ACCELERATOR BASED NEUTRON SOURCE FOR THE NEUTRON CAPTURE THERAPY AT HOSPITAL

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Recently, the ever increasing interest in curing malignant tumors has been in using boron neutron capture therapy (BNCT). The idea of BNCT is simple and elegant. A tumor-seeking compound containing stable isotope ^{10}B is introduced into blood and given time to be accumulated in the tumor. The tumor is then irradiated with epithermal neutrons, which are captured by ^{10}B isotope. Capturing neutrons causes the boron nuclei to break apart, resulting in the emission of α-radiation and recoiling ^{7}Li nuclei. Both α-particles and lithium are high in energy but short in range, which means that they destroy the malignant cells in which boron is embedded without hurting the adjacent healthy cells.

In this paper, accelerator source of neutrons for the hospital-based boron neutron capture therapy is proposed and discussed. Kinematically collimated epithermal neutrons are produced via near-threshold $^{7}\mathrm{Li}(p,n)^{7}\mathrm{Be}$ reaction at proton energies of 1.883÷1.9 MeV. At proton energy of 2.5 MeV, the neutron beam is produced for fast neutron therapy and for BNCT usage after moderation. DC proton current of tens of milliampers allows to provide therapeutically useful beams with treatment times of tens of minutes. The basic components of the facility are: a hydrogen negative ion source, an electrostatic tandem accelerator with vacuum insulation, a charge-exchange target, a sectioned rectifier, and a thin lithium neutron production target on the surface of tungsten disk cooled by liquid metal heat carrier. Design features of facility components are discussed.

Project № 1484 "Accelerator based neutron source for the neutron-capture and fast neutron therapy" was supported by International Science and Technology Center. Work on the project is accomplished in accordance with the Agreement now. 2.5 MeV tandem accelerator is under construction. A set of experiments on study of high voltage durability of vacuum gap with large square electrodes is realized on available 1 MeV tandem-accelerator. A 5 mA 25 keV dc H^{-} ion beam with required emittance was obtained. The first specimen of neutron production target with liquid metal heat-carrier was made. In this paper, current results are presented.

Investigations of elements of the whole accelerator-based neutron source are expected to be carried out by the close of the project (May 2002). As a result of the project, a conception of accelerator based neutron source for the neutron-capture and fast neutron therapy at hospital appropriate for commercial use will be presented.

Then the work is assumed to be continued on construction an experimental neutron source basing on the tandem accelerator produced, and usage of neutron beam will be started. The extended project is proposed. Financial support needs prolongation.

Introduction

The concept of neutron capture therapy was introduced in 1936 [1], four years after the discovery of neutrons. The idea of boron neutron capture therapy (BNCT) is simple and elegant. A tumor-seeking compound containing stable isotope ^{10}B is introduced into blood and given time to be accumulated in the tumor. The tumor is then irradiated with epithermal neutrons, which are captured by ^{10}B isotope. Capturing neutrons causes the boron nuclei to break apart, resulting in the emission of α-radiation and recoiling ^{7}Li nuclei. Both α-particles and lithium are high in energy but short in range and high relative biological effectiveness, which means that they destroy the malignant cells in which boron is embedded without hurting the adjacent healthy cells.

Therefore, BNCT will make it possible to destroy selectively tumor cells at higher ^{10}B concentration than in normal ones. In 1951 it was first demonstrated that certain boron compounds would allow higher boron concentration in human brain tumor cells in comparison with normal brain tissue.

During 1950-60 at the Brookhaven Medical Research Reactor and Massachusetts Institute of Technology Research Reactor first clinical trials were conducted. Unfortunately, these trials failed to show any evidence of therapeutic efficacy of the method. Later, it became clear that major reason for their lack of success was low ^{10}B concentration in tumor. Elastic scattering of neutrons and $^{14}N(n,p)^{14}C$ and $^{1}H(n,\gamma)^{2}H$ nuclear reactions resulting in recoil nuclei and γ-rays are possible besides nuclear reactions related to neutron capture by boron nuclei at neutron radiation. Although the neutron capture cross-sections for hydrogen and nitrogen are several orders of magnitude lower then those for ^{10}B, hydrogen and nitrogen are present in such high concentrations that their neutron capture "background" contributed significantly to the total absorbed dose.

However, Dr. Hatanaka, a Japanese neurosurgeon who received training with Dr. Sweet at Massachusetts General Hospital at Harvard University, returned to Japan in 1968 and continued to develop the technique. He used BSH ($Na_2{}^{10}B_{12}H_{11}SH$, sodium borocaptate) that concentrated selectively in tumor. In this way they began to perform open skull irradiations of brain tumors using thermal neutron beams (energy < 0.025 eV) to reach the target without losing significant amounts of energy. In this way several groups worked at different reactors and treated over 200 patients with some encouraging results.

At the same time, great progress was achieved in synthesis of boron containing compounds enriched in the ^{10}B isotope. This compound introduced into patient blood produce in a tumor cell the ^{10}B isotope concentration up to 40 μg/g that is three times larger than that in a normal tissue cell. This enables selective destruction of malignant tumors.

In 1994 BNCT irradiations were re-initiated in the US. Glioblastoma multiforme patients have been treated at Massachusetts Institute of Technology Research Reactor and Brookhaven Medical Research Reactor. In 1997, clinical trials began in Petten, the Netherlands, as a result of joint effort of the European Community. In June 1999 clinical trials began in Finland. Today England, Australia, Argentina, Italy, Germany, Sweden, Slovakia, Russia have been settled down to the trials. Extremely encouraging results have been obtained with the treatment of melanoma. Studies currently underway in biological models for other tumors and for non-oncological applications such as rheumatoid arthritis are encouraging and suggest the possibility of new applications of BNCT in the future.

The clinical trials at neutron reactors showed BNCT to be quite perspective. This technique is not available for wide use at hospitals, because there are active discussions of issues on development and construction of neutron source based on a compact and reasonably priced accelerator.

At present, the boron neutron capture therapy (BNCT) is very attractive method for curing malignant tumors, especially therapy for glioblastoma multiforme and melanoma. Glioblastoma multiforme afflicts approximately one of 20,000 peoples every year. The disease is always fatal, usually within six months of onset. Surgery and conventional radiation therapies may prolong life for as much as a year but do not stop the spread of tumors throughout the brain. Experiments involving BNCT have tantalized researchers with hints that successful treatment of glioblastoma multiforme is possible.

Neutron source proposed

In 1998, an accelerator based neutron source for the neutron-capture and fast neutron therapy at hospital is proposed [2]. Negative hydrogen ion beam is injected into electrostatic tandem accelerator with vacuum isolation. After charge-exchange of negative hydrogen ion in proton inside charge-exchange tube in the center of high voltage electrode, a proton beam is formed at the outlet of the tandem, which is accelerated to double voltage of high voltage electrode. Neutron generation is proposed to be carried out by dropping an intensive proton beam onto lithium target using $^7\mathrm{Li}(p,n)^7\mathrm{Be}$ threshold reaction.

In ordinary mode, at proton energy of 2.5 MeV, the neutron source produces neutron beam with maximum energy board of 790 keV appropriate for neutron-capture therapy after moderation. Usually, a patient is placed at 0.5 meter or farther from the target behind the shield.

The most efficient operating mode of facility is at proton energy of 1.9 MeV that is 20 keV higher the threshold of the $^{7}\text{Li}(p,n)^{7}\text{Be}$ reaction. In this mode, neutron beam is provided kinematically collimated with good forward direction and average energy of 30 keV, directly applicable for boron neutron-capture therapy. Due to very fast increase in cross-section, which is the feature of this reaction, and pronounced forward direction, the forward yield of 30 keV mean energy neutrons is only one order lower than the full neutron flux in forward direction generated at 2.5 MeV proton energy and possessing wide energy spectrum. In this case, patient may be placed at 10 cm distance from the target, that increase considerably the neutron flux density or decrease the current requirements.

Creation of accelerator with proton beam intensity of tens milliamperes will decrease exposure time for necessary therapeutic dose to tens minutes. The most attractive and elegant operating mode in the near-threshold area requires high monochromaticity and energy stability of the proton beam. This makes use of widely discussed type of high frequency accelerator RFQ impossible, and the requirement can be met only for the case of electrostatic accelerator. Characteristic feature of the neutron source is use of tandem accelerator with vacuum insulation instead of direct accelerator. The tandem accelerator with vacuum insulation also provides the higher reliability compared to tandem based on accelerating columns with ceramic insulation and proton accelerator at high intensity of beam.

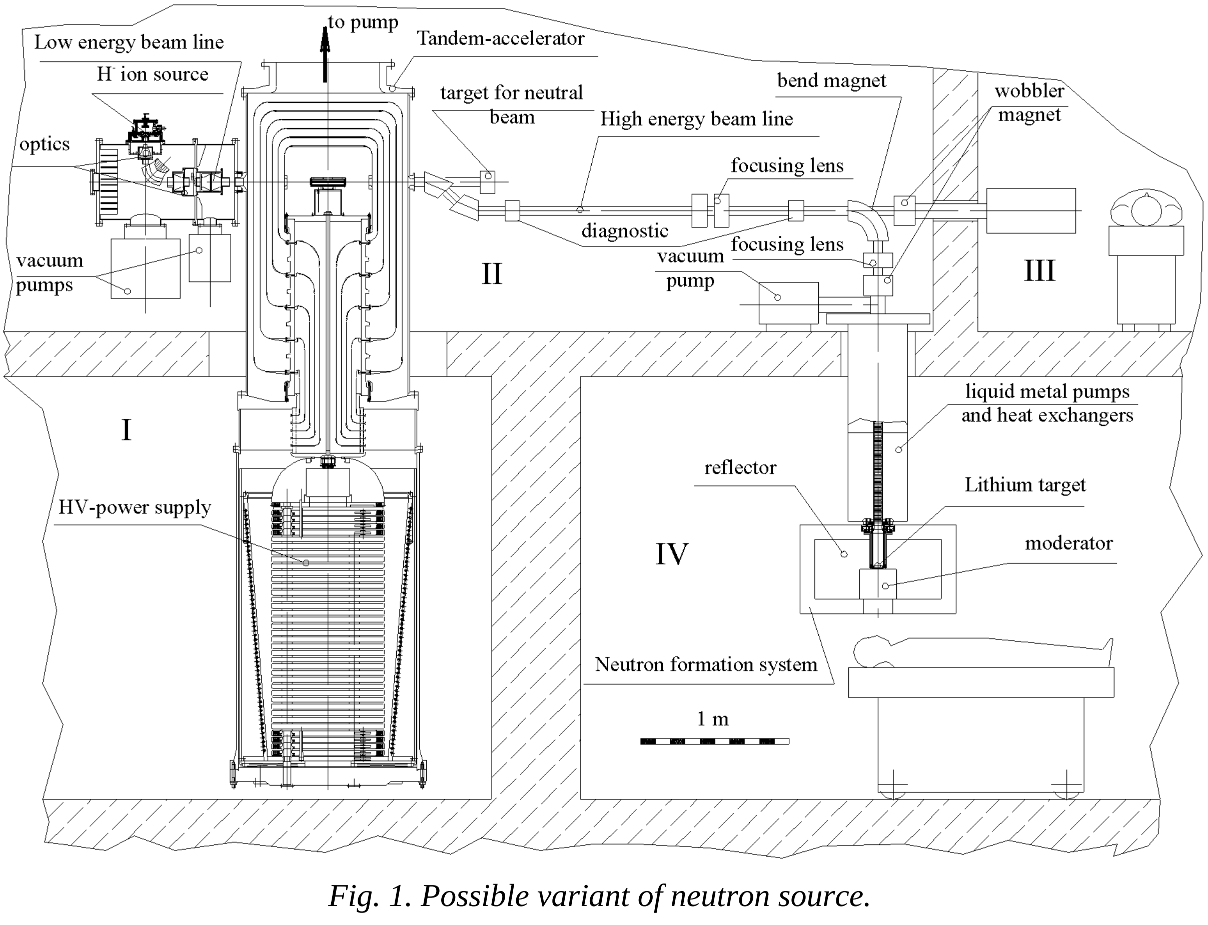

Fig. 1. Possible variant of neutron source.

Experience

Investigation and design work was carried out on all components of the proposed neutron source, and rich experience was stored.

A surface plasma technique for negative ion generation was proposed and realized in Budker Institute of Nuclear Physics (BINP), basic modifications of surface plasma sources operating at most of the large proton accelerators all over the world were developed.

At BINP original electrostatic vacuum insulation tandem accelerator was developed. Specifics of geometry of accelerating electrodes and tandem optics allow to reach maximum reliability. It was tested on 1 MeV prototype which was used as an injector in a synchrotron.

An industrial ELV-type electron accelerator was developed at BINP and widely used for technological aims in Russia and abroad in Japan, China, Poland, Korea, Germany, etc. It is proposed to use a sectional rectifier (a part of the industrial ELV-type accelerator) as a powerful high voltage source. Reliability of high voltage ELV rectifier was confirmed by many years of operation of such accelerators in industry.

Cylindrical lenses with solid or liquid lithium and liquid metal targets (lithium, gallium, plumbum) applied in high energy physics for secondary particles beam generation were produced.

Great experience have been accumulated in experimental and theoretical investigations of spatial-energy distribution of neutrons produced in $^7\mathrm{Li}(p,n)^7\mathrm{Be}$ reaction and neutronic calculations of spatial distribution of the absorbed doze at Institute of Physics and Power Engineering, Obninsk (IPPE). New fundamental knowledge on nature of neutrons biological effect was obtained at IPPE in collaboration with Medical Radiological Research Center, Obninsk, physical and dozimetrical characteristics of the neutron beams of reactor and accelerators were studied, and basing on the results obtained the curing of malignant tumors of about 350 patients using fast neutron therapy technique.

Current results

Realization of the Project is one of the main objectives of the Inter-Department Program "Development of progressive techniques of cure for tumors using of neutron and neutron capture therapy on base of reactors and accelerators". The Program was accepted by Presidium of Russian Academy of Medical Sciences on May 27, 1998.

Development of conception project of accelerator based neutron source for the neutron-capture and fast neutron therapy at hospital appropriate for commercial use was supported by International Sciences and Technology Center (Project № 1484) on October 28, 1999. During the project realization period (May 1, 2000 — April 30, 2002) experimental modelling and investigation of the most important elements of the whole facility are expected to be carried out, namely, i) construction of the tandem accelerator; ii) design of charge-exchange target; iii) construction of quasi-stationary prototype of ion H^- source and study of its operation. A computer simulation of transport of a beam in electric and magnetic fields taking into account space charge is expected to be carried out, and optimal geometry of focusing optics is to be chosen. Proton energy stability is expected to be provided with accuracy of 0.1 %. A lithium target is to be produced, and a thermal mode of its operation is to be analyzed at high power. On this base, a conception project of accelerator based neutron source for the neutron-capture and fast neutron therapy at hospital appropriate for commercial use will be presented. Work is accomplished in accordance with the Agreement now.

At the test desk available, dc H^- ion beam of 5 mA was obtained at the model of negative ion source with Penning geometry electrodes (Fig. 2). Preliminary measurements of dc H^- ion beam emittance were carried out [3]. The value obtained for the normalized emittance 0.3 π mm mrad meets the requirements.

Development of tandem surface plasma source of H^- ions was continued to obtain dc 40 mA H^- ion beam with small emittance, high gas efficiency and low attendant electron current. Design drawings were finished for plasma generator, the first stage of the source.

Fig. 2. Negative ion source with Penning geometry electrodes.

Computer simulation of transport of a dense H^- beam from the source to the charge-exchange target in electric and magnetic fields taking account of space charge and emittance of the beam is carried out. Focusing optic system is to be optimizes for transporting negative hydrogen ion beam without significant increase of the beam emittance. Minimization of effect of spatial charge compensation is desirable. It was determined that transporting may be provided by both electrostatic and magnetic lenses. A beam was conducted through a strong lens at the tandem entrance. A "soft" introduction into tandem was proposed which is realized by more fluent increase of electric field for Pierce geometry of electrodes.

An analysis of application of different charge-exchange target has been made [4]. A gas target was chosen for use. The charge-exchange target is a pipe with an inner hole of 6 - 15 mm diameter and ~ 400 mm length. In the center of the pipe, gas leaks at a rate providing the efficient density of the target 3×10^{16} cm^{-2} required for the 99 % charge-exchange. The next gas charge-exchange targets were assigned to be used: i) argon gas target with outer pumping; ii) argon gas target with recycling turbo-molecular pumping inside the high voltage electrode; iii) gas target with gas freezing on the nitrogen trap inside the high voltage electrode.

A set of experiments on study of high voltage durability of vacuum gap with large square electrodes is carried out at 1 MeV tandem-accelerator (Fig. 3). The results of first previous experiments showed that breakdowns of vacuum gaps took place at electrostatic intensity of higher than 40 kV/cm; frequency of the breakdowns was about ones an hour at 70 kV/cm; and storage energy of 10 J released at breakdown did not result in detraining of 4.5 cm vacuum gap. Experiments at storage energy of 20 J, H^- ion pulse beam injection experiments, and charge-exchange target experiments, are planned.

Fig. 3. 1 MeV tandem-accelerator

Fig. 4. High voltage power supply tank.

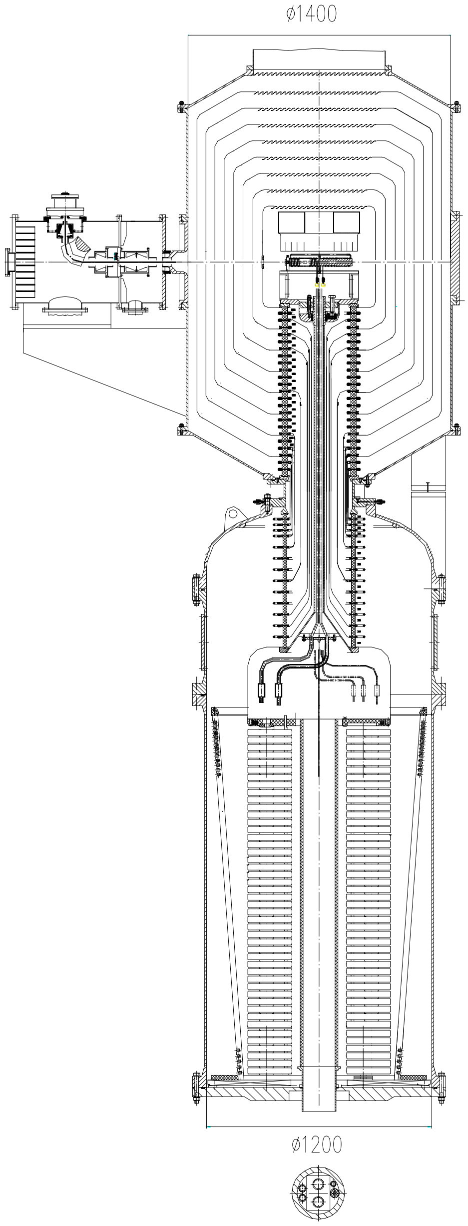

Fig. 5. 2.5 MeV tandem accelerator.

2.5 MeV tandem accelerator is under construction now (Fig. 5) [5]. The tank diameter was determined to be 1400 mm, high voltage electrode diameter — 600 mm. Electrostatic intensity at accelerating gap is 32 kV/cm. The high voltage electrode is surrounded by system of different potential shields providing homogeneous distribution of potential and preventing full voltage effects. Energy storage in vacuum gap is lower then 20 J. It is determined that overvoltages on the rest vacuum gaps and insulators are permissible at ELV breakdown at full power or breakdown of one of vacuum gap. Therefore, there is no need to mount a compensating capacity divider from high voltage condensers with low reliability, that increases significantly the tandem's reliability. High voltage input insulator through which the potential is transferred into the vacuum cavity from the tank filled with SF_6 gas with the transformer of the ELV-type industrial accelerator being the powerful source of high voltage is under construction. Electrodes and glass insulators were manufactured for vacuum part of input insulator. Three coaxial insulating tubes (ceramics, polyethylene) 12, 20, and 50 mm diameter are placed in the center of the rectifier to provide liquid nitrogen supply into the pump that is under high voltage. It was determined that heat up to 5 kW can be taken from high voltage electrode using transformer oil. A 3-layer protected bunker with necessary infrastructure and supporting rooms was found for construction of accelerator. Rectifying sections mounting is in progress (Fig. 4).

The first specimen of neutron production target with liquid metal heat-carrier was made (Fig. 6) [6]. Steel disk 50 mm in diameter, 3 mm thick, is a proton beam absorber. It is cooled by liquid metal flowing in opposite directions in neighboring channels. A molybdenum plate 0.2 mm thick is diffusely welded on the disk, a proton beam is directed on it. The plate is covered with a layer of lithium several micrometers thick.

A system is developed for pumping liquid metal heat-carrier including pump, liquid metal circuit with switching systems, heat exchanger, metal velocimeter and pressure distribution measuring device (Fig. 6). A test desk for testing water pinion pump in a liquid

Fig. 6. Neutron production target before assembling (left) and liquid metal heat-carrier pump with heat-exchanger (right).

metal pumping mode was made. A magnetic clutch was manufactured to provide noncontact transmission of angular momentum to mechanic pump in a liquid metal volume of vacuumed circuit filled with liquid metal. A prototype of heat-exchanger with water cooling was manufactured designed for several tens kilowatts power removal.

A vacuum device for developing techniques and choice of modes of lithium evaporation was constructed. First experiments were carried out on evaporation of lithium layer on ceramics plate.

The second variant of neutron production target development is using thin jet liquid lithium target placed in the center of moderator-reflector of neutrons and partial drop of energy by proton beam of 2.5 MeV up to the threshold energy of 1.881 MeV. To provide this energy drop of 0.6 MeV by protons, the target thickness should be 100 μm, so that less than 30 % of the beam full power will be released in the target. The proton beam is focused into less than 1 cm on the target 100 μm thick and 1 cm wide, flowing from a narrow nozzle with a velocity of ≈ 10 m c^{-1}. After passing through the target, a horizontal proton beam of 1.9 MeV will have an angle of multi-scattering 40 mrad and energy dispersion of ± 10 %. Short permanent magnet with the field of 1 T placed in the output of the moderator turns the beam 30° up and spreads it over the distant proton absorber surface of the large square with a simple water-cooling system. Two neutron beams come out of the moderator in the opposite directions perpendicularly to the proton beam and may be used independently in two therapeutic ports. A device with 15 mm width and 100 μm nozzle was constructed. Formation of water stream flowing from a nozzle with velocity of 15 m c^{-1}. Study of thin lithium stream interaction with powerful proton beam requires both hydrodynamical simulation and preliminary experiments.

Spatial-energy distribution of source neutrons and attendant γ, and spatial distribution of the absorbed doze and optimization of physical shield are now under calculating.

Studies on accumulation of boron introduced have been started in Obninsk, and radiation with horizontal beam of BR-10 reactor has been started.

Accompanying ideas

As neutrons with energies of $0.5 \div 1.5$ MeV are optimal for fast neutron therapy, the optimal neutron source is accepted to be realized by drop of 1 mA 2 MeV deuterium beam onto beryllium target. Construction of such source is supposed to be simpler than one for BNCT.

2 MeV proton/deuterium accelerator with appropriate targets is considered as a neutron source for nitrogen detection, or γ-source for nitrogen detection, or an intense compact positron source.

Rheumatoid arthritis, which affects between 1-3 % of adults, is characterized by inflammation of the synovial membrane in articular joints. Rheumatoid arthritis is painful, and if left unchecked, will lead to destruction of articular cartilage and to joint disability. The disease can be treated with drugs but about 10 % of patients remain unresponsive to drug therapy, and removal or ablation of the synovial membrane, termed synovectomy, is necessary. Synovectomy can be accomplished surgically or by the intra-articular injection of β-emitting particles. The latter method is not used in some countries because of concerns regarding leakage of the radionuclide from the joint. An alternative approach is boron neutron capture synovectomy (BNCS). In BNCS a stable ^{10}B labeled compound is injected directly into the joint, and the joint is irradiated with an epithermal neutron beam.

Conclusion

Accelerator based neutron source for boron neutron capture therapy for cancer is under realization now. Investigations of elements of the whole accelerator-based neutron source are expected to be carried out by the close of the project (May 2002). As a result of the project, a conception of accelerator based neutron source for the neutron-capture and fast neutron therapy at hospital appropriate for commercial use will be presented.

Then the work is assumed to be continued on construction an experimental neutron source basing on the 2.5 MeV tandem accelerator produced, and usage of neutron beam will be started. The extended project is proposed. Financial support needs prolongation.

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