 30 m (length) with a building area of 920 m^2. The total building area of the prototype facility is 1 145 m^2.

4.2.3 Design finalization and industrialization of prototype facilities

After years of site evaluating of Wards Zone Tiantan Hospital in Chongwen District of Beijing, No. 401 Hospital premises, Mentougou Economy Development Zone, etc. it is finally decided to build the prototype facilities on the site of an independent courtyard at north zone of Xinzhen, Fangshan District.

Beijing Environment Protection Bureau (BEPB) issued document JINGHUANSHEN[2007]819 on September 5, 2007 and approved the above mentioned site in principle.

National Environment Protection Bureau (NEPB) gave analysis and evaluation to "Environment Impact Report of Prototype Facilities Project" on October 11, 2007, reached conclusion that the project was acceptable and issued approval document HUANSHEN[2007] 414 accordingly.

The National Nuclear Safety Authority (NNSA) issued Construction Permit for IHNI facilities via document HEANZHENZI No. 0804 document on July 16, 2007.

The post fuel loading commissioning measurement shall be done accordingly, and overall performance of neutron source facility at rated power of 30 kW as well as radiation dose level of each systems and rooms of prototype facilities shall be verified. After obtaining the Operation Permit, the IHNI facilities can be initialed for experiment of BNCT preclinical basic researches. Then it might be the time for us to consider the preparation of the first "Protocol on BNCT Clinical Trial".

During the period of IHNI-I Prototype Facilities preclinical experiments and clinical preparation, the following three typical beam facilities design modules are to be worked out for combined utilization in three to five years by incorporating the operation and experiments experiences of IHNI-I Prototype Facilities:

1) Strongly directional beam facility module

2) Isotropy homogeneous irradiation field module

3) Epithermal-thermal neutron mixed field irradiation beam module

In the same period, the types of IHNI series products including IHNI-I Double Beam Therapeutical Facility, IHNI-II Double Beam Research Facility and IHNI-III Triple Beam Therapeutical & Research Facility are to be gradually developed for the purpose of realizing our target of providing IHNI series facilities in an industrialized way.

4.3 IHNI-I prototype neutron source facilities (**Fig. 8 central part**)

4.3.1 Type of reactor

The modified miniature neutron source reactor, i. e. the low enriched uranium deeply-undermoderated reactor core designed with full natural circulation heat removal, light water cooling and moderating, full reflector made of metal beryllium and reactor vessel in water pool.

4.3.2 Reactor core

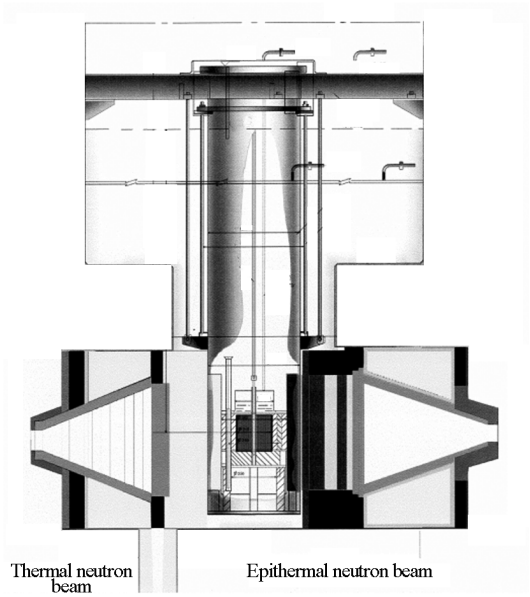


Fig. 8 In-hospital neutron irradiator

The reactor core is composed of 302 integrated element rods (highly sintered density UO_2 pellets with ^{235}U enrichment of 12.43 %), which are in array of concentric circles and equi-radian length. The reactor core is of 240 mm in height and diameter respectively, and the core volume is 10.9 L only. The total reactor core UO_2 fuel loading is about 10.64 kg, and total weight of ^{235}U is 1 173 g. The radial reflector i. e. metal beryllium annulus vertically installed around the reactor core, is of 440 mm in outside diameter, 100 mm in thickness and 246 mm in height. The lower reflector, i. e. metal beryllium disc beneath the reactor core, is of 350 mm in outside diameter, 100 mm in thickness. The upper reflector i. e. metal beryllium sheets on the top of reactor core, is of 133 mm in radius with a maximum laminated thickness of 100 mm (thickness calculation of metal beryllium sheets to be added is subject to the reactivity loss from fuel burn-up in the lifetime of reactor operation). The total reactivity worth of upper reflector attains to 16.11 mk. The above mentioned three metal beryllium reflectors enable reactor core neutrons to have a full reflection effect.

4.3.3 Control rod

There is a cadmium control rod with total reactivity value of - 6.4 mk installed at the center of the reactor core for the purposes of reactor startup, shutdown reactor power adjustment as well as stable operation automatic control under rated power, compensation of reactivity loss of daily operation and of fuel burn-up in fuel cycle. In case of center control rod failure, the auxiliary control rod with reactivity equivalent of - 3.78 mk installed in the radial reflector annulus, drops automatically by incorporating reactor shutdown procedure.

4.3.4 Output neutron energy regulator

In the water gaps between inside wall of the reactor vessel lower section and ex-annulus of reflector, arc-shaped graphite block and metal aluminum block shall be installed on left and right respectively for water displacement. Graphite block serves as moderated core thermal neutron energy regulator for delivering source neutron to thermal neuron beam facility, whereas aluminum block serves as epithermal neutron energy (converted from the core high energy neutron of > 1 MeV after being filtrated) regulator for delivering source neutron to epithermal beam facility.

4.3.5 Reactor vessel

The cylinder-shaped reactor vessel made of Mark LT-21 aluminum material is composed of upper and lower sections connected by studs with pressing PVC gasket packed at joints. Reactor core, metal beryllium reflectors, control rods, neutron energy regulators and reactor core parameters measurement device are to be installed in the lower section. Five meters above the top of reactor core is the reactor vessel water surface. The nuclear fission heat produced by the core is to have natural convection in reactor water (volume of reactor water is 1 621.5 L) flow through conductivity in vessel wall to the pool water. Reactor water and pool water will form the human exposure protective barrier against neutron and γ-ray released by the reactor core.

4.3.6 Reactor water pool

The rectangular reactor water pool has a total water inventory of 40 m^3. It is a heavy concrete shielding structure added with Mark LF_2 metal aluminum plate lining of 8 mm in thickness on the pool wall and 10 mm on the pool bottom. The water surfaces of the reactor pool and reactor are to be maintained at the same level. Through heat conduction of heavy concrete shielding and heat radiation from pool water surface, the pool water is to let out heat produced in the reactor core and provide radiation protection to reactor operation staff. In addition to supporting the pool water load, heavy concrete shielding structure is also able to strictly control the exposure dose to patients, medical staffing, reactor process engineers and reactor radiation protection engineers, who are involved in treatment activities in medical preparation room, measurement room and operation activities in irradiation room, corridors, and the auxiliary process system, at a range tolerable to limits.

4.3.7 Major technical parameters of the IHNI-I prototype neutron source facilities (calculated values)

Reactor rated power: 30 kW;

Temperature at reactor water inlet: 30 °C;

Temperature difference of reactor water inlet and water outlet: 20 °C;

Temperature of reactor pool water: 18 °C;

Maximum excess reactivity in clean cold system: 4.5 mk;

Full power daily operation time: 6 hours;

Mean core fuel loading cycle: 10 to 20 years

4.4 IHNI-I prototype neutron beam facilities (Fig. 8 left and right part)

One thermal neutron beam and one epithermal neutron beam are to be respectively branched out from left and right sides of metal beryllium annulus reflector around the core of IHNI-I facilities. In the vertical direction of thermal neutron beam, one measurement beam is to be branched out.

4.4.1 Thermal neutron beam facility (calculated value)

Neutron beam energy field is < 0.4 eV. Three adjustable apertures (10 cm, 12 cm and 14 cm) are designed at the beam port. At aperture 12 cm, the thermal neutron flux at beam port (along centre horizontal axial line of the beam) in air i.e. on patient's irradiation spot, is 2×10^9 n/ cm^2 · s. The contamination ratio of transthermal energy neutron i.e. the epithermal and fast neutron dose rate in unit thermal neuron flux is $< 2.0 \times 10^{-13}$ Gy · cm^2. The contamination ratio of γ-ray, i.e. γ-ray dose rate in unit thermal neuron flux is $< 1.0 \times 10^{-13}$ Gy · cm^2. The directionality of neutron beam (parallel to the horizontal axial line of neutron beam facility) is 0.8. The mixed spectrum neutrons released from annulus reflector will be collected and intercepted by arc-shaped graphite block on the left side of the core, which has been arrayed in a radian range of 120°, and 5-fold higher than the core height and high density nuclear class graphite block, and moderated to thermal neutron beam suitable to BNCT in the end. In the framework of 1.2 m × 1.2 m × 1.45 m, the scattered neutrons will be reflected by the surrounding graphite block so as not to release to outside. In IHNI-I facility, a cone collimator made of metal bismuth is installed, and the conical cavity is designed to straighten neutron beam flow parallelly at beam port. The primary γ-ray radiated by the core and the secondary γ-ray induced by components of beam shall all be absorbed by metal bismuth material. Compared with metal lead, metal bismuth has the advantage of higher neutron availability and lower secondary γ-ray contamination compositions. A nose-shaped aperture pressed from ^{6}Li contained PVC material has been installed at the collimator outlet for eliminating thermal neutrons escaped to the outside, which produces contaminative radiation to normal issues of human body, that is to say, beam flow penumbra effect shall be reduced to the minimum level. Thermal neutron beam facility can be used in irradiation research of tumor cell culture dish and test tube T/N boron concentration distribution measurement as well as clinical trials of tumors developed at brain and other shallow tissues of human body.

4.4.2 Epithermal neutron beam facility (calculated value)

Neutron beam energy field is at the range of > 0.4 eV to < 10 keV. Three adjustable apertures (10 cm, 12 cm and 14 cm) are designed at the beam port. At aperture 12 cm, the epithermal neutron flux at beam port (along centre horizontal axial line of the beam) in air i.e. on patient's irradiation spot, is 4.3×10^8 n/ cm^2 · s. The contamination ratio of fast neutron ($E_f > 10$ keV) i.e. the fast neutron dose rate in unit epithermal neuron flux is $< 6.0 \times 10^{-13}$ Gy · cm^2. The contamination ratio of γ-ray, i.e. γ-ray dose rate in unit epithermal neuron flux is $< 2.0 \times 10^{-13}$ Gy · cm^2. The ENF-TNF ratio is > 24.4 and directionality of neutron beam is 0.81. The mixed spectrum neutrons released from annulus reflector will be collected and intercepted by arc-shaped metal aluminum block on the right side of the core, which has been arrayed in a radian range of 120°, and 5-fold higher than the core height and Al_2O_3 ceramic block so as to filtrate neutrons with energy fields of < 1 MeV and > 10 keV respectively and deliver neutron beam suitable to BNCT to the patient's focus through cone collimator made of metal bismuth. The thermal neutron composition will be absorbed by cadmium of 1 mm in thickness lined on the metal aluminum segmental block arrayed in a radian range of 120°. The scattered neutrons will be reflected by the surrounding graphite reflector clad with boron containing PVC so as not to release to the outside, and in the same time, boron containing cladding can absorb the escaped and harmful neutrons. The conical cavity is designed to straighten neutron beam flow parallelly at beam port. The primary γ-ray radiated by the core shall be decayed after passing through high density metal lead blocks and spectrum converter i.e. Al_2O_3 ceramic block. The secondary γ-ray induced in beam facility shall all be blocked by collimator made of metal bismuth material. A nose-shaped aperture pressed from ^{6}Li contained PVC material has been installed at the collimator outlet for eliminating possible penumbra effect induced by neutron flux.

In the course of IHNI-I Prototype Facilities installation, we have to abandon the ideal spectrum convert-

er material FLUNTAL™ and replace it with cheaper product of Al_2O_3 ceramics due to insufficient budget, and in the consequence of material change, epithermal flux is reduced by 50 %. In the finalized design, spectrum converter material FLUNTAL™ will be the first option.

After entering to patient's tumor focus, using the normal tissue of human body as the moderator, neutrons in epithermal energy will be transmuted to thermal energy in the depth range of 20 mm to 40 mm, which is to bring about capture reaction with boron atoms deposited in patient's tumor focus. The epithermal neutrons will not act on normal tissues (scalp and skull) and produce harmful radiation contamination damages, and the possibility of acting on hydrogen and nitrogen atoms in normal brain in the process of moderation and producing proton contamination dose can be ruled out, that is to say, objective of direct BNCT treatment without craniotomy can be realized.

4.4.3 Thermal neutron measurement beam (calculated value)

Neutron beam energy field is < 0.4 eV. The beam port is designed with a diameter of 2 cm. The thermal neutron flux at beam port in air is 3.0×10^6 n/ $cm^2 \cdot s$. The contamination ratio of transthermal neutron ($E_n > 0.4$ eV) is $< 1.0 \times 10^{-13}$ Gy· cm^2. The contamination ratio of γ-ray is $< 2.0 \times 10^{-13}$ Gy· cm^2. The directionality of neutron beam is 0.98. The measurement beam is able to provide prompt γ-ray neutron activation analysis (PGRNAA) data of real time boron concentration in the course of BNCT treatment.

4.5 Medical facilities layout

4.5.1 Irradiation room

An irradiation room of 2.0 m(H) ×4.0 m (W) ×4.6 m(L) has been designed at thermal neutron beam and epithermal neutron beam ports respectively. The setups in the room are as follows:

1) Operation bed designed of positioning patient at irradiation aperture from different directions

2) Floor rail installed movable beam aperture shielding hatch

3) Neutron and γ-ray dose measuring and monitoring system equipment and alarm detectors

4) Remote control closed circuit television system for monitoring irradiation status of the patient

4.5.2 Boron compound disposing and delivering room

Prescribed boron compound is to be disposed prior to the irradiation operation and infused into patient's body in due course.

4.5.3 Medical irradiation detection room

Gold wires and foils are to be prepared for pre-measurement or real-time measurement of neutron flux on the patient's tumor focus. Thermo-luminescence detectors are to be prepared for measurement and evaluation of γ-ray or the total dosage of gamma and neutrons.

4.5.4 Boron concentration detection room

Blood samples are to be taken before, in the course of and after irradiation operation, and measured by high-purity germanium gamma spectrometer and computer system for obtaining real-time boron concentration measurement data.

4.5.5 Medical wastes storage room

The room is designed for temporary storage of various medical wastes and wastes of low-level radioactivity, which are to be regularly sent to urban sanitation prevention station for further disposal.

4.5.6 Reserved operating room

According to requirement of medical treatment process, the conference room on the second floor can be modified to the sterilized operating room.

4.6 Preparation of computer software for MCDB treatment plan

We have developed the following data process programs for BNCT brain tumor Mont Carlo dose calculation (Software MCDB Rev. II) by taking reference of advanced BNCT treatment plans of the USA, Japan, etc.

1) Pre-process program for converting medical image data to Mont Carlo input data

2) Thermal neutron, fast neutron and photon dose calculation program

3) Post-process program for isohypses and isopleths of the ultimate dose calculation

The development of Software MCDB Rev. II has induced application of technologies of fast particle tracing and mesh tally matrix. The calculation results achieved by Software MCDB Rev. II is 2.7 to 3.5 times faster than that done by the general MCNP program. MCDB-II is able to meet accuracy and time requirement for clinical trials, and conduct parallel calculations[28].

4.7 Characteristics and values of the IHNI-I Prototype Facilities

The IHNI-I Prototype Facilities Project was initially put forward in April 2001, and the proposal received encouragement, support and the anticipative comments from the President of Chinese Academy of Engineering (CAE), Mr. Song Jian and the Vice Presidents of CEA, Mr. Zhu Gaofeng and Mr. Hou Yunde.

Design and construction of the IHNI-I Prototype Facilities have completed under the concerns, support and guidance of China National Nuclear Corporation

(CNNC) with active and devoted involvement of China Zhongyuan Engineering Corporation (CZEC), China Institute of Atomic Energy (CIAE), Northwest Nuclear Technology Institute (NNTI), Beijing Applied Physics & Computational Mathematics Institute (BAPCMI) and Beijing Capture Technology Co. Ltd. (BCT). I would like to express my special gratitude to those retired experts from the Beijing Nuclear Engineering Institute (BENI), China Nuclear Power Design & Research Institute (CNPDRI) and Nuclear Safety Assessment Center (SAC), they have offered their invaluable experiences and made earnest contributions to the IHNI-I Prototype Facilities Project in different stages of the project e. g. site selection, facilities design and construction and nuclear safety and environment review.

Compared with MNSR, the following significant modifications made in the design of IHNI-I Prototype Facilities:

1) After making comparative analysis to U_3Si_2 and UO_2 of nuclear fuel types and enrichments, pellets of sintered high density UO_2 ceramic fuel elements have been finally selected for IHNI-I Prototype Facilities to replace that of UAl_4 alloy fuel elements for MNSR, and ^{235}U enrichment of 90 % has been reduced to 12.5 %.

2) Keeping in view that the different application objectives, we removed the five small pneumatic samples transfer devices and five big ones respectively located in and out of annulus beryllium reflector designed for MNSR's neutron activation analysis application, and for providing neutron beam to IHNI-I BNCT application, we designed and installed two neutron beam facilities at reactor vessel lower section outsides. Such a modification will reduce reactivity loss of in-core structures and heighten the operation safety.

3) Thanks to the first adoption of the internationally advanced MCNP-4C computer program in the unified calculation of neutron flux distribution in core and in beams as well as neutron and γ-ray radiation dose distribution to patient's phantom, the refinement and accuracy in calculation has been improved significantly. In addition, we have conducted considerable amount of scheme analysis and parameters design calculations for the reactor and beam facilities[29,30], performed 1∶1 facilities full-scale thermo-hydraulic simulating test[31], 1∶1 core components and major beam facility components physics zero power test[32], fuel elements performance analysis[33], and verified design of IHNI-I Prototype Facilities through independent calculations of Hammercap AB-BNCT Development Co. in Sweden. The completion and operation of the IHNI-I Prototype Facilities is at sight now.

Characteristics and Values of the IHNI-I Prototype Facilities are as follows:

4.7.1 The new medical treatment facilities having unique user-friendly safety features

IAEA reviewed TRIGA in the USA, SLOWPOKE-2 in Canada and MNSR in China as the three reactors having unique user-friendly safety features, and described that "The siting and containment requirements for this class of reactors is much less restrictive. Most of the reactor facilities were housed in normal buildings (with controlled access) and in populated area"[34]. In respect of MNSR, its unique safety features can be seen from the relational curves of atom numbers ratio (N_H/N_{235U}) of hydrogen (N_H) in reactor core moderator water and ^{235}U in fuel pellet with critical mass (M_c) as given in Fig. 9.

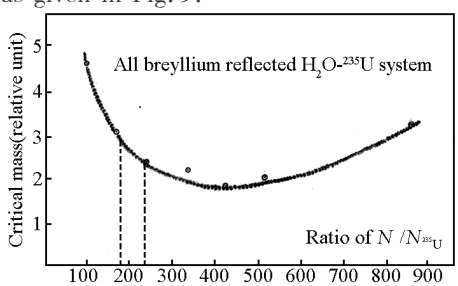


Fig. 9 Relation curve of critical mass with ratio of N_H/N_{235U}

MNSR's N_H/N_{235U} ratio has been selected at the curve tangential point on the left side i. e. 240, it means when water temperature rises, water density drops, or when reactor core water level drops, N_H atom numbers decrease. N_{235U} remains as a constant, under the circumstances of loaded fuel, the reactor is inclined to subcritical state and then stops nuclear chain reaction. The safety features demonstrated by the curve provide a full verification to the actual operation of MNSR. Fig. 10 indicates MNSR's reactivity transient curve. When the only center control rod fully withdrew from the core quickly, and suspended on top of the core, the reactor power will be raised suddenly in the wake of instant release of 3.6 mk equivalent rod reactivity, however, neutron leakage increment depends on water temperature rise. After the power rate attained to its peak of 76 kW, the system reactivity will be consumed in line with water temperature rise, and reactor power rate will be dropped accordingly and maintained in a safety state. Even if the reactor is at its peak power rate, the maximum cladding surface temperature of fuel elements is still lower than saturated temperature corresponding to water level.

The IHNI-I Prototype Facilities has made full use

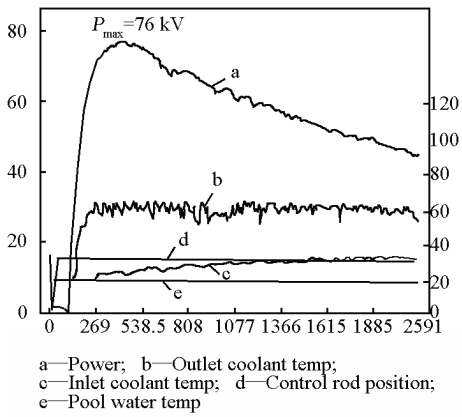


Fig. 10 MNSR Transient 3.6 mk 1984.12.5

of the MNSR's characteristics and adopted deeper undermoderation in the reactor core design i. e. selecting N_H/N_{235U} ratio of 180, and steeper gradient of N_H/N_{235U} on the corresponding points at M_c curve compared with those on 240 ratio for demonstrating further enhanced safety trend. Using the same calculation methodology, the six groups delayed neutron fractions of the IHNI-I Prototype Facilities have been obtained i. e. $\beta_{eff} = 8.321\ 7 \times 10^{-3}$, the reactivity coefficient of moderator under temperature ranging from 20 °C to 100 °C is $-1.693\ 918 \times 10^{-4}\Delta k/k/°C$, the reactivity coefficient of fuel ranging from 20 °C to 800 °C is $-9.914\ 498 \times 10^{-6}\Delta k/k/°C$[35]. For the transient features of reactor power rate at different positive reactivity refer to Fig. 11, and safety features are at the first glance. Thanks to this physics intrinsic safety features, such a reactor neutron source facilities of low operation power rate, low uranium fuel loading and low inventory of fission yield can openly and legally be placed in the hospitals for treatment of patients with cancers, adopted as an indispensible facility for extensive application of BNCT routine treatment.

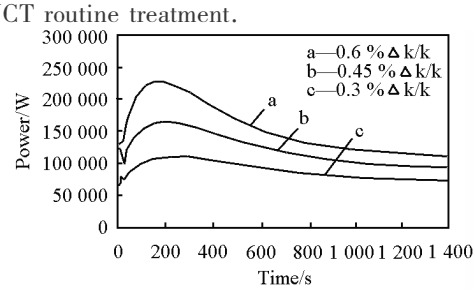


Fig. 11 A series of IHNI-I reactivity transient

4.7.2 The Low Enriched Uranium (LEU) core free from restrain of the Non-Proliferation Treaty (NPT)

The IHNI-I Prototype Facilities is designed with the LEU core, its fuel temperature reactivity coefficient is 26-fold higher than that of MNSR's HEU core, and its β_{eff} value is also raised by 0.04 %. In addition to its further enhanced safety features and further optimized adjustability, the LEU facilities are free from restrain and surveillance in its application, which the NPT enforced on HEU facilities. The freedom of the LEU facilities in this aspect will significantly simplify nuclear license application procedures and shorten the project approval time. As the LEU has been designed with UO_2 and Zr-4 cladding, which is extensively used in fuels fabrication for nuclear power plants, the cost of the LEU will be much lower than that of the HEU from the special production line. The finalized design of the LEU core for the IHNI-I Prototype Facilities will surely have a broad domestic market vista, and it has paved way for the similar facilities dealings in the international market in future, as the products detoured many restrictive factors, and as uranium with enrichment of < 20 % is allowed to have free trade in the international nuclear market.

4.7.3 The IHNI-I Prototype Facilities is in compliance with the requisites given by the IAEA in descriptions of new reactors specially designed for BNCT

According to the IAEA's requisites, the IHNI-I Prototype Facilities give the first priority to its extreme safety. It means "a limited maximum excess reactivity during all normal and abnormal conditions, together with a safe self-limiting power excursion behavior for positive reactivity insertions greatly in excess of this maximum excess reactivity." As the facilities have adopted fully natural convection heat release design instead of the nuclear reactor coolant circulation system, and possibilities like loss-of-coolant accident (LOCA) or power failure induced LOCA can be ruled out. Even in case of fuel element failure, the following four radiation barriers can efficiently prevent the occurrence of radioactivity release accident:

1) The first radiation barrier Pellets with density of >95 % theoretical density value UO_2 will retain the fission gas in lattices without releasing to the outside of pellet.

2) The second radiation barrier Seal welding formed reliable Zr-4 cladding will strictly restrain fission products in the cladding.

3) The third radiation barrier The fully sealed reactor vessel.

4) The fourth radiation barrier Under the circumstance of the postulated accident occurrence i. e. when fission products overcome the above mentioned three barriers, the pool water of huge inventory will efficiently restrain the fractional radiation escape.

According to operation feedback of nine MNSRs in two hundred reactor operating years in China and the

other countries, the zero record of radiation leakage accident provides strong evidence to the extreme safety of the IHNI-Ⅰ Prototype Facilities.

The dual neutron beams design of the IHNI-Ⅰ Prototype Facilities is rare in BNCT reactors in the world. The finalized product of the IHNI-Ⅰ Prototype Facilities will enable to realize at least two hundred person-times of BNCT irradiation in a year, moreover, while administrating clinical irradiation to patients, the facilities can have in-situ and real-time blood boron concentration PGRNAA measurement. The installed thermal neutron beam and epithermal neutron beam are able to cope with all the experiments, tests and researches and as well as relevant clinical trials of all kinds of cancers having done by all the reactor neutron sources facilities in the world. The construction cost of the IHNI-Ⅰ Prototype Facilities is around RMB Forty Million (price of 2008), which is within the estimate done by the IAEA experts.

4.7.4 The new type of nuclear facilities for cancer treatment without special installation requirements to conventional hospitals

Conventional hospital or medical research centers equipped with advanced CT and MRI diagnosis setups or with clinical treatment facilities like γ-knife, X-knife and electron accelerator are all the qualified candidates for adding the IHNI series products. The therapeutical operation of the IHNI series products will be at the hands of physician-in-charge after being trained in a short period. There is no need to employ the professional reactor engineers, electric engineers, electronic engineers, chemical engineers, etc. for operation and maintenance of the IHNI series products. Those mechanical technicians, electric-electronic technicians employed by hospitals for service of diagnosis and treatment setups can concurrently undertake maintenance and routine inspection of the IHNI series products. No specified requirements to power, water and gas supply of the IHNI series products. With the exception of pipeline connection and cable wiring, hospitals do not need to have the large-scaled expansion project for matching with the facilities. In the routine application and operation of the IHNI series products, there will be no daily contaminated emission of radwastes. The decomposed hydrogen will be inspected in every week then discharged after being filtrated. The small amount of liquid of low radioactivity possibly produced by reactor water and pool water purification system and operation of facilities will be collected alone with other radwastes of low radioactivity for aged decay to disposable level, then regularly (in every six months or a year) sent to urban sanitation prevention station for further disposal.

The original framework design of IHNI project was conferred with invention patent certificate by China Intellectual Property Rights Bureau on October 4, 2006[36].

There is no doubt, the completion and operation of the IHNI-Ⅰ Prototype Facilities will fill up the notch of China's science and technology researches in the field of BNCT application, and build a hi-tech platform for our scientists in the efforts of catching up with new technology on binary targeting radiation therapy of cancer. As an optional hospital based neutron source, the IHNI-Ⅰ Prototype Facilities will make its possible contribution to BNCT application process toward to objective of therapeutical routinization.

References

[1] G L Locher. Biological effects and therapeutic possibilities of neutrons[J]. Am. J. Roentgenol, 1936, 36: 1-13.

[2] L E Farr, W H Sweet, et al. Neutron Capture Therapy with boron in the treatment of glioblastoma multiforme[J]. Am. J. Roentgenol, 1954, 71: 279-291.

[3] H Hatanaka. The Importance of Selective Treatment of Tumor [M]. 1986.

[4] D Gabel, R Moss. Preface, BNCT toward Clinical Trials of Glioma Treatment[M]. 1992.

[5] A Zonta. Proc. The 13th ICNCT, President's Address[C]. Florence, 2008.

[6] Y. Nakagawa. Clinical Practice in BNCT to the Brain, Current Status of BNCT[C]. IAEA-TECDOC-1223, 2001.

[7] H Hatanaka, et al. Clinical Experience of BNCT for Gliomas - A Comparison with Conventional Chemo-Immuno-Radiotherapy, BNCT for Tumors[M]. 1986, 360-362.

[8] H Hatanaka, et al. Clinical Experience of BNCT for Gliomas - A Comparison with Conventional Chemo-Immuno-Radiotherapy, BNCT for Tumors[M]. 1986, 362-363.

[9] W H Sweet. Dedication to the memory of professor Hiroshi Hatanaka[A]. Proc. The 6th ICNCT[C]. 1994.

[10] I Kato, et al. Effectiveness of BNCT for recurrent head and neck malignancies[J]. Applies Rad and Isotopes, 2004, 61:1069-1073.

[11] I Kato, et al. Effectiveness of BNCT for recurrent head and neck malignancies[J]. Applies Rad and Isotopes, 2004, 61:1069-1073.

[12] T Pinelli, et al. TaorMINA: from the first idea to the application to the human liver[A]. Research and Development in NCT[C]. Essen, Germany, 2002.

[13] M Ichihashi. BNCT for Malignant Melanoma [A]. invited lecture. Program of the 9th ICNCT[C]. Osaka, 2000.

[14] P R Menenez, et al. BNCT for Skin Melanoma in Extremities: Updated Argentine Clinical Results[A]. Proc. The 13th ICNCT [C]. Florence, 2008.

[15] E Binello, et al. In vitro analysis of ^{10}B uptake for NCT synovectomy [A]. Advances in NCT, Vol. II[C]. 1997, 609-613.

[16] E Binello, et al. BNC as an immunological tool[A]. Research and Development in NCT[C]. Essen: Proc. The 10th ICNCT, 2002.

[17] R G Fairchild. Boron Thermal/Epithermal NCT[A]. BNL-31402. Workshop on Radiobiology and Tumor Therapy with Heavy Particles, and IAEA Research Coordination Meeting Vil-

liger[C]. Apr. 27-29, 1982, 1-16
[18] H. R. Snyder, et al. Synthesis of dromatic boronic acids, aldehydo boronic acids and a boronic acidanalog of Tyrosina[J]. J. Am Chemsoc, 1958, 20: 835-838.
[19] A. H. Soloway, et al. Penetration of brain and tumor. VII. tumor-binding sulthydry boron compounds[J]. J. Med Chem. 1967;10:714.
[20] Wu G., et al. NCT of An EGF Receptor Positive Glioma Using Boronated Cetuocimab alone or in Combination with Boronphenylalanine [C]. Proc. The 12th ICNCT, Kagawa, 2006, 149-152.
[21] K. J. Riley. Collective Analysis of Clinical Outcomes: Globally Advantage BNCT[A]. Proc. 13th ICNCT[C]. Florence, 2008, 132.
[22] MIT Nucl. Reactor Lab. BNCT Facilities Fission Converter Beam (FCB) [EB/OL], http://web. mit. edu/url/www/bnct/facilities/FCB/fcb. html 2004-12-07
[23] R. F. Barth et al. BNCT for the Treatment of Glioblastomas and Extracranial Tumors: As Effective, More Effective or Less Effective than Photon Irradiation? [J]Radiotherapy and Oncology. 82 [2007]119-122
[24] I. Auterinen, et al. Reactor based BNCT facilities: current status and future prospects[A]. Proc. The 13th ICNCT[C]. Florence, 2008, 383.
[25] IAEA-TECDOC-1223. Current Status of NCT[C]. May 2001, 9-12
[26] O. K. Harling. Fission Reactor based epithermal neutron irradiation facilities for routine clinical application in BNCT—Hatanaka memorial lecture[A]. The 13th ICNCT[C]. Florence, 2008.
[27] Yongmao Z. The Miniature Neutron Source Reactor[A]. IAEA-TECDOC-384[C]. Vienna, 1986, 89-98.
[28] Li D., et al. MCDB Monte Carlo code with fast track technique and mesh tally matrix for BNCT[J]. Nuclear Science and Technology. 2007, 44(12). 1518-1525.
[29] Ke G. T., et al. The study of physics and thermal characteristics for IHNI[A]. Proc. The 13th ICNCT[C]. Florence, 2008, 474-477.
[30] Jiang X. B., et al. Neutron beam theoretic design and calculation of the IHNI-prototype facilities. Northwest Nuclear Technique Institute. Feb. 24, 2006
[31] Chen Y. Z., et al. Thermohydraulic Simulating Test of IHNI-Prototype Facilities. China Institute of Atomic Energy, October 2006
[32] Li Y. G., et al. The physics experimental study for IHNI[A]. Proc. The 13th of ICNCT[C]. Florence, 2008, 486-489.
[33] Zhang Y. Z., et al. Fuel Elements Performance Analysis of IHNI-Reactor. China Institute of Atomic Energy, July 2004
[34] Conclusions, technology and use of low power research reactor [A]. IAEA_TECDOC-384[C]. Vienna, 1986. 19-20.
[35] Liu Z., et al. The self-stabilization character analysis[J]. Nuclear Power Engineering, ISSN 0258-0926, August 2006, 36-38.
[36] The In-Hospital Neutron Irradiator [P]. Chinese patent: ZL021580987, 2006-10-04.

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