Perspectives of boron-neutron capture therapy of malignant brain tumors

V. V. Kanygin, A. I. Kichigin, A. L. Krivoshapkin, and S. Yu. Taskaev

Citation: AIP Conference Proceedings **1882**, 020030 (2017); doi: 10.1063/1.5001609
View online: http://dx.doi.org/10.1063/1.5001609
View Table of Contents: http://aip.scitation.org/toc/apc/1882/1
Published by the American Institute of Physics

Perspectives of Boron-Neutron Capture Therapy of Malignant Brain Tumors

V. V. Kanygin[1,2,3,4,a)], A. I. Kichigin[1,2,5,b)], A. L. Krivoshapkin[1,2,3,6,c)], and S. Yu. Taskaev[1,2,d)]

[1] *Burker Institute of Nuclear Physics, Novosibirsk, 630090 Russia*
[2] *Novosibirsk State University, Novosibirsk, 630090 Russia*
[3] *Novosibirsk State Medical University of Minzdrav of Russia, Novosibirsk, 630005 Russia*
[4] *"Russian Railways" Open Joint Stock Company Railway Clinical Hospital on the Station Novosibirsk-Glavnyi, Novosibirsk, 630003 Russia*
[5] *Irkutsk State Medical University, Ministry of Health Care, Irkutsk, 664003 Russia*
[6] *Department of Neurosurgery, European Medical Center, Moscow, 129110 Russia*

[a)] Corresponding author: kanigin@mail.ru
[b)] sam@211.ru
[c)] alkr01@yandex.ru
[d)] taskaev@inp.nsk.su

Abstract. Boron neutron capture therapy (BNCT) is characterized by a selective effect directly on the cells of malignant tumors. The carried out research showed the perspective of the given kind of therapy concerning malignant tumors of the brain. However, the introduction of BNCT into clinical practice is hampered by the lack of a single protocol for the treatment of patients and the difficulty in using nuclear reactors to produce a neutron beam. This problem can be solved by using a compact accelerator as a source of neutrons, with the possibility of installation in a medical institution. Such a neutron accelerator for BNCT was developed at Budker Institute of Nuclear Physics, Novosibirsk. A neutron beam was obtained on this accelerator, which fully complies with the requirements of BNCT, as confirmed by studies on cell cultures and experiments with laboratory animals. The conducted experiments showed the relative safety of the method with the absence of negative effects on cell cultures and living organisms, and also confirmed the effectiveness of BNCT for malignant brain tumors.

INTRODUCTION

The technique of neutron capture therapy (NCT) designed for selective targeting of radiation of heavy charged particles with high energy on the tumor cells combines the principles of target organ used in the chemotherapy along with the anatomical localization principles of conventional radiotherapy. Most studies of NCT are conducted using compounds ^{10}B (BNCT) because other isotopes are actually unsuitable to be used for therapeutic purposes. The principle of BNCT is based on the capture reaction of isotope ^{10}B of thermal neutron and the creation of isotope ^{11}B which is extremely unstable and breaks into an alpha-particle and lithium ion the path length of whom varies from 5 to 9 microns that leads to the DNA's damage. DNA's repair requires a huge amount of energy from the cells, which often leads to their slow death [1]. Thus, if ^{10}B is accumulated by the tumor cells selectively and radiation by neutrons is carried out these cells die soon.

Because the affecting ability of thermal neutrons is much lower than the destructive power of the products of the boron neutron capture reaction the creation of a significant gradient between the concentrations of ^{10}B in the tumor and surrounding tissues ensures the maximum damage to malignant cells while minimizing damage to healthy tissue. The application of the BNCT in oncology is based on it. Scientific research in this direction is carried out intensively in many countries of the world (Japan, EU, the USA, Argentina, Taiwan, etc.). At the present time several thousands

Physics of Cancer: Interdisciplinary Problems and Clinical Applications
AIP Conf. Proc. 1882, 020030-1–020030-10; doi: 10.1063/1.5001609
Published by AIP Publishing. 978-0-7354-1562-1/$30.00

of patients have completed successfully the procedure of NCT on the basis of specialized or rebuilt nuclear reactors. Clinical studies have shown that it is possible to cure many oncological diseases using the method of neutron capture therapy (NCT). Nowadays, it is used for the treatment of various forms of gliomas, melanomas, sarcomas, metastatic cancer and metastatic lesions [2].

Malignant gliomas are the most common tumors among the adult population. This type of tumor includes a wide variety of types of tumors that differ by their levels of cell differentiation and malignancy. The accurate and effective destruction of the cells of malignant gliomas using the method of NCT is a more complex task due to the presence of additional blood-brain barrier and high infiltrative nature of glioma cells and their molecular heterogeneity.

Glioblastoma is the most common and malignant tumor of the central nervous system of adults (60% of all primary tumors). Usually patients live just about 1 year after the symptoms were diagnosed [3]. This type of tumor may occur primarily or as a result of the transformation of the fibrillary astrocytoma (II grade of malignancy according to the World Health Organization's classification) or anaplastic astrocytomas (III grade of malignancy according to the World Health Organization's classification) [4]. The primary glioblastoma occurs mostly among the people over 50 years old (60%).

As a rule, it is characterized by short history of the disease. Probably, it may be connected with the amplification of the EGFR's gene that is found in the 40% of all cases of primary glioblastomas and also depends on the age of the patients as it does not occur among patients younger than 35 years practically [5]. Secondary glioblastoma often develops in the young age among individuals younger than 45 years. The transformation of the tumor into glioblastoma may last from 1 to 10 years (on the average, 4–5 years). The research showed that mutation of the p53 gene is a main event that plays a role in the development of secondary glioblastomas. The mutation is detected in 2/3 of tumors preceding secondary glioblastoma, but rarely in primary one (less than 30% of cases) [6].

The malignant tumors of the glial tissue are characterized by a powerful invasive phenotype, the lack of clear boundaries of the tumor's spreading and the ability to relapse after surgical removal that leads to difficulties in its treatment. The greatest prognostic importance in the treatment of malignant brain tumors has the volume of residual tumor after surgical treatment.

Other factors influencing the treatment prognosis are the age of patients, their functional condition before surgery, the presence of comorbidity, histologic characteristics of the tumor, localization of tumor, etc.

BORON DELIVERY AGENTS

One of the first boron compounds for BNCT is sodium borocaptate (BSH) that is composed of 12 boron atoms. Its use as an agent for BNCT allows achieving the required therapeutic concentration of the isotope ^{10}B in tumor cells more likely. After the infusion of BSH is made ^{10}B is located in the tumor cells of the brain in concentrations similar to concentrations in the blood but almost not present in the healthy cells of the central nervous system and the ratio of the concentration of the tumor/healthy tissue is appropriate for making therapy. BSH was investigated for its application in the treatment of gliomas of high malignancy grade. It was suggested to consider the possibility of BSH transport from the blood into the tumor cells due to changes in blood-brain barrier. According to this hypothesis, the medicine is captured by tumor cells during the contact with them and can be detected in the cytoplasm and the nuclei of glioma cells [7].

Another boron compound for BNCT is 4-Borono-L-phenylalanine (BPA) that contains one boron atom only in its structure. The idea of using BPA as the delivery agent is based on its metabolic activity. A number of studies showed that BPA is accumulated in various types of malignant cells [7–9].

The main difficulty in the development of delivery agents of the boron into the tumor is to achieve their tumor's target. One of the ways to improve the selectivity of boron's delivery agents is to affect the blood-brain barrier. For example, the delivery of BPA to the tumor may be improved by the simultaneous use of the medicine "Cereport" (Cereport) an analogue of bradykinin that has pharmacological opening of the blood brain barrier [10]. A significant increase of BPA absorption in the model of C6 glioma with the prior use of L-dihydroxyphenylalanine (L-DOPA) was observed [11]. The injection of L-phenylalanine prior to the injection of BPA may be one of the ways of enhancing its selectivity and leads to a reduction of BPA's accumulation in normal brain tissues compared to tumor tissues [12]. Also, the increasing accumulation of BSH in the brain tumor is marked by simultaneous injection of buthioninesulfoximine (buthioninesulfoximine-BSO) [13].

It is believed that a significant increase of the gradient of boron's concentration on the border of the tumor-healthy tissue can be achieved with new tumorectomy remedies having a higher selectivity than the current ones.

Thereby, the feasibility and potential of targeted medicine delivery using nanotubes made of boron nitride, boron amino acid-conjugated antibodies to receptor of epidermal growth factor EGFR and the growth factor EGF, monoclonal antibodies, liposomes and immunoliposome, in particular VEGF-immunoliposome is researched in actively nowadays [14].

The liposomal method of active substance delivery has special perspective in terms of creating medications to treat cancer. The potential benefits of liposome use can be conceived as their high cell-penetrating ability [15]. As a result, it is possible to create high concentrations of active ingredients in a very small volume. The inclusion of the active ingredients into the liposomes isolates them from contact with the biological tissues, thereby reducing the toxic load on the body and the risk of biodegradation of included substances. Liposomes are able to include both hydrophilic and hydrophobic and amphiphilic substances which can be used as carriers of various boron-containing compounds [16]. Encapsulation of boron-containing substances into liposomes can improve the effectiveness of treatment and reduce the standard dose of drugs, due to which the toxicity of therapy, as well as its cost, decreases. This is due to the fact that liposomes have the property of "passive targeting". The phenomenon of passive targeting shows itself in the fact that liposomes come from the bloodstream primarily through fenestrated capillary walls, and malignant tumors are one of the causes of fenestration of vessels. Thanks to the "passive targeting" the accumulation of liposomal formulations takes place near the tumor [17]. One of the requirements for the success of BNCT is the intracellular delivery of 10B. Liposomes can penetrate well into the cells only together with the contained substances. In the bloodstream liposomes are quickly eaten by macrophages. Polyethylene glycol, which is included in the structure of liposomes, limits their recognition and capture of cells of the reticuloendothelial system, resulting in the accumulation of liposomes in tumor tissue due to passive targeting effect. Furthermore, this type of support may be used in the treatment of brain tumors, since boron liposome formulations allow transport through the blood brain barrier [18].

EXPERIMENTAL RESEARCH

The first experiments with BSH as a delivery agent of boron for BNCT were held in 1967 with mice (C3H) with implanted hypodermic tumor of cell line of murine ependymoblastoma [19]. Also the experiments of combining BNCT with remote radiation therapy for rats implanted with F98 glioma were held [20]. All the animals from the groups that underwent BCT showed an increase in life expectancy compared with the control group of rats that received BPA and BSH without irradiation. Matalka and others used the brain tumor of rats as a model using intracerebral implanted cells from human melanoma. The authors came to the conclusion that the use of BPA in BNCT is effective when rodents have an internal melanoma [21]. Investigations of biodistribution and the possibility of carrying out of BNCT for glial tumors were conducted by J.A. Coderre et al. in 1992 [22]. The experiments demonstrated a longer life expectancy of rats implanted with 9L intracerebral gliosarcoma which were injected with BPA and underwent BNCT in Brookhaven's medical research reactor (BMRR) compared to the control group.

The neutron beams at reactors have been used for clinical investigations in Finland (FIR1), the USA (MIT-FCB), the Netherlands (HFR), Sweden (R2-0), the Czech Republic (LVR-15) and Japan (JRR-4 and KUR).

One of the first clinical investigations for treatment of gliomas was carried out for 28 patients in the US' Brookhavens reactor in 1951–1953 where borax and sodium pentaborate were used as the agent ^{10}B. The average survival rate after irradiation with borax was 97 days, 147 days after using pentaborate intravenously and 96 days after the medicine was injected by intracarotid way [23, 24].

Between 1959 and 1961 there were 18 patients with gliomas who had medical treatments for a medical research in Brookhaven BMRR reactor. The average survival was 3 months [25]. There were 17 patients with brain tumors who underwent irradiation on the reactor of Massachusetts Institute of technology where the median of survival was equal to 5.7 months. The obtained results differed just a little from the survival results of similar groups of patients treated with standard methods. These results could be connected with non-selective and insufficient accumulation of ^{10}B in the tumor and inadequate characteristics of the beam.

In 1968 Hatanaka continued investigations in Japan using BSH and low energy neutrons as agent ^{10}B. Patients were irradiated immediately after surgical removal of the tumor. As a result of treatment the 5-year's survival rate of patients with gliomas of III and IV grades was 58% [26]. In the scientific work by Y. Nakagawa the application of BNCT in the treatment of 149 patients with glioblastomas allowed achieving the life expectancy of 1.8 years.

The emergence of reactor epithermal neutron sources in the early 1990s created conditions to start controlled clinical investigations in the Brookhaven national laboratory [27] and in Massachusetts Institute of technology [28]

in 1994, in Petten [29] in 1996. The similar laboratories were soon established in Finland [30], Sweden [31], the Czech Republic [32], Japan [33], Argentina [34] and Taiwan [35].

In Russia NCT was conducted in different centers. In Moscow (MIFI in collaboration with Institute of Biophysics and Cancer center) the research was done on dogs. Gadolinium was used as the neutron capture agent with purpose of treatment of melanoma of the mucosa of the oral cavity [36]. ^{157}Gd being an alternative of ^{10}B using BNCT has almost the maximum capture cross section among the stable isotopes: 254 000 barn has gadolinium while boron has just 3840 barn. The result of neutron capture reaction of ^{157}Gd (n, γ) ^{158}Gd is the emission of γ-quant with energy of 7.8 MeV accompanied by the emission of auger electrons with energy of $\leq$41 Kev. It determines the characteristics of tissue damage during possible use of ^{157}Gd as agent for NCT not only close to the gadolinium atom but considering the high penetrating power of γ-rays of the specified energy in the distance.

In Medical Radiological Research Center and Joint Stock Company "State Scientific Centre of the Russian Federation—Institute for Physics and Power Engineering" in Obninsk the therapy with fast neutrons was conducted at the reactor BR-10 [37]. In Snezhinsk according with Chelyabinsk Cancer center the therapy with fast neutrons was conducted at a neutron generator with a deuterium ion beam with energy of 250 KeV and the tritium target [38]. In Tomsk the therapy with fast neutrons was conducted at the cyclotron with a beam of deuterium ions with energy of 13 MeV and a beryllium target [39].

The international experience of using the reactors for production of epithermal neutrons revealed a number of problems connected with organizational aspects, ensuring the safety of research, restrictions on the use of the reactor for medical purposes and, the most significant, the wrong parameters of the beam for therapy due to the presence of gamma-component and fast neutrons. The majority of nuclear reactors used for BNCT had to be closed by various reasons; however, it was due to political and economic causes but not because of the clinical results of the method.

Accelerators of charged particles can be used as safe relatively inexpensive compact sources of neutrons with relevant neutron-generating targets and systems for beam formation. Accelerators allow getting the best quality therapeutic neutron beam and also to relatively simply and quickly change the spectrum and the neutron flux variation of energy and beam current of charged particles and target replacement.

Moreover, accelerators of neutrons can be placed in the clinic [40]. Nowadays there are several project solutions of accelerators for producing neutrons in the world. At the cyclotron HM-30 30 MeV proton beam was received with a projected current of 1.1 mA at the Institute of reactor research at the University of Kyoto (Japan) on [41]. At the University of Tsukuba together with Mitsubishi Heavy Industry Co. and KEK in Tokai (Japan) the project of 8 MeV 10 mA linac with beryllium target is conducted [42]. At the national cancer center in Tokyo a 2.5 MeV 20 mA linac is developed (Hitachi, Japan and Acc Sys Technology, Inc., California, USA) with lithium neutron-generating target [43]. One more Japanese project is developing at Nagoya University of [44]. The company Ion Beam Application (IBA, Belgium) is developing a 1.9 to 2.8 MeV 15 mA Dynamitron [45]. In the future there will be developed new projects of accelerators as a vector of development of BNCT in the field of getting of neutrons beam shifted towards compact units-based accelerators.

Taking into account the current trends in the community of neutron capture therapy at the Institute of nuclear physics of Siberian Branch of Russian Academy of Science (Novosibirsk) a compact source of epithermal neutrons based on accelerator was built that can be placed in the clinic. It is based on the accelerator-tandem with vacuum insulation and a lithium target. A stationary proton beam with energy of 2 MeV and current up to 5 mA was generated on the plant [46]. A series of studies was performed *in vitro* and *in vivo* in different periods.

CURRENT STATUS OF RESEARCH ON THE SOURCE OF NEUTRONS INP SB RAS

Evaluation of the effect of epithermal neutrons on viability of tumor and normal cells exposed to various irradiation doses. The irradiation dose of 1.9 Sv doubled the content of dead cells in the samples (from 16 to 30%). Further increasing the radiation dose from 1.9 to 4.1 Sv even more increased the content of dead cell (from 13 to 38%). The absence of apoptosis activation in irradiated cells and the dose-dependence of the biological effect of neutron radiation attest to the necrotic mechanism of the death among the tumor cells. This study showed that irradiation of human glioblastoma U87 cells with epithermal neutrons promotes necrotic death of tumor cells. Increasing the irradiation dose to 4.1 Sv even more enhances cell death indicating a principal possibility to apply neutron radiation as an efficient tool to kill tumor cells (Fig. 1). The therapeutic potential of neutron radiation should be studied further [47].

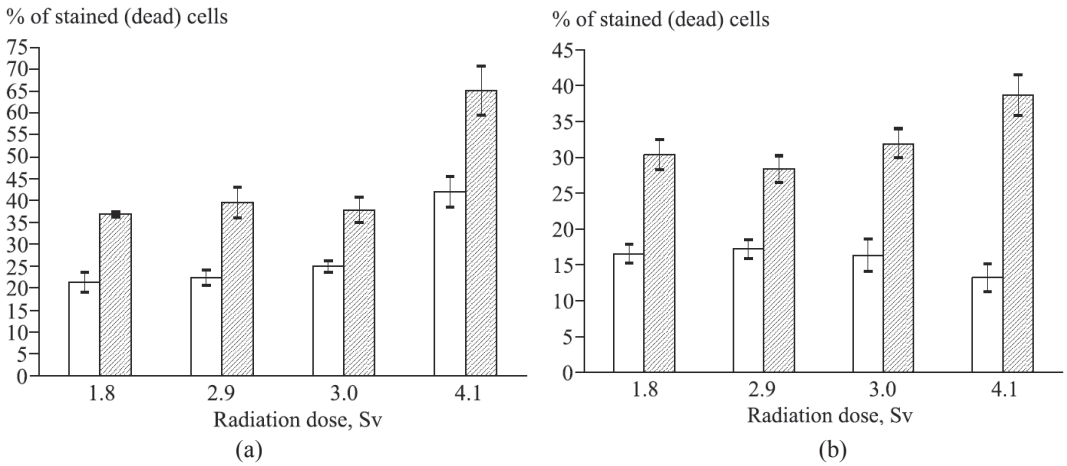


FIGURE 1. Effect of epithermal neutron irradiation on cell death, 30. Dead cells were counted 72 h postradiation. Light bars: control cells; shaded bars: irradiated cells. (a) Fibroblasts, (b) U87

To study the effect of the influence of generated neutron flux on the survivability of human tumor cells together with colleagues from Japan cell lines of human glioma U251, human glioblastoma T98G, Chinese hamster ovary CHO-K1 and Chinese hamster lung fibroblasts and V-79 were irradiated. As a boron-containing agent the boron-10 L-p-biphenylene was used (KatchemLtd., the Czech Republic). The analysis of cell survivability after irradiation was performed using a clonogenic test. The results of the clonogenic test showed that neutron irradiation of tumor cells with boron leads to a significant suppression of their survivability that confirms the quality of generated neutron beam generated by Institute of nuclear physics demanding for BCT (Fig. 2) [48].

We also investigated the effects of neutron flux and boron-neutron capture therapy on the organs of animals. All animal experiments were approved by the inter-institutional commission on bioethics of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences and comply with the principles of the Guide for the care and use of laboratory animals published by USNIH (No. 85-23 revised in 1985). In experiments with animals we used immunodeficient mice of SCID's line, males (SHO-PrkdcscidHrhr) of SPF status at the age of 8–12 weeks.

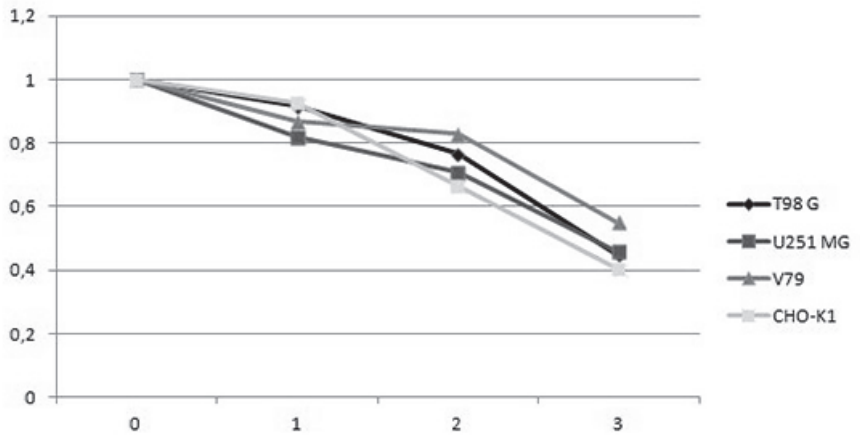
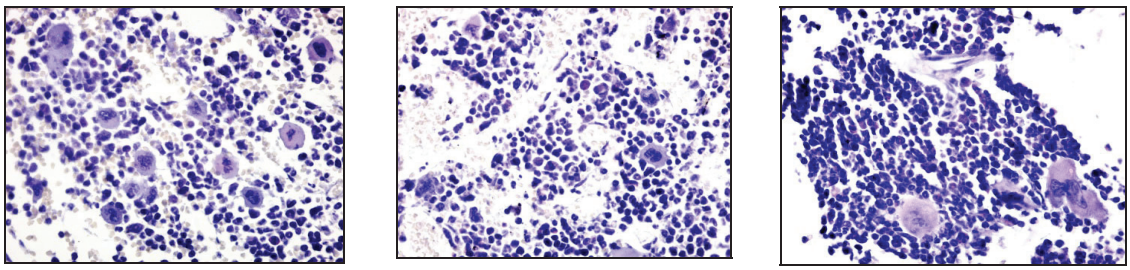


FIGURE 2. Clonogenecity of 4 cell lines depending on the received doses of radiation (horizontally—the group of cell lines: 0 group—control, 1st group—exposition of 50 million neutrons, 2nd group—double exposure, 3rd group—triple exposure; T98 G—epithelioid cell line of human glioblastoma; U251 MG—glial cell culture of human glioblastoma; CNO-K1—epithelioid culture of Chinese hamster ovary; V-79 fibroblastoma culture of Chinese hamster's lung; vertically—clonogenicity (the proportion of surviving cells)



(a) (b) (c)

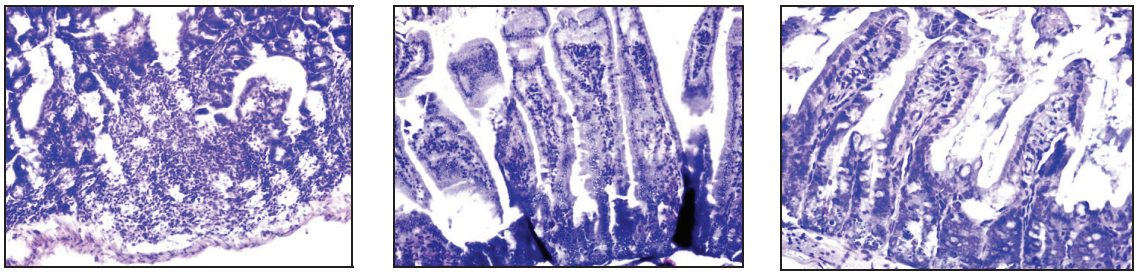
FIGURE 3. (a) Bone marrow on the 2 day after irradiation. A plethora of bone marrow tissue, a large number of immature cellular forms, megakaryocytes; (b) hyperemia of the bone marrow tissue, a large number of immature cellular forms, mitosis; (c) bone marrow on the 9th day after irradiation. The recovery phase in the bone marrow. Enlarged 600×

IIn one experiment the animals were divided into two groups. One group was injected by BSH at a dose of 200 mg/kg intraperitoneally and was irradiated; a second group was irradiated without introduction of BSH. The radiation dose of mice that were injected by BSH did not exceed 5.7 Gr EQ and without injection of BSH – 2 Gr EQ. The euthanasia was performed on the 30th day after irradiation by CO_2 overdose followed by cervical dislocation. The result of the experiment shows that the dose received by healthy tissues of immunodeficient mice during the irradiation time is tolerant and pathological structural changes in the studied tissues that have been exposed to radiation are not detected [49].

In the following experiment the animals were studied for the radiobiological effects of neutron irradiation in different periods of observation. The proton beam current with energy of 2 MeV on the neutron-generating target amounted to 1.8 mA, 90 mA/hour. The number of neutrons registered in the detector was 190 million. The tissue picking was held on the 2nd and 9th day after irradiation. Animals' organs (femur, small intestine, kidneys, liver, brain, heart, spleen) were split and fixed in the solution of formaldehyde.

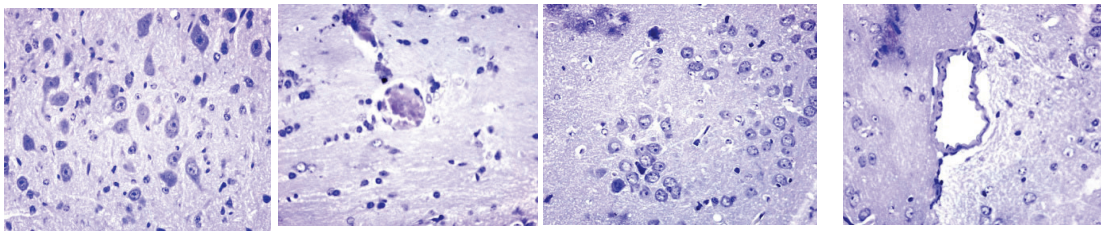
Firstly, the changes in the proliferative pool of the bone marrow were evaluated: the number of young and dividing cells—the first three pools, the number of divided cells (a total amount, with fatal chromosomal aberrations, healthy). The estimation of survival rate of stem cells, the dynamics of the content of myelokaryocytes (%) was held after irradiation. On the second day of irradiation in the bone marrow its plethora with a large number of immature cellular forms and megakaryocytes was noted. On the 9th day after irradiation the reversible changes with restoration of the usual view of the bone marrow were observed (Fig. 3).

In the small intestine the devastation of the villi and crypts that occurs because of apoptosis of stem cells was observed. During the histological examination the denudation of the villi, infectious processes, damage of blood vessels were visualized. It is noted that in the early phase a stromal edema is identified, increasing the number of mirabiliandia and stromal lymphocytes, proliferation of the epithelium's base of the villi that is more typical for acute diffuse ileitis; the presence of acute ulcers of the mucous membranes, a degenerative phase. In the later phase the proliferation of the epithelium of the base of the villi is visualized—the reparative phase; a stromal fibrosis and shortening of the villi are marked—the moderate atrophic changes (Fig. 4).



(a) (b) (c)

FIGURE 4. (a) The wall of small intestine on the 2nd day after irradiation. Acute ulcer of the mucosa (degenerative phase). (b) The wall of small intestine on the 2nd day after irradiation. Club-shaped thickening of the tops of the villus, stromal edema, the increasing number of mirabiliandia and stromal lymphocytes, proliferation of the epithelium of the base of the villi (acute diffuse ileitis). (c) The wall of small intestine on the 9th day after irradiation. Proliferation of the epithelium of the base of the villi (reparative phase). A stromal fibrosis and shortening of villi (moderate atrophic changes) are observed. Enlarged 400×



(a) (b) (c) (d)

FIGURE 5. (a) The brain on the 2nd day after irradiation. The neurons of the cerebral cortex of various shapes and sizes with pinnatifida or hyperchromatic nuclei, lose their processes. (b) The brain on the 2nd day after irradiation. Paresis of the capillary bed with blood stasis, perivascular and paracellular edema. (c) The brain on the 9th day after irradiation. The neurons of the cerebral cortex are relatively monomorphic but are distributed unevenly, there were discovered cells with a deep degenerative disorders (hyaline balls). (d) The brain on the 9-th day after irradiation. The restoration of the microvasculature. Enlarged 600×

As for the brain, on the 2nd day after irradiation a paresis of the capillary bed with blood stasis, perivascular edema and pericellular is marked. On the 9th day after irradiation in the brain of the tested animals cells with a deep degenerative disorders—hyaline balls—were detected (Fig. 5).

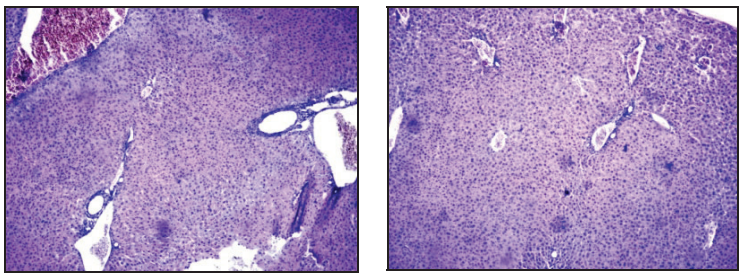
In the liver a congestion of the vessels of the portal tracts is observed, which is more specific for disorders of blood circulation which decreased in the later phase. Meanwhile, the hepatocytes retained their structure (Fig. 6).

In the late period in the tubules and glomeruli of the kidney the changes typical for the consequences of acute renal failure are marked (Fig. 7).

The minimal changes were observed in the myocardium. The part of the cardiomyocytes has the enlightenment of cytoplasm on the 2nd day after irradiation. Pathological structural changes in the spleen are not detected. Lymphoid follicles (white pulp) and the reticular tissue of the spleen are without features.

The second group after irradiation was kept in the SPF- vivarium of the Institute of Cytology and genetics of the Siberian Branch of the Russian Academy of Sciences with same-sex family groups of 2–5 animals in individually ventilated cages (IVC) system OptiMice (Animal Care Systems) under controlled conditions (at a temperature of 22–26°C, a relative humidity of 30–60% and a light regime light/dark 14/10 h with sunrise at 01:00).

The observation period lasted one month. During the experiment the condition of mice was recorded daily. In particular, the changes of skin condition, physical activity and behavior were evaluated. According to observations within 30 days the external signs of the pathological effects of radiation and lethal outcome of mice have not been identified. The LD50/30 = 0.



(a) (b)

FIGURE 6. (a) The liver on the 2nd day after irradiation. The lobular structure of liver tissue is preserved, the vessels of the portal tracts paretic expanded, full-blooded (circulatory disorders). The hepatocytes retain their structure. (b) The liver on the 2nd day after irradiation. The lobular structure of liver tissue is preserved, the vessels of central parts of lobules and portal tracts slightly red-blooded (minimal circulatory disturbances). The hepatocytes retained their structure. Enlarged 100×

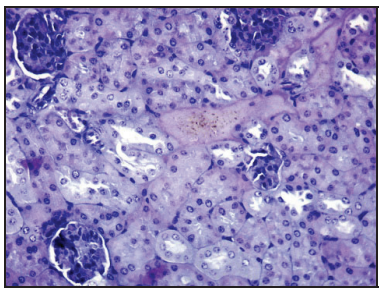


FIGURE 7. The kidney on the 9th day after irradiation. Elements of the renal parenchyma are without pathological changes but in a small vessel are discovered the lysed erythrocytes and pigment, probably due to undergoing acute renal failure. Enlarged 400×

CONCLUSION

BNCT is a promising technology due to the unsolved problem of treatment of malignant brain tumors in the world as well as the high relevance of past and present work on this problem and significant progresses of BNCT in the treatment of CNS tumors. However, at the present time this method is in the experimental stage due to the complexity of its implementation. The use of accelerators is promising technology for BNCT as a neutron source. Thus, the results of the studies carried out at the Institute of nuclear physics of Siberian Branch of Russian Academy of Science allowed to make a conclusion that the obtained beam is safe and meets the requirements of BNCT best. However, it has not yet produced a single mechanism to transfer data obtained during the evaluation of biological effects of BNCT on the cell lines and tumor models of animals concerning the man. A number of clinical tests on the accelerator neutron sources must be performed for widespread adoption of BNCT in clinical practice that could show the effectiveness of this method. The problem of insufficient selectivity of delivery of 10B to the tumor can be solved using innovative tumorectomy carriers of 10B that will increase significantly the gradient of boron concentration at the border of the tumor and healthy tissue. But the most important factor significant for the success of BNCT in the future will be the good collaboration of specialists of different disciplines.

ACKNOWLEDGMENTS

This work was funded by the Russian Science Foundation under project No. 14-32-00006 and was supported by Budker Institute of Nuclear Physics and Novosibirsk State University.

REFERENCES

1. Y. Kinashi, Y. Sakurai, S. Masunaga, M. Suzuki, K. Nagata, and K. Ono, Topics in Neutron Capture Therapy: Proceedings of the Eleventh World Congress on Neutron Capture Therapy **61**(5), 899–903 (2004).
2. W. Sauerwein, A. Wittig, R. Moss, and Y. Nakagawa, *Neutron Capture Therapy Principles and Applications* (Springer-Verlag, Berlin Heidelberg, 2012), pp. 19–37.
3. V. A. Byvaltsev, I. A. Stepanov, E. G. Belykh, V. V. Kanygin, and A. I. Kichigin, Sib. Med. J. **2**, 5–9 (2015).
4. H. Ohgaki, P. Dessen, B. Jourde, S. Horstmann, T. Nishikawa, P. L. Di Patre, C. Burkhard, D. Schüler, N. M. Probst-Hensch, P. C. Maiorka, N. Baeza, P. Pisani, Y. Yonekawa, M. G. Yasargil, U. M. Lütolf, and P. Kleihues, Cancer Res. **64**(19), 6892–6899 (2004).
5. A. J. Ekstrand, N. Sugawa, C. D. James, and V. P. Collins, Proc. Natl. Acad. Sci. USA **89**(10), 4309–4313 (1992).
6. E. Hulleman and K. Helin, Adv. Cancer Res. **94**, 1–27 (2005).
7. A. H. Soloway, W. Tjarks, B. A. Barnum, F. G. Rong, R. F. Barth, I. M. Codogni, and J. G. Wilson, Chem. Rev. **98**, 1515–1562 (1998).
8. R. Kubota, S. Yamada, K. Ishiwata, M. Tada, T. Ido, and K. Kubota, Brit. J. Cancer **67**(4), 701–705 (1993).
9. S. Chandra, G. W. Kabalka, D. R. Lorey, and D. R. Smith, J. A. Clinical Cancer Res. **8**(8), 2675–2683 (2002).
10. R. F. Barth, W. Yang, R. T. Bartus, M. L. Moeschberger, and J. H. Goodman, Neurosurgery (Baltimore) **44**, 351–359 (1999).
11. S. Capuani, T. Gili, M. Bozzali, S. Russo, P. Porcari, C. Cametti, E. D'Amore, M. Colasanti, G. Venturini, B. Maraviglia, G. Lazzarino, and F. S. Pastore, Int. J. Rad. Oncol. Biol. Phys. **72**(2), 562–567 (2008).
12. T. Watanabe, H. Tanaka, S. Fukutani, M. Suzuki, M. Hiraoka, and K. Ono, Cancer Lett. **370**, 27–32 (2016).
13. F. Yoshida, T. Yamamoto, K. Nakai, A. Zaboronok, M. Matsuda, H. Akutsu, E. Ishikawa, M. Shirakawa, and A. Matsumura, Appl. Rad. Isotopes **88**, 86–88 (2014).
14. P. Olsson, L. Gedda, H. Goike, L. Liu, V. P. Collins, J. Pontén, and J. Carlsson, Anti-Cancer Drug Design **13**, 279–289 (1998).
15. J. Fang, H. Nakamura, and H. Maeda, Adv. Drug Delivery Rev. **63**(3), 136–151 (2011).
16. M. F. Hawthorne and K. Shelly, J. Neuro-Oncology **33**(1-2), 53–58 (1997).
17. N. Maurer, D. B. Fenske, and P. R. Cullis, Expert Opinion Biolog. Therapy **1**(5), 1–25 (2001).
18. S. Yu. Taskaev, V. V. Kanygin, R. A. Muhamadiarov, and A. I. Kichigin, RU Patent No. 2589822C2 (2016).
19. A. H. Soloway, H. Hatanaka, and M. A. Davis, J. Med. Chem. **10**, 714–717 (1967).
20. R. F. Barth, J. C. Grecula, W. Yang, J. H. Rotaru, M. Nawrocky, N. Gupta, B. J. Albertson, A. K. Ferketich, M. L. Moeschberger, J. A. Coderre, and E. K. Rofstad, Int. J. Rad. Oncol. Biol. Phys. **58**, 267–277 (2004).

21. K. Z. Matalka, M. Q. Bailey, R. F. Barth, A. E. Staubus, A. H. Soloway, M. L. Moeschberger, J. A. Coderre, and E. K. Rofstad, Cancer Res. **53**, 3308–3313 (1993).
22. J. A. Coderre, "A Phase 1 Biodistribution Study of p-Boronophenylalanine," in *Boron Neutron Capture Therapy: Towards Clinical Trials of Glioma Treatment* (Plenum Press, New York, 1992), pp. 111–121.
23. J. Godwin, L. Farr, W. Sweet, and J. Robertson, Cancer **8**, 601–615 (1955).
24. H. Locksle and L. Farr, J. Pharmacol. Exp. Therapeutics, 484–489 (1955).
25. D. Slatkin, Brain **114**, 1609–1629 (1991).
26. H. Hatanaka, Basic Life Sci. **54**(15), 15–21 (1990).
27. A. Chanana, J. Capala, M. Chadha, J. Coderre, A. Diaz, E. Elowitz, J. Iwai, D. Joel, H. Liu, R. Ma, N. Pendzick, N. Peress, M. Shady, D. Slatkin, G. Tyson, and L. Wielopolski, Neurosurgery **44**(6), 1182–1193 (1999).
28. P. Busse, O. Harling, M. Palmer, W. Kiger III, J. Kaplan, I. Kaplan, C. Chuang, J. Goorley, K. Riley, T. Newton, G. Santa Cruz, X. Lu, and R. Zamenhof, J. Neuro-Oncology **62**(1-2), 111–121 (2003).
29. W. Sauerwein and A. Zurlo, Eur. J. Cancer **38**(4), 31–34 (2002).
30. H. Joensuu, L. Kankaanranta, T. Seppala, I. Auterinen, M. Kalio, M. Kulvik, J. Laakso, J. Vahatalo, M. Kortesniemi, P. Kotiluoto, T. Seren, J. Karila, A. Brander, E. Jarviluoma, P. Ryynanen, A. Pauteu, I. Ruokonen, H. Minn, M. Tenhunen, J. Jaaskelainen, M. Farkkila, and S. Savolainen, J. Neuro-Oncology **62**(1-2), 123 (2003).
31. J. Capala, B. Stenstam, K. Skold, P. Munck af Rosenschold, V. Giusti, C. Persson, E. Wallin, A. Brun, L. Franzen, J. Carlsson, L. Salford, C. Ceberg, B. Persson, L. Pellettieri, and R. Henriksson, J. Neuro-Oncology **62**(1–2), 135–144 (2003).
32. V. Dbaly, F. Tovarys, H. Honova, L. Petruzelka, K. Prokes, J. Burian, M. Marek, J. Honzatko, I. Tomandl, O. Kriz, I. Janku, and V. Mares, Neurol. Neurochirurgia Polska **66/99**(1), 60–63 (2002).
33. Y. Nakagawa, K. Pooh, T. Kobayashi, T. Kageji, S. Uyama, A. Matsumura, and H. Kumada, J. Neuro-Oncology **62**(1-2), 87–99 (2003).
34. S. Gonzalez, M. Bonomi, G. Santa Cruz, H. Blaumann, O. Calzetta Larrieu, P. Menendez, R. Jimenez Rebagliati, J. Longhino, D. Feld, M. Dagrosa, C. Argerich, S. Castiglia, D. Batistoni, S. Liberman, and B. Roth, Appl. Rad. Isotopes **61**(5), 1101–1105 (2004).
35. Y.-W. Liu, T. Huang, S. Jiang, and H. Liu, Appl. Rad. Isotopes **61**(5), 1039–1043 (2004).
36. V. N. Mitin, V. N. Kulakov, and V. F. Khokhlov, "GdNCT of Spontaneous Canine Melanoma," in *Advances in Neutron Capture Therapy 2006*, Proceedings of ICNCT-12, edited by Y. Nakagawa, T. Kobayashi, H. Fukuda (International Society for Neutron Capture Therapy, Kagawa, Japan, 2006), pp. 127–130.
37. S. E. Ulianenko, V. A. Sokolov, and S. N. Koryakin, Int. J. Sci. Res. **16**, 97–100 (2006).
38. A. V. Vazhenin, G. N. Rykovanov, E. P. Magda, Z. Z. Munasipov, G. V. Mokichev, Ye. Yu. Kandakova, T. M. Sharabura, A. S. Domozhirova, D. N. Astaf'yev, and A. I. Stepanova, "Neutron Therapy as a Way to Overcome the Radioresistance of Neoplasms," in *X Russ. Cancer Congress*: *Results and Prospects of the Ural Center for Neutron Therapy* (Moscow, 2006).
39. L. I. Musabaeva and V. A. Lisin, Appl. Neutrons Oncology, 72 (1998).
40. A. I. Yarullina, V. V. Kanygin, A. I. Kichigin, M. G. Zhdanova, R. A. Mukhamadiyarov, and S. Yu. Taskaev, Pacific Med. J. **4**, 6–11 (2015).
41. H. Tanaka, Y. Sakurai, M. Suzuki, S. Masunaga, T. Mitsumoto, K. Fujita, G. Kashino, Y. Kinashi, Y. Liu, M. Takada, K. Ono, and A. Maruhashi, Appl. Rad. Isotopes **69**, 1642–1645 (2011).
42. M. Yoshioka, T. Kurihara, S. Kurokawa, H. Kobayashi, H. Matsumoto, N. Matsumoto, H. Kumada, A. Matsumura, H. Sakurai, S. Tanaka, T. Sugano, T. Hashirano, T. Nakamura, F. Hiraga, T. Ohba, N. Nagura, T. Nakamoto, T. Zagar, and T. Ouchi, "Construction of Accelerator-Based BNCR Facility," in *Ibaraki Neutron Medical Research Center*: *Proceedings of LINAC2014* (Geneva, Switzerland, 2014), pp. 230–232.
43. Y. Abe, M. Fuse, and R. Fujii, "Hospital-Based Boron Neutron in National Cancer Center. An Installation Design for the Accelerator-Based Epithermal Neutron Source," in *Abstracts of 15 ICNCT* (Tsukuba, Japan, 2012), pp. 109–110.
44. K. Tsuchida, Y. Kiyanagi, and A. Uritani, "Development of an Accelerator Driven Compact Neutron Source for BNCT in Nagoya University," in *Book of Abstracts of the 16 Int. Congress on Neutron Capture Therapy* (Helsinki, Finland, 2014), pp. 206–207.
45. E. Forton, F. Stichelbaut, and A. Cambriani, Appl. Rad. Isotopes **67**(7-8), 262–265 (2009).

46. V. V. Kanygin, A. I. Kichigin, N. V. Gubanova, and S. Yu. Taskaev, Vestnik Rentgenol. Radiol. **6**, 36–42 (2015).
47. L. A. Mostovich, N. V. Gubanova, O. S. Kutsenko, V. I. Aleinik, A. S. Kuznetsov, A. N. Makarov, I. N. Sorokin, S. Yu. Taskaev, G. I. Nepomnyashchikh, and E. V. Grigor'eva, Bull. Exp. Biol. Med. **151**(2), 264–267 (2011).
48. O. Y. Volkova, L. V. Mechetina, A. V. Taranin, A. A. Zaboronok, K. Nakai, S. I. Lezhnin, S. A. Frolov, D. A. Kasatov, A. N. Makarov, I. N. Sorokin, T. V. Sycheva, I. M. Shchudlo, and S. Y. Taskaev, Vestnik Rentgenol. Radiol. **97**(5), 283–288 (2016).
49. A. Zaboronok, V. Byvaltsev, V. Kanygin, A. Iarullina, A. Kichigin, O. Volkova, L. Mechetina, S. Taskaev, R. Muhamadiyarov, K. Nakai, E. Sato, T. Yamamoto, B. Mathis, and A. Matsumura, New Armen. Med. J. **11**(1), 1–9 (2017).