Boron Neutron Capture Therapy (BNCT)

Part II: Worldwide Network for Clinical BNCT – Clinical Experiences and Mandatory Requirements for Clinical Practice

Introduction to Part II:

In Part I "Principles and Challenges of BNCT", we dealt with Boron Neutron Capture Therapy (BNCT): its progression towards a clinical modality thanks to hospital-based accelerators for powerful neutron sources, the situation worldwide and our claim for an urgent need for BNCT. The take home message was: For treating the estimated number of more than 2 million patients a year, several hundred BNCT centers are needed, each of them with a capacity of 1,500 patients/year. In Part II we are concentrating on the clinical implementation of BNCT and are not regarding the efforts needed from basic science for optimizing BNCT.

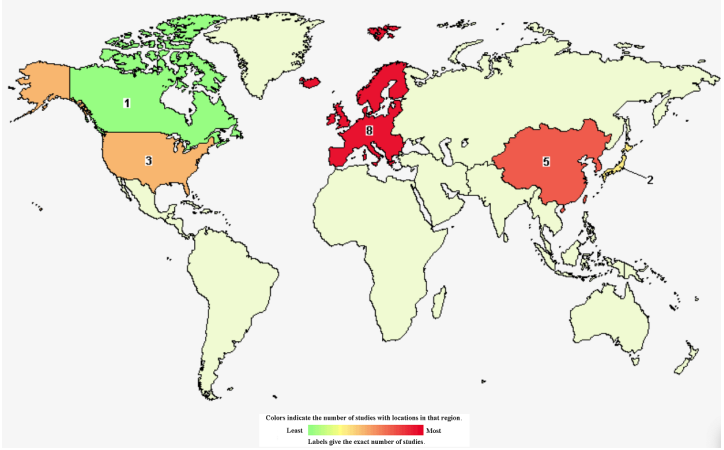
Clinical data

In Part I we have shown that even concentrating on such clinical situations that deemed to be incurable, there are more than 1.000.000 patients around the world every year, who might benefit greatly from BNCT therapy.

For this purpose, the establishment of a network of BNCT treatment centers, strategically distributed, is sensible and necessary. This very large number of potential patients for BNCT, if we want to guide them responsibly to an appropriate therapy, **requires a whole series of national and international procedures and approval steps**. A network of this size can only be established if quality and safety are ensured. A concentrated effort is necessary to implement such a hopeful and promising concept, with a considerable benefit for the patients to be treated - also from a business point of view

The most important prerequisites for globally applied BNCT Therapy are clinically validated data obtained through well-designed, controlled clinical trials.

Do we have clinical data that give us an evidence that this promising therapy achieves better results than conventional treatments?
On the webpage of the U.S. National Library of Medicine of the NIH several clinical studies are documented (see Annex I). The most important countries for such kind of clinical BNCT trials are shown here:



NIH U.S. National Library of Medicine: *clinicaltrials.gov*

As Annex II to this Part II you will find a table summarizing papers reporting clinical outcome after BNCT. Unfortunately, all papers are reporting small numbers of patients who were treated with different protocols, only few studies were designed as a prospective clinical trial and none were made with the intention of collecting data to be submitted to a regulatory authority for establishing BNCT as an accepted treatment. Only recently the 4 centers with accelerator-based neutron sources in Japan have performed trials for obtaining the permission to treat patients. The results are still not yet publicly available. Barth and Grecula[1] published recently a review paper, summarizing some of the clinically relevant data obtained with BNCT with different therapy protocols and made a short comparison with results obtained using established therapies. Their and our conclusion is:

We urgently need more well-designed clinical trials.

In the following, we try to summarize briefly some important aspects concerning clinical trials. Trial strategies will have to be designed following the goal that should be reached.

Clinical trials for establishing the method

Clinical trials are necessary for establishing the method but first of all for certifying the facility. An accelerator-based radiation source for BNCT consists of a high current proton accelerator, a target and a Beam Shaping Assembly (BSA). The sources will be marketed and have to be certified as a medical device. Nowadays in many countries, such certification includes a clinical trial. Clinical studies with BNCT have to demonstrate to the regulatory authorities that this new modality can be safely used for routine clinical applications. The trials have to be conducted in accordance with the established standards of evidence-based medicine. In particular, they have to follow the principles of the Declaration of Helsinki, and Good Clinical Practice. The well-established trial system for drugs consists of phase I trials to evaluate the maximum tolerated dose and determining the spectrum of side effects and unexpected toxicities. International guidelines for evaluating medical devices such as the new European Medical Device Regulation 2017/745 and Guidelines on Medical Devices in MEDDEV 2.7.1, Rev 4 do not mention how such clinical trials have to be designed because of the big differences between different medical devices. However, as long as a new radiation source is tested with an

[1] Rolf F. Barth and John C. Grecula. Boron neutron capture therapy at the crossroads – Where do we go from here? Applied Radiation and Isotopes 160 (2020) doi.org/10.1016/j.apradiso.2019.109029

existing and “accepted” drug, the difficulties to design such trial are manageable. This latter condition does not mean that the compounds used since longtime, namely BSH and BPA can be considered as certified drugs (this is only the case for BPA in Japan, which is available on the market since May 20th, 2020 under the name Steboronine®). However, for these 2 drugs, there is no need to initiate a Phase I trial for drug toxicity, Phase I can directly start for the combination drug and neutron irradiation. Depending on the requests of the relevant regulatory authority, even Phase II trials might be used for obtaining a certification of the facility. Nevertheless, the drug used for such trials will also be an experimental drug under investigation. As long as no pharmaceutical company is involved, a special licensing will be mandatory for the pharmacists concerned.

In addition of the licensing of the radiation source, there is a periphery of medical devices that only are necessary for BNCT, which also need to be licensed, namely the system for measuring boron concentration in blood and the treatment planning system (TPS).

All this might be done in one single center by clinicians having some experience with early clinical trials in radiation oncology and certification trials for medical products, in a close collaboration with industry and regulatory authorities. In addition, a CRO (Clinical Research Organization) and specialized lawyers will be necessary to avoid problems. It will be wise to organize this certification trial(s) in such way that the most important regulatory authorities worldwide will accept the results and that not several trials in different countries are becoming necessary. It has to be stressed: these first trials have to be designed for establishing the method. These investigations for proving safety of the method and the certification of all elements needed for the therapy (Phase I clinical trial) might be performed at one (research oriented) center.

It is important to stress another aspect: Everything that was briefly described above is only the first step and even if the accelerator and all other devices are allowed to be marketed as medical products and used to treat patients **there is no reimbursement**.

Clinical trials for obtaining reimbursement

The difficult period between construction of the center and start of reimbursement, should be as short as possible. This can only be achieved by organizing clinical trials by a multi-institutional coordinated network of BNCT facilities. Well-designed Phase II trials targeting situations deemed to be incurable are the most promising strategy for obtaining an early reimbursement. In Part I, we already quoted such an approach[2]. It will make sense to focus in a first step inoperable loco-regional tumor recurrences after full dose of radiation therapy that do not respond to systemic therapies. In parallel, radio-resistant malignancies might be a good target for obtaining data to negotiate an early reimbursement.

Such Single-arm prospective studies have to be of very high quality by including:

- clearly articulated eligibility criteria,
- a priori null and alternate hypotheses and
- explicit sample size calculations.

By combining efforts and following the same protocol, a global network of BNCT centers will be able to perform Phase III trials in a reasonable time frame by comparing the gold standard of treatment with an innovative BNCT approach. A good target for such trials could be Non-Small Cell Lung Cancer (NSCLC) with early lymph node metastases.

[2] Boron neutron capture therapy for locally recurrent head and neck squamous cell carcinoma: An analysis of dose response and survival, Koivunoro H et al. Radiotherapy and Oncology 137 (2019) 153–158

Clinical trials for new boron compounds

All the above is feasible using the existing boron compounds BPA and BSH. A very different situation has to be handled when an innovative boron carrier is to be marketed. Following the established procedures for drug development, in a very first step the toxicity of the compound needs to be established. Without irradiation there is no hypothetical benefit for the patient. A testing that only looks on toxicity in healthy probands without any surrogate for an expected efficacy is not appropriate either. A study design might be oriented at EORTC trial 11001[3], combining a preoperative application of the drug with sampling of tissues during surgery for measuring the boron uptake in tumor and normal tissues as surrogate endpoint for expected efficacy. The ethical issues linked to a protocol searching for toxicities but without any benefit for the patient are a special challenge. More important is the fact that such a trial for a really innovative boron carrier never has been done. Very careful discussion with the regulatory authorities will be mandatory prior to develop the protocol. If such a Phase 0 trial[4] once have been done and further investigation with the new drug will be permitted, a Phase I trial combining drug and irradiation can be performed as already described.

Having all this in mind and being able developing highly performing protocols, can we start such an early trial? Unfortunately not as there are many other steps that are mandatory before a first patient can be treated in the frame of such a trial protocol. The next paragraph will very briefly list some of the most important aspects and requirements that have to be fixed before the important clinical trials can start.

The BNCT concept sounds simple.
It can be realized!

Mandatory Requirements for Clinical BNCT

The application of BNCT in human patients needs a multi-institutional and multi-disciplinary collaboration that should be initiated as soon as a group of researchers, decides to investigate the possibility to perform patient treatment. By treating patients, a high responsibility and a risk associated with the resulting liability will be on each individual participant and institution. Such a situation needs contractual agreements that must define unambiguously the responsibilities and tasks of all the partners.

Regulatory Affairs and Licensing for a BNCT Facility

As there are up to now no regulations or guidelines to perform BNCT, it is necessary to obtain a complete, multifunctional portfolio of approvals, documentation and infrastructural needs in order to have a sound case to be permitted performing BNCT in patients. The issues that need to be addressed are listed briefly below and are applicable to all BNCT Centers worldwide:

3 ^{10}B-uptake in different tumors using the boron compounds BSH and BPA. EORTC Protocol 11001 (Study coordinator W. Sauerwein), NTC-PRC outline approval March 2001, PRC Full Protocol approval October 2002

4 Wittig A., Sauerwein W. (2012): Clinical trials in BNCT: A challenging task. In: Sauerwein W., Wittig A., Moss R., Nakagawa Y.(eds) Neutron Capture Therapy. Principles and Applications. Springer Heidelberg New York Dordrecht London.
ISBN 978-3-642-31333-2, DOI 10.1007/978-3-642-31334-9, p.369-376

Short list of topics to be resolved with regulatory authorities:

- **Infrastructure** (building, parking, water, power supply, and IT connections)
- **Hardware** (accelerator, target, beam delivery system, instruments for boron analysis)
- **Software** (including treatment planning system)
- **Boron carrier** (handling an up to now non-registered drug to be used in the treatment protocols following the relevant ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) guidelines , as published by the European Medicines Agency EMEA)
- **Clinical trials**
- **Staff**

Everybody is aware that all these points are strongly regulated and need special permissions, certifications and qualifications following dedicated laws that are different in each country. Very often however **managerial aspects** are underestimated. Here some examples from our experience:

- **Clinical trial protocol related**: reconciling the different points of view of different ethics committees in different countries (if applicable); gaining approval of the study protocol by different review boards
- **Patient related**: obtaining insurance for patients and building up the local infrastructure for patient care, travel and nursing, including all anticipated emergencies.
- **Personnel and institution related**: describing the tasks of all participants and creating the appropriate agreements and contracts to define such structures and applying the appropriate rules for radiation protection of the patients and the staff and concluding contracts (if applicable) with all involved parties. A special issue is the training of all staff members.
- **Radiation Protection:** Special issues in addition to those in conventional radiotherapy are related to the activation of the neutron source (especially the target), the room, all instruments and materials for positioning the patient, and the patient himself.
- **Quality Management:** The complexity of BNCT requires a dedicated, reliable and safe quality assurance system. An entire philosophy has to be adapted for the needs of BNCT, in which Standard Operating Procedures (SOP) play a role, but are still the simpler part of the whole.
- Establishing the **interdisciplinary collaboration** with the neighboring and pre-existing clinical departments and medical institutions.

The Concept of BNCT Global

Up to now, all BNCT centers were some “stand alone” solutions and had to find their way through the jungle of bureaucracies on their own and set up the entire organization themselves.

BNCT Global is an international network of BNCT facilities with one (or several) research-oriented Reference Center or headquarter offering services to the clinical oriented facilities that are focusing on treating patients. International cooperation between the local BNCT centers and the radiotherapy/oncology centers is essential for good clinical practice (**GCP**), evidence-based medicine and economic success. BNCT Global will streamline procedures and reduce the efforts necessary to reach the goal by doing the paperwork for all treatment centers at once, by creating clear organizational structures that will work everywhere and by offering central services on highest level of quality that have not be performed decentralized at high costs.
Details will be described in **Part III: Mandatory Requirements for clinical BNCT – Concept of BNCT Global.**

Conclusions

We have shown that concentrating on such clinical situations that deemed to be incurable, there are more than 1.000.000 patients every year around the world, who might benefit greatly from BNCT therapy. For decades, the clinical use of BNCT was limited by the need for reactor-based neutron sources.

Recently, hospital-based accelerators have become available, leading to a renewed and now growing interest from the medical community. In Japan, patient treatments with BNCT have been continuously performed since the 1970s. A substantial body of clinical experience has been gathered but highest quality evidence of efficacy of BNCT is lacking.

These preconditions, regulations, standardization, licensing etc. described in this Part II pose an immense challenge for the establishment of a clinical BNCT center. With a reasonable time, personnel and economic/financial commitment, a single project development cannot afford this immense effort within the next years.

BNCT is thwart with danger and has the potential, if incorrectly applied, to be harmful to the patient. Apart from designing optimal physical facilities, it is therefore of utmost importance that special attention is given to a management structure that provides safety beyond normal rules. This involves strict quality management (QM) procedures that offer guaranteed reliable and safe functioning of the treatment. QM is therefore a mandatory task. In order to obtain comparable procedures, it is recommended to follow an international standard when designing the QM structure for a BNCT facility. The most convenient way to reach an international standard and to have the possibility to become a licensed quality management system is offered by EN ISO 9001:2015.

The establishment of a sustainable, scientifically founded clinical BNCT that functions as a business case requires the efforts of the entire BNCT community in the world. Here it is especially important that all the preliminary work and fundamental basic findings made so far are assembled together. All efforts and resources must be focused on the establishment of an international clinical BNCT network.

Ready for a Business Case?

To initiate a new therapeutic medical procedure, four basic steps are needed:

I. Basic research for the essential individual factors of this procedure (mostly done)
II. Studies at clinical level (partly, most of it is still missing)
III. Mandatory requirements for clinical BNCT – structure of an international organized, interdisciplinary network that fulfillls these conditions (these conditions must be met in an essential way)
IV. Proof of a functioning business case

We will focus on these topics in Part III and IV.

Prof. Wolfgang Sauerwein **Essen/Germany July 4th, 2020**

Deutsche Gesellschaft für Bor-Neutroneneinfangtherapie
Universitätsklinikum Essen
Hufelandstr. 55
45147 Essen Germany
w.sauerwein@dgbnct.de

Upcoming Publications:

1. W. Sauerwein, K. Ono, A. Wittig, R. Moss, Y. Nakagawa (Eds.): **Neutron Capture Therapy – Principles and Applications (second edition)** will be published by Springer in 2020.
2. In addition, a special issue of the journal "***Cells***" will be published in 2020 on Biology of Boron Neutron Capture Therapy (BNCT)
   Editors: W. Sauerwein, A. Schwint, M. Masutani, J. Hopewell
   https://www.mdpi.com/journal/cells/special_issues/cells_BNCT

Annex I: BNCT Clinical trials registered at NIH U.S. National Library of Medicine:
(clinicaltrials.gov)

Study Title	Tumors	Interventions	Locations
Boron Neutron Capture Therapy (BNCT) for Locally Recurrent Head and Neck Cancer	Head and Neck Cancer	Radiation: Boron Neutron Capture Therapy	Cancer Center, Taipei Veterans General Hospital Taipei, Taiwan
In-hospital Neutron Irradiator (IHNI)-Based Boron Neutron Capture Therapy (BNCT) in the Treatment of Malignant Melanoma	Melanoma Boron Neutron Capture Therapy	Radiation: Boronophenylalanine and IHNI-based BNCT	The Third Xiangya Hospital of Central South University Changsha, Hunan, China
BNCT and IG-IMRT for Recurrent Head and Neck Cancer	Head and Neck Cancer Recurrence	Radiation: boronophenylalanine-based BNCT	Department of Oncology, Helsinki University Central Hospital Helsinki, Finland
BNCT to Treat Glioma That Has Progressed Following Radiotherapy	Glioblastoma Anaplastic Astrocytoma	Radiation: Bononophenylalanine (BPA)-based BNCT	Department of Oncology, Helsinki University Central Hospital Helsinki, Finland
Boron Neutron Capture Therapy (BNCT) Combined With Cetuximab in the Treatment of Locally Recurred Head and Neck Cancer	Head and Neck Cancer	Radiation: BNCT Drug: cetuximab	Department of Oncology, Helsinki University Central Hospital Helsinki, Finland
Boron Neutron Capture Therapy Using CICS-1 and SPM-011 for Malignant Melanoma and Angiosarcoma	Malignant Melanoma Angiosarcoma	Other: CICS-1 (investigational device), SPM-011(investigational drug)	National Cancer Center Hospital Chuo Ku, Tokyo, Japan
Boron Neutron Capture Therapy, Radiation Therapy, and Temozolomide in	Brain and Central Nervous System Tumors	Radiation: BNCT (boron neutron capture therapy) Radiation: XRT (X-ray radiation treatment)	Osaka Medical College Takatsuki, Osaka, Japan

Treating Patients With Newly Diagnosed Glioblastoma Multiforme		Drug: TMZ (temozolomide)	
Boron Neutron Capture Therapy (BNCT) as Treatment of Glioblastoma	Glioblastoma	Radiation: irradiation	Department of Oncology, Helsinki University Central Hospital Helsinki, Finland
Boron Neutron Capture Therapy Following Surgery in Treating Patients With Glioblastoma Multiforme Removed During Surgery	Brain and Central Nervous System Tumors	Drug: sodium borocaptate Procedure: adjuvant therapy	Karl-Franzens-University Graz Graz, Austria Toronto Sunnybrook Regional Cancer Centre at Sunnybrook Health Sciences Centre Toronto, Ontario, Canada Hopital Pasteur Nice, France (and 5 more...)
Boron Neutron Capture Therapy in Treating Patients with Stage III Melanoma	Melanoma (Skin)	Drug: boronophenylalanine-fructose complex	Boston University School of Medicine Boston, Massachusetts, United States Beth Israel Deaconess Medical Center Boston, Massachusetts, United States
Boron Neutron Capture Therapy in Treating Patients with Melanoma	Melanoma (Skin)	Radiation: boron neutron capture therapy	Beth Israel Deaconess Medical Center Boston, Massachusetts, United States Massachusetts Institute of Technology Cambridge, Massachusetts, United States
Boron Phenylalanine With or Without Mannitol in Treating Patients With Glioblastoma Multiforme	Brain and Central Nervous System Tumors	Drug: boron phenylalanine Drug: mannitol Other: biologic sample preservation procedure Radiation: radiation therapy treatment planning/simulation	England, United Kingdom Cancer Research UK Clinical Trials Unit - Birmingham Birmingham, England, United Kingdom

Boron Neutron Capture Therapy in Treating Patients with Glioblastoma Multiforme or Melanoma Metastatic to the Brain	Brain and Central Nervous System Tumors Melanoma (Skin) Metastatic Cancer	Drug: boronophenylalanine-fructose complex	Beth Israel Deaconess Medical Center Boston, Massachusetts, United States Massachusetts Institute of Technology Cambridge, Massachusetts, United States
Boronophenylalanine-Fructose Complex (BPA-F) and/or Sodium Borocaptate (BSH) Followed By Surgery in Treating Patients With Thyroid Cancer, Head and Neck Cancer, or Liver Metastases	Colorectal Cancer Head and Neck Cancer Metastatic Cancer	Drug: boronophenylalanine-fructose complex Drug: sodium borocaptate Procedure: conventional surgery	Universitaetsklinikum Essen Essen, Germany

Annex II:

Reports on clinical experiences with BNCT (as it stands today, June 2020)

First author	Year	Publication
Malignant Glioma		
Hatanaka	1991	Hatanaka, Hiroshi, 1991. Boron neutron capture therapy of brain tumors. In: Laws E., Karin, A.B.M.F. (Eds.), Glioma. Springer, Berlin
Nakagawa	1997	Nakagawa, Y., Hatanaka, H., 1997. Boron neutron capture therapy. Clinical brain tumor studies. J. Neuro Oncol. 33, 105-115
Wittig	2002	Wittig A, Hideghety K, Paquis P, Heimans J, Vos M, Goetz C, Haselsberger K, Grochulla F, Moss R, Morissey J, Bourhis-Martin E, Rassow J, Stecher-Rasmussen F, Turowski B, Wiestler M, De Vries M, Fankhauser H, Gabel D, Sauerwein W, 2002. Current clinical results of the EORTC-study 11961. In: Sauerwein W, Moss R, Wittig A (eds) Research and development in neutron capture therapy. Monduzzi Editore, Bologna, pp 1117–1122
Burian	2002	Burian J, Marek M, Rataj J et al, 2002. Report on the first patient group of the phase I BNCT trial at the LVR-15 reactor. In: Sauerwein W, Moss R, Wittig A (eds) Research and development in neutron capture therapy. Monduzzi Editore, Bologna, pp 1107–1112
Capala	2003	Capala, J., Stenstam, B.H., Skold, K., Munck af Rosenschold, P., Giusti, V., Persson, C., Wallin, E., Brun, A., Franzen, L., Carlsson, J., Salford, L., Ceberg, C., Persson, B., Pellettieri, L, Henriksson, R., 2003. Boron neutron capture therapy for glioblastoma multiforme: clinical studies in Sweden. J. Neuro Oncol, 62, 135-144
Diaz	2003	Diaz AZ, 2003. Assessment of the results from the phase I/II boron neutron capture therapy trials at the Brookhaven National Laboratory from a clinician's point of view. J Neurooncol 62,101–109
Busse	2003	Busse PM, Harling OK, Palmer MR et al, 2003. A critical examination of the results from the Harvard-MIT NCT program phase I clinical trial of neutron capture therapy for intracranial disease. J Neurooncol 62:111–121
Joensuu	2003	Joensuu H, Kankaanranta L, Seppälä T et al, 2003. Boron neutron capture therapy of brain tumors: clinical trials at the Finnish facility using boronophenylalanine. J Neurooncol 62:123–134
Yamamoto	2009	Yamamoto T, Nakai K, Kageji T et al (2009) Boron neutron capture therapy for newly diagnosed glioblastoma. Radiother Oncol 91:80–84
Skold	2010	Skold, K., Gorlia, T., Pellettieri, L., Giusti, V., Stenstarn B, H., Hopewell, J.W., 2010. Boron neutron capture therapy for newly diagnosed glioblastoraa multiforme: an assessment of clinical potential. Br. J. Radiol. 83, 596-603
Kawabata	2011	Kawabata, S., Miyatake, S., Hiramatsu, R., Hirota, Y., Miyata, S., Takekita, Y., Kuroiwa, T., Kirihata, M., Sakurai, Y., Maruhashi, A., Ono, K., 2011, Phase II clinical study of boron neutron capture therapy combined with X-ray radiotherapy/ temozolornide in patients with newly diagnosed glioblastoma multiforme-study design and current status report. Appl. Radiat. h o t 69, 1796-1799
Kankaanranta	2011	Kankaanranta, L., Seppala, T., Koivunoro, H., Valimaki, P., Beule, A., Collan, J., Kortesniemi, M., Uusi-Simola, J., Kotiluoto, P., Auterinen, I., Saran, T., Paetau, A., Saarilahti, K., Savolainen, S., Joensuu, H., 2011. 1-boronophenylalanine-mediated boron neutron capture therapy for malignant glioma progressing after radiation therapy: a Phase I study. Int. J. Radiat Oncol. Biol, Phys. 80, 369-376
Yamamoto	2012	Yamamoto T, Matsumura A, 2012. External Beam BNCT for Glioblastoma Multiforme. In: Sauerwein W., Wittig A., Moss R., Nakagawa Y.(eds) Neutron Capture Therapy. Principles and Applications. Springer Heidelberg New York Dordrecht London

Malignant Menigioma		
Kawabata	2012	Kawabata S, Miyatake S-I, 2012. Boron Neutron Capture Therapy for Malignant Meningiomas In: Sauerwein W., Wittig A., Moss R., Nakagawa Y.(eds) Neutron Capture Therapy. Principles and Applications. Springer Heidelberg New York Dordrecht London
Takeuchi	2018	Takeuchi, K., ICawabata, S., Hiramatsu, R., Matsushita, Y., Tanaka, H., Sakurai, Y., Suzuki, M., Ono, K., Miyatake, St., Kuroiwa, T., 2018. Boron neutron capture therapy for high-grade skull-base meningioma. J. Neurol. Surg. B Skull Base 79, 322-327
Head and Neck Malignancies		
Kato	2004	Kato, I., Ono, K., Sakurai, Y., Ohmae, M., Maruhashi, A., Imahori, Y., Kirihata, M., Nakazawa, M., Yura, Y., 2004. Effectiveness of BNCT for recurrent head and neck malignancies. Appl. Radiat. Isot. 61, 1069-1073
Aihara	2012	Aihara T., Morita , 2012. BNCT for Advanced or Recurrent Head and Neck Cancer. In: Sauerwein W., Wittig A., Moss R., Nakagawa Y.(eds) Neutron Capture Therapy. Principles and Applications. Springer Heidelberg New York Dordrecht London
Suzuki	2014	Suzuki, M., Kato, I., Aihara, T., Hiratsuka, J., Yoshimura, K., Niimi, M., Kimura, Y., Ariyoshi, Y., Haginomori, S., Sakurai, Y., Kinashi, Y., Masunaga, S., Fukushima, M., Ono, K., Maruhashi, A., 2014. Boron neutron capture therapy outcomes for advanced or recurrent head and neck cancer. J. Radiat. Res. 55, 146-153
Haapaniemi	2016	Haapaniemi, A., Kankaanranta, L., Saat, R., Koivunoro, H., Saarilahti, K, Makitie, A., Atula, T., Joensuu, H., 2016. Boron neutron capture therapy in the treatment of recurrent laryngeal cancer. Int. J. Radiat. Oncol. Biol. Phys. 95, 401-410
Wang	2018	Wang, LW., Liu, Y.H., Chou, Ft., Jiang, S.H., 2018. Clinical trials for treating recurrent head and neck cancer with boron neutron capture therapy using the Tsing-Hua Open Pool Reactor. Canc. Commun, 38, 37
Koivunoro	2019	Koivunoro, H., Kankaanranta, L., Seppala, T., Haapaniemi, A., Makitie, A., Joensuu, H., 2019. Boron neutron capture therapy for locally recurrent head and neck squamous cell carcinoma: an analysis of dose response and survival. Radiother. Oncol, 137, 153-158.
Skin Melanoma		
Mishima	1989	Mishima Y, Honda C, Ichihashi M et al, 1989. Treatment of malignant melanoma by single neutron capture treatment with melanoma-seeking ^{10}B-compound. Lancet II:388–389
Fukuda	1994	Fukuda H, Hiratsuka J, Honda C et al, 1994. Boron neutron capture therapy of malignant melanoma using ^{10}B-paraboronophenylalanine with special reference to evaluation of radiation dose and damage to the normal skin. Radiat Res 138:435–442
Mishima	1996	Mishima Y, 1996. Selective thermal neutron capture therapy of cancer cells using their specific metabolic activities—Melanoma as prototype Cancer. In: Mishima Y (ed) Neutron Capture Therapy. Plenum Press, New York, pp 1–26
Palmer	2002	Palmer MR, Goorley JT, Kiger WS III et al, 2002. Treatment planning and dosimetry for the Harvard-MIT PhaseIIclinical trial of cranial neutron capture therapy. Int J Radiat Oncol Biol Phys 53:1361–1379
Hiratsuka	2012	Hiratsuka J, Fukuda H, 2012 Malignant Melanoma In: Sauerwein W., Wittig A., Moss R., Nakagawa Y.(eds) Neutron Capture Therapy. Principles and Applications. Springer Heidelberg New York Dordrecht London
Genital Malignancies		
Hiratsuka	2018	Hiratsuka, J., Kamitani, N., Tanaka, R., Yoden, E., Tokiya, R., Suzuki, M., Barth, R.F., Ono, K., 2018. Boron neutron capture therapy for vulvar melanoma and genital extramarrunary Paget's disease with curative responses. Canc. Commun. 38, 38
Brain malignancies in children		
Nakagawa	2012	Nakagawa Y, Kageji T, 2012. Boron Neutron Capture Therapy for Children with Malignant Brain Tumors. In: In: Sauerwein W., Wittig A., Moss R., Nakagawa Y.(eds) Neutron Capture Therapy. Principles and Applications. Springer Heidelberg New York Dordrecht London