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IMPLEMENTING BNCT THROUGH THE USE OF AN ELECTRON ACCELERATOR*

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Abstract. Boron Neutron Capture Therapy (BNCT) application methods and models are being studied worldwide with increasingly rates of success; however, aside from boron delivery issues and tumor treatment, sources of neutrons are also a major problem.
While linear accelerators are readily available for classic radiotherapy, neutron sources for BNCT are usually represented by nuclear reactors, some of which are specifically designed for this purpose. However, these reactors might not be available or easily accessible in every country. The increased prevalence of cancer patients requiring radiation therapy often results in delaying radiotherapy up to two months, overuse of available LINACs (Linear accelerators) and extended periods of inpatient care.
Currently used LINACs are capable of delivering thermal neutrons needed for BNCT. Implementing classic radiotherapy equipment into modern methods of tumor treating would not only hasten the advancement of such therapies, but it would also reduce the costs and ensure a greater number of patients being treated.
This article reviews the recent studies and techniques currently being implemented in an effort to emphasize the need and success of BNCT implemented through electron accelerators.

Key words: boron neutron capture therapy, cancer, radiation.

1. INTRODUCTION

Boron Neutron Capture Therapy (BNCT) was first described in 1936 by Gordon J. Locher. Since then, numerous studies regarding boron delivery agents, epithermal neutron sources, efficiency against various tumor types have proven this method of radiation therapy to be not only safe, but also tissue-sparing, precise and able to destroy previously undetected cancerous cells. However, clinical studies and BNCT as a treatment option have been sparingly implemented and research as

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well as therapy is limited to certain regions of the world. This is because of development of other types of radiation therapy, insufficiently developed boron delivery agents and the necessity of increased funding and effort in obtaining a neutron source near or within hospitals [21].

This paper reviews recent developments in BNCT, including boron delivery agents and studies regarding linear accelerators as neutron sources, in order to emphasize the efficiency and ease of implementation of BNCT through the use of an electron accelerator.

1.1. BNCT BASIS

The BNCT represents a rather specific type radiotherapy, since it uses internal radiation for destroying cancerous cells, rather than using an external beam directly for this purpose. The BNCT process consists of two steps: first, a boron (^{10}B) delivery agent is administered intravenously to the patient; secondly, an external source applies a bath of epithermal neutrons which irradiates the tumor.

$$^{10}B + n_{th} \rightarrow [^{11}B] \rightarrow {}^{4}He + {}^{7}Li. \quad (1)$$

As a result of nuclear decay, alpha radiation is obtained along with ^{7}Li – both reaction products work towards destroying the cancer cells; however, their maximum effective range inside tissue are 9 and 5 μm.

This can be both a positive and negative characteristic of BNCT: alpha radiation and LiOH (a very strong base, resulted from ^{7}Li in presence of H_2O; highly toxic to cancerous cells, but rapidly diluted in an aqueous environment) will be limited to affected tissue which has taken up ^{10}B, thus sparing healthy tissue. This emphasises the need of a „perfect" boron delivery agent – high tumoral uptake, low/zero healthy tissue uptake.

The downside of such a short range of action is that ^{10}B must be present in all tumoral cells, and within those cells it must be sufficiently close to the radiosensitive structures of the nucleus; otherwise, tumoral control will not be achieved properly.

1.2. TYPES OF TUMOR TREATABLE WITH BNCT

BNCT is mainly indicated in cerebral metastasis and other types of head and neck cancer, such as glioblastoma multiform, mucoepidermoid carcinoma, melanomas, primary and recurrent thyroid cancers and theoretically any type of tumor where treatment must preserve as much healthy tissue as possible.

The main two factors in deciding whether BNCT is useful or not are possibility of delivering epithermal neutrons and the uptake of boronated drugs inside cancerous cells (again, must be higher than surrounding healthy tissue) [28].

Glioblastoma multiforme (GBM). The glioblastoma is the most common type of cerebral neoplasm (approximately 50-60% of diagnosed glial tumors and 10-15% of total cerebral tumors), with various localizations, invasion degrees and different responsivity to treatment.

Primary glioblastoma multiform is the most frequent type of GBM, with a greater incidence over the age of 50.

Secondary GBM is usually found in young adults (< 45yrs) and is derived from lesions with a lower degree of malignity than primary GBM; however, evolution towards high malignity status can vary from 1 year up to 10 years, with a mean period of 4-5 years [1].

BNCT benefit in GBM treatment. Glioblastoma multiform, from an anatomopathological point of view, has a number of indications towards BNCT. By nature, it is a highly aggressive type of tumor, with poorly defined limits and possibility of multifocal development, thus requiring fast and efficient treatment.

It is also possible to include central necrosis, occupying up to 80% of the tumoral volume. In this case, radiotherapy must avoid generating further necrosis, which means irradiation dose is limited; BNCT could prove to be more efficient, provided that boronated drugs have a much higher uptake in cancerous cells and that side effects, such as gamma irradiation and fast neutron contamination are kept to a minimum.

In certain cases, applying intermediate-energy neutrons in combination with a highly effective boron delivery agent could replace surgery in GBM. Up to 40% of patients who have undergone surgery have neurological deficiencies and 30% do not show signs of neurological improvement [16, 23, 25].

Mucoepidermoid carcinoma (MEC). Mucoepidermoid carcinoma, the most common salivary gland tumor, contains three types of cellular elements: squamous cells, mucosecretant cells and intermediate cells. Malignancy is determined based on the varying proportions of these cells; low grade MEC present well differentiated cells, with a higher proportion of mucus secreting cells; high grade MEC present poorly differentiated cells and a higher proportion of squamous cells.

Mucoepidermoid carcinomas usually have a slow, painless and undetected development, followed by aggressive and noticeable evolution period, during which the patient usually seeks medical advice, accusing pain, dizziness, even swelling or lumps in the oral cavity and in some cases exoftalmia.

Degree of invasion is also taken into consideration when applying treatment, as MEC tend to invade all structures of the viscerocranium, with major osteolisis. In such cases, treatment may prove difficult; irradiation fields must spare as much of the brain as possible, while delivering sufficient doses to stop tumoral development and kill cancerous cells.

BNCT proved to be efficient in treating mucoepidermoid carcinomas, with rates of success growing. Mucoepidermoid carcinomas can be irradiated more efficiently with this type of radiotherapy; in addition, since MEC are not encapsulated and do not spread uniformly, usually causing severe osteolysis, undetected tumoral mass can be efficiently treated.

There has been a large number of reported cases with either mucoepidermoid carcinoma, MEC variants or other similar types of head and neck cancer which have responded better to BNCT than regular treatment. Some cases of mandibular carcinomas and thyroid tumors have been treated with BNCT and avoided surgery (thus avoiding surgical removal of a large part of the lower mandible and improving the quality of life) [6, 9, 17, 19, 20, 21, 26, 36].

1.3. BORON DELIVERY AGENTS (BDA)

Due to its nature, boron neutron capture therapy provides alpha particles (^{4}He) and recoiling lithium nuclei (^{7}Li) as a result of nuclear capture, fission and boron decay. The effective radiation has a very short penetration range, which implies that a sufficient amount of boron must be present within every cancerous cell in order for BNCT to be successful (approximately 10^9 boron atoms per cancer cell).

Boron chemical compounds must meet certain requirements in order to be a successful delivery agent for BNCT:

a) High tumoral uptake, normal to low healthy tissue uptake
b) Low systemic toxicity
c) High tumor: brain or tumor: blood concentration ratios (approximately 20 μg of boron per gram of tumor, or 10^9 ^{10}B atoms per cell)
d) Fast and eventually complete clearance (blood, healthy tissue) with persistence in cancerous cells for the duration of the BNCT session.

Various boron delivery agents are being researched, however only two are currently being used in BNCT: BPA, or *boronophenylalanine*, and BSH, or *sodium borocaptate*. Depending on tumor type, degree of malignity, invasion and other characteristics, these boron delivery agents may be used separately or together, in different proportions. It has been noted that using both types of agents has proven to be more efficient in most aggressive types of tumors.

Delivering methods. In order for ^{10}B to be efficiently delivered inside tumoral cells, a few factors have to be taken into consideration: the ability to traverse the hematoencephalic barrier, tumoral blood supply, plasma concentration and the agent's lipophilicity. In addition, delivering methods greatly influence the uptake.

Usually, boron delivery agents are injected intravenously, slowly, over 1–2 hours. Administering the drug intra-arterially or even through intra-cardiac injections has proven more efficient; when delivered via IA injection, a

hyperosmotic mannitol solution is used in order to bypass the hematoencephalic barrier; animal studies show a 117-295% increase of mean survival times, especially when both BPA and BSH are delivered by intra-cardiac injection [11, 29, 34, 37].

1.4. RECENT DEVELOPMENTS OF BDA

Although numerous delivery agents are constantly being researched, BPA and BSH are being most commonly used, and most agents do not sufficiently meet the requirements to be used in BNCT; there is ongoing research towards finding a „perfect" boron delivery agent [27].

Boron Nitride NanoTubes. Recently, there has been increased interest in developing a drug that could deliver a large amount of boron atoms in the form of boron nitride nanotubes. Due to their structure and nature, BNNTs deliver a higher concentration of boron; delivery methods include attaching the BNNTs to antibodies (immunoglobulin G –IgG) and attaching radioactive isotopes to carbon nanotubes (CNT) and then attaching the resulted radioactive CNT to another species of IgG.

Overall, boron nitride nanotubes show promising delivery efficiency and improvement of BNCT results in any type of tumor [3, 12, 14, 22, 23, 39].

2. DELIVERING EPITHERMAL NEUTRONS

Beside boron delivery agents, the other main problem in BNCT is obtaining and perfecting a neutron source.

Nuclear reactors are usually used in BNCT, with good epithermal neutrons delivery and already calculated and simulated neutron fields. However, certain aspects of nuclear reactors are to be considered in conjuncture with BNCT and the general status of patients needing treatment. First and foremost, the nuclear reactor must be installed near (or within) a clinic / hospital, or vice versa; this raises further issues, such as building the necessary facility within hospitals situated in an urban setting; permissions from the governing nuclear activity control agency, as well as providing trained and licensed personnel. On the other hand, building a clinic near an already existing nuclear reactor used for research may prove equally difficult, as such locations are often under military control and off-limits to general population, thus including patients and their families or relatives. In addition, any nuclear reactor must be specially adapted for BNCT use, which includes further licensing and permissions. Further details of nuclear reactor use (such as technique, neutron types – high energy fission neutrons versus direct use of core neutrons) will not be discussed here.

Cyclotrons are also used in BNCT, mostly in Japan and USA. While these types of facilities are more easily accessed and implemented, and recent development have greatly reduced cyclotron size and increased the accelerator's efficiency, the costs of implementation such an accelerator may yet prove prohibiting, especially for developing countries. In addition, in order for a cyclotron to be introduced in any hospital, BNCT alone is insufficient as a requirement for such an upgrade.

Recently (2012), efforts were made toward building a BNCT facility in Japan by using an 8MeV, 10 mA, 80kW accelerator based on the radio frequency quadruple accelerator; the target material consists of a 0.5mm beryllium piece attached to a heat sink disk of 150mm in diameter. First beam acceleration is scheduled for March 2013, and clinical studies are to begin in March 2014 [2, 15].

3. USING ELECTRON ACCELERATORS FOR BNCT

Neutron sources that can be used for boron neutron capture therapy are not limited to nuclear reactors, cyclotrons or newly developed accelerators. It has been proved that epithermal neutrons are already produced with linear (electron) accelerators and the neutron field can be calculated and adapted for actual use with BNCT.

The main benefit of implementing BNCT on electron accelerators is that the neutron source is already available in most radiotherapy clinics and therefore necessary funding is substantially lower than if other sources are considered. The only requirement is that such a LINAC (Linear accelerators) must be able to produce a beam of at least 15MeV, and most already installed LINACS have this capability.

3.1. ADAPTING LINACS FOR BNCT

Linear accelerators currently used within hospitals and clinics already have sufficient radioprotection, since neutron contamination and other types of radiation have been taken into consideration, especially when such LINACs are capable of more than electron therapy with classic irradiation fields (modern accelerators also have a photon operation mode) – they have to be decommissioned for use with BNCT, however (after which classic radiotherapy can still be applied).

Although the shielding design used in electron and photon therapy is also effective and sufficient, in some cases adaptation is required. However, such modifications are simple, have reduced costs and do not alter the main purpose or capabilities of the accelerator.

3.2. LIMITATIONS

Due to the nature of interaction of neutrons (thermal, epithermal, fast neutrons) – dominated by scattering – the required epithermal neutrons cannot be delivered in a beam-like manner. As a result, the irradiation field consists of a bath of neutrons, rather than a direct beam; a subtherapeutic dose is administered – sufficient for boron atom degradation; the cumulative dose (neutrons and radiation resulted from boron decay) achieves therapeutical efficiency [18].

Although mean energy of photoneutrons and its decrease (as distance to isocenter increases) are common to all types of electron accelerators, epithermal neutrons have different strengths at isocenter and different penetration distances different for each manufacturer of linear accelerator. Thus, Monte Carlo simulations are required, as well as neutron field calculations. These are already available, as most linear electron accelerators have been considered for BNCT, and in some cases not only calculated and studied, but also applied in clinical trials [4, 5, 8, 17, 24, 31, 32, 33, 35, 38].

Target materials. Depending on the mentioned calculation, certain issues may arise. For example, in some cases it has been observed that the maximum SSD (Source-Skin Distance) for efficient delivery of epithermal neutrons is 25cm. In this case, shielding may prove difficult when considering currently used target material (wolfram mostly) and cooling required.

Recent studies have shown that the most efficient target material is either lithium or beryllium; considering that BNCT sessions may last from 20 to 90 minutes (unlike classic radiotherapy – 5 to 15 minutes), lithium may prove difficult to handle, with a low melting point and heat dissipation issues (poor thermal conductivity), which means high risk of target failure. Liquid lithium targets are being considered and developed, however, it seems that beryllium and carbon targets are more efficient, with high melting points and superior thermal conductivity. Average neutron energy is higher with Be or C targets, thus other moderators are required and resulting in fewer neutrons being delivered to the tumor [7, 10, 13, 30].

4. CONCLUSIONS

Boron neutron capture therapy has proven to be more efficient than classic radiotherapy in various cancer types, especially in aggressive forms or inoperable brain tumors (either primary or metastasis).

Although single sessions of BNCT can last longer than regular electron radiotherapy, the overall duration of such treatment is shortened and accelerated, thus being able to treat advanced, aggressive and invasive tumors, even undetected localizations. Moreover, BNCT is known to be tissue sparing; in some cases it can even replace surgery.

Boron delivery agents have been developed and enhanced recently, and are constantly improved; boron nitride nanotubes show a promising future, with capabilities of delivering enough ^{10}B atoms and having a higher tumoral uptake.

Neutron sources, however, are limited and in some cases unavailable. Necessary funding for new sources within close proximity to treatment centers may prove to be an impediment; however, most radiotherapy clinics are already equipped with electron accelerators capable of delivering needed epithermal neutrons.

Implementing BNCT through the use of an electron accelerator can prove to be not only cost effective (reduced funding with similar results as other neutron sources), but can also be done in a much shorter time period; licensing and trained personnel is already available as well.

REFERENCES

1. A.D. Chanana, M.D., *Boron Neutron-Capture Therapy of Glioblastoma Multiforme at the Brookhaven medical research reactor. A Phase I/II Study (FDA IND # 43,317)*, Protocol #4, Dep., Brookhaven Natl. Lab., Upton, NY 11973-5000, January, 1996.
2. Allen, D. A. and Beynon, T. D., *A design study for an accelerator-based epithermal neutron beam forBNCT*, Physics in Medicine & Biology, 1995. Doi: 10.1088/0031/-9155/40/5/007.
3. Amartya Chakrabarti, Narayan S. Hosmane, *Nanotechnology-driven chemistry of boron materials*, Pure Appl. Chem., **84**, *11*, pp. 2299–2308 (2012).
4. B. A. Ludewigt *et al.*, *Clinical Requirements and Accelerator Concepts for BNCT*, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, Conf. Proc. C970512(1997) 3791.
5. Barth R.F., Coderre JA, Vicente MG, *Blue TE: Boron neutron capture therapy of cancer: current status and future prospects*, Clin. Cancer Res., **11**, 3987–4002, 2005.
6. Barth R.F., *A critical assessment of boron neutron capture therapy: an overview*, J. Neurooncol., **62**, 1–5, 2003.
7. Blackburn, B. W., Klinkowstein, R. E., Yanch, J. C., Song, H. and Howard, W., *Development of a high-power, water-cooled beryllium target for the production of neutrons in a high-current tandem accelerator*, International Conference on the Application of Accelerators, Denton, Texas, Nov. 1995.
8. Blue T.E., Yanch J.C., *Accelerator-based epithermal neutron sources for boron neutron capture therapy of brain tumors*, J. Neurooncol., **62**, 19–31, 2003.
9. Coderre J.A., Turcotte J.C., Riley K.J., Binns P.J., Harling O.K., Kiger W.S., *Boron neutron capture therapy: cellular targeting of high linear energy transfer radiation*, Technol. Cancer Res. Treat., **2**, *5*, 355–375, 2003.
10. D.L. Bleuel *et al.*, *On Optimizing the $^{7}Li(p,n)$ Proton Beam Energy and Moderator Material for BNCT*, AIP Conference Proceedings, Vol. **392**(1), 1997.
11. Feakes D.A., *Design and development of polyhedral borane anions for liposomal delivery*, in *Boron Science: New Technologies and ApplicationsI*, **12**, Edited by Hosmane NS, CRC Press, 2011.
12. C. Dai *et al.*, *Folate receptor-mediated boron-10 containing carbon nanoparticles as potential delivery vehicles for boron neutron capture therapy of nonfunctional pituitary adenomas*, Science China Life Sciences, **56**, *2*, 163–173 (2013).
13. G. Randers-Pehrson and D. J. Brenner, *A practical target system for accelerator-based BNCT which may effectively double the dose rate*, Med. Phys., **25**, 894 (1998).

14. Gianni Ciofani, Serena Danti, Giada Graziana Genchi, Barbara Mazzolai,Virgilio Mattoli, *Boron Nitride Nanotubes: Biocompatibility and Potential Spill-Over in Nanomedicine*, Article first published online: 19 FEB 2013, DOI: 10.1002/smll.201201315.
15. H. Kobayashi, T. Kurihara, H. Matsumoto, M. Yoshioka, H. Kumada, A. Matsumura, H. Sakurai, F. Hiraga, Y. Kiyanagi, T. Nakamura, H. Nakashima, T. Shibata, T. Hashirano, F. Inoue, K. Sennyu, T. Sugano, T. Ohba, Su. Tanaka, *Construction of a BNCT Facility Using an 8-MeV High Power Proton LINAC in Tokai*, Proceedings of IPAC2012, New Orleans, Louisiana, USA THPPR048.
16. Itsuro Katoa, Koji Onob, Yoshinori Sakuraic, Masatoshi Ohmaed, Akira Maruhashic, Yoshio Imahorie, Mitsunori Kirihataf, Mitsuhiro Nakazawaa, Yoshiaki Yuraa, *Effectiveness of BNCTfor recurrent head and neck malignancies*, Applied Radiation and Isotopes, **61**, 1069–1073 (2004).
17. J. Becker *et al*., *Photoneutron production of a Siemens Primus linear accelerator studied by Monte Carlo methods and a paired magnesium and boron coated magnesium ionization chamber system*, Phys. Med. Biol., **52**, 6375 (2007).
18. J.W. Kim, J.S. Chai., *Design Study of a Linear Accelerator System for Neutron Capture Therapy*, American Physical Society, Particle Acceleration Meeting, May 12–16, 1997, abstract #7, P.107.
19. Kankaanranta L., Seppälä T., Koivunoro H., Saarilahti K., Atula T., Collan J., Salli E., Kortesniemi M., Uusi-Simola J., Valimaki P., *et al*., *Boron neutron capture therapy in the treatment of locally recurred head-and-neck cancer: final analysis of a phase I/II trial*, Int J Radiat Oncol Biol Phys, 2012. Doi: 10.1016/g.ijirobp.2010.
20. Kato I., Fujita Y., Maruhashi A., Kumada H., Ohmae M., Kirihata M., Imahori Y., Suzuki M., Sakrai Y., Sumi T., *et al.*, *Effectiveness of boron neutron capture therapy for recurrent head and neck malignancies*, Appl Radiat Isot, **67**, S37–S42 (2009).
21. Locher G.L., *Biological effects and therapeutic possibilities of neutrons*, Am J Roentgenol Radium Ther, 1936.
22. Menichetti L., De Marchi D., Calucci L., Ciofani G., Menciassi A., Forte C., *Boron nitride nanotubes for boron neutron capture therapy as contrast agents in magnetic resonance imaging at 3''–T''*, Appl. Radiat. Isot., **69**, 17–25 (2011).
23. R. Ferdinand *et al.*, *RFQ design for High-Intensity Proton Beams*, Proc. of 1995 Partl. Accel. Conf., 1995, p. 1146.
24. Rassow J., Stecher-Rasmussen F., Voorbraak W., Moss R., Vroegindeweij C., Hideghéty K., Sauerwein W., *Comparison of quality assurance for performance and safety characteristics of the facility for Boron Neutron Capture therapy in Petten/NL with medical electron accelerators*, Radiother Oncol., **59**, *1*, 99–108 (2001).
25. Rolf F Barth, M. Graca H. Vicente, Otto K. Harling, W.S. Kiger, Kent J. Riley, Peter J. Binns, Franz M. Wagner, Minoru Suzuki, Teruhito Aihara, Itsuro Kato, Shinji Kawabata, *Current status of boron neutron capture therapy of high grade gliomas and recurrent head and neck cancer*, Radiation Oncology, **7**, 146 (2012).
26. S. Halfon, *Current status of the liquid lithium target development*, 4th High-Power Targetry Workshop, May 3, 2011.
27. Sibrian-Vazquez M., Vicente MGH., *Boron tumor-delivery for BNCT: Recent developments and perspectives*, in Boron Science: New Technologies & Applications, Edited by Hosmane NS, CRC Press, 2011, pp. 209–232.
28. Slakin, D.N., *A history of boron neutron capture therapy of brain tumors-postulation of a brain radiation dose tolerance limit*, 1991.
29. Suzuki M., Sakurai Y., Nagata K., Kinashi Y., Masunaga S., Ono K., Maruhashi A., Kato I., Fuwa N., Hiratsuka J., Imahori Y., *Impact of intra-arterial administration of boron compounds on dose-volume histograms in boron neutron capture therapy for recurrent head-and-neck tumors*, Int J Radiat Oncol Biol Phys., **66**, *5*, 1523–1527 (2006).

30. Tanaka K., Kobayashi T., Sakurai Y., Nakagawa Y., Ishikawa M., Hoshi M., *Irradiation characteristics of BNCT using near-threshold ^{7}Li(p,n)^{7}Be direct neutrons: application to intra-operative BNCT for malignant brain tumors*, Phys. Med. Biol., **47**, 3011–3032 (2002).
31. Thomas E. Blue and Jacquelyn C. Yanch, *Accelerator-based epithermal neutron sources for boron neutron capture therapy of brain tumors*, Journal of Neuro-Oncology, **62**, 19–31 (2003).
32. Tieh-Chi Chu, Sung-Yen Lin, Jao-Perng Lin, Mu-Tai Liu, *The Measurement of Photoneutron in the Vicinity of Siemens Primus Linear Accelerator*, Applied Radiation and Isotopes, **10**, 2001.
33. V.M. Sanin, V.A. Bomko, B.V. Zaitsev, A.S. Zadvorny, A.P. Kobets, Yu.P. Mazalov, Z.E. Ptukhina, B.I. Rudjak, *Proton Linear Accelerator for Boron-Neutron Capture Therapy*, NSC KIPT, Kharkov, Ukraine.
34. Verónica A. Trivillin, Elisa M. Heber, David W. Nigg, Maria E. Itoiz, Osvaldo Calzetta, Herman Blaumann, Juan Longhino, and Amanda E. Schwint, *Therapeutic Success of Boron Neutron Capture Therapy (BNCT) Mediated by a Chemically Non-selective Boron Agent in an Experimental Model of Oral Cancer: A New Paradigm in BNCT Radiobiology*, Radiation Research, **166**, *2*, 387–396 (2006).
35. Wang C.K., Blue T.E., Gahbauer R., *A neutronic study of an accelerator-based neutron irradiation facility for boron neutron capture therapy*, Nucl. Tech., **84**, 93–107 (1989).
36. Yamamoto T., Matsumura A., Nakai K., Shibata Y., Endo K., Sakurai F., Kishi T., Kumada H., Yamamoto K., Torii Y., *Current clinical results of the Tsukuba BNCT trial*, Appl. Radiat. Isot., **61**, 1089–1093 (2004).
37. Yamamoto T., Nakai K., Nariai T., Kumada H., Okumura T., Mizumoto M., Tsuboi K., Zaboronok A., Ishikawa E., Aiyama H., *et al*., *The status of Tsukuba BNCT trial: BPA-based boron neutron capture therapy combined with X-ray irradiation*, Appl. Radiat. Isot., **69**, 1817 (2011).
38. Yanch J.C., Zhou X.-I., Shefer I.E., Klinkowstein R.E., *Accelerator-based epithermal neutron beam design for neutron capture therapy*, Med. Phys., **19**, 709–721 (1992).
39. Yinghuai, Zhu; Cheng Yan, Koh; Maguire, John A.; Hosmane, Narayan S., *Recent Developments in Boron Neutron Capture Therapy (BNCT) Driven by Nanotechnology*, Current Chemical Biology, **1**, *2*, 141–149(9) (2007).