Boron Neutron Capture Therapy (BNCT)

Part I: Principles and Challenges of BNCT

1. BNCT: progression and key milestones

BNCT relies on the results of the strong progress in the interdisciplinary clinical research between physics, chemistry, pharmaceutics and technology for its large-scale utilization in modern and advanced medicine. It combines state-of-the-art technological development with the requirements of one of the most important disciplines of medicine, namely oncology. This has also opened up very promising, additional possibilities for scientific applications[1].

BNCT is based on the ability of the non-radioactive isotope boron-10 capturing thermal neutrons resulting two charged particles namely a helium and lithium nucleus. Both particles have a high LET (linear energy transfer) and therefore a very high biological effectiveness in killing cells. Their range in tissue is very short (about 10 µm), which corresponds approximately to the diameter of one mammalian cell. If these reactions can be selectively triggered in tumor cells, some kind of "cell-surgery" will be reached: single tumor cells invading normal tissues can be destroyed without damaging the surrounding healthy structures - thus, a highly effective weapon in the fight against cancer.

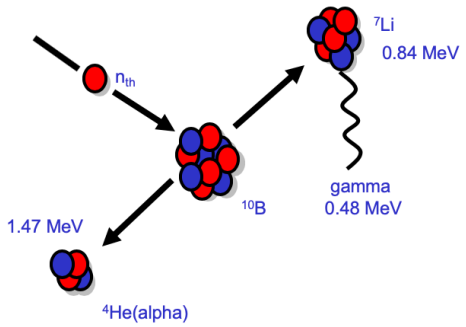


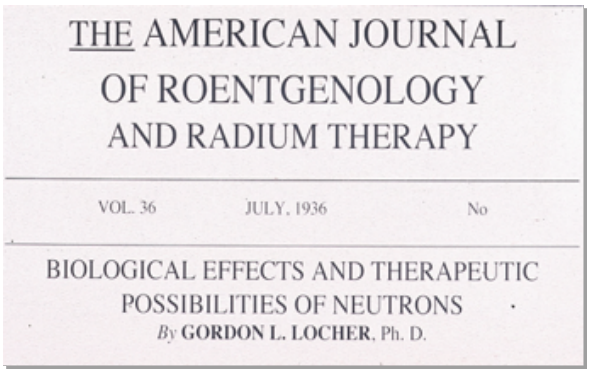
FIG 1 *BNCT is based on the ability of the isotope ^{10}B to capture low energy neutrons to produce two highly energetic particles with low range in tissue*

To use this reaction for medical applications was first suggested early in 1936 by Gordon L. Locher[2]. The first clinical applications were performed by US scientists at Brookhaven and MIT in the1950s, but with a disappointing outcome, results being similar to those obtained by conventional radiotherapy [3].

[1] Neutron Capture Therapy - Principles and Applications. Editors Wolfgang A.G. Sauerwein • Andrea Wittig Raymond Moss • Yoshinobu Nakagawa, Springer, 2012 ISBN 978-3-642-31333-2

[2] Locher GL. Biological effects and therapeutic possibilities of neutrons. Am J Roentgenol Radium Ther. 1936;36(1):1–13

[3] Sauerwein WAG: Principles and Roots of Neutron Capture Therapy, in: Sauerwein et.al (edts): Neutron Capture Therapy – Principles and Applications. Springer 2012, p 1-16



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BIOLOGICAL EFFECTS AND THERAPEUTIC POSSIBILITIES OF NEUTRONS

By GORDON L. LOCHER, Ph. D.

FIG 2 *First publication concerning BNCT: Gordon Locher 1936*

In 1968, in Japan, Hiroshi Hatanaka introduced BNCT into clinical practice using the new boron compound BSH. The treatment was performed after tumor excision as an intraoperative radiotherapy exposing directly the tumor bed and shielding of the skull. Hatanaka reported exciting results, the 5-year survival rate being 58 % in a small group of highly selected patients suffering from malignant glioma grades 3 and 4 (Fig.3)[4]. After some hesitations, this data stimulated new efforts worldwide to start new clinical trials outside of Japan.

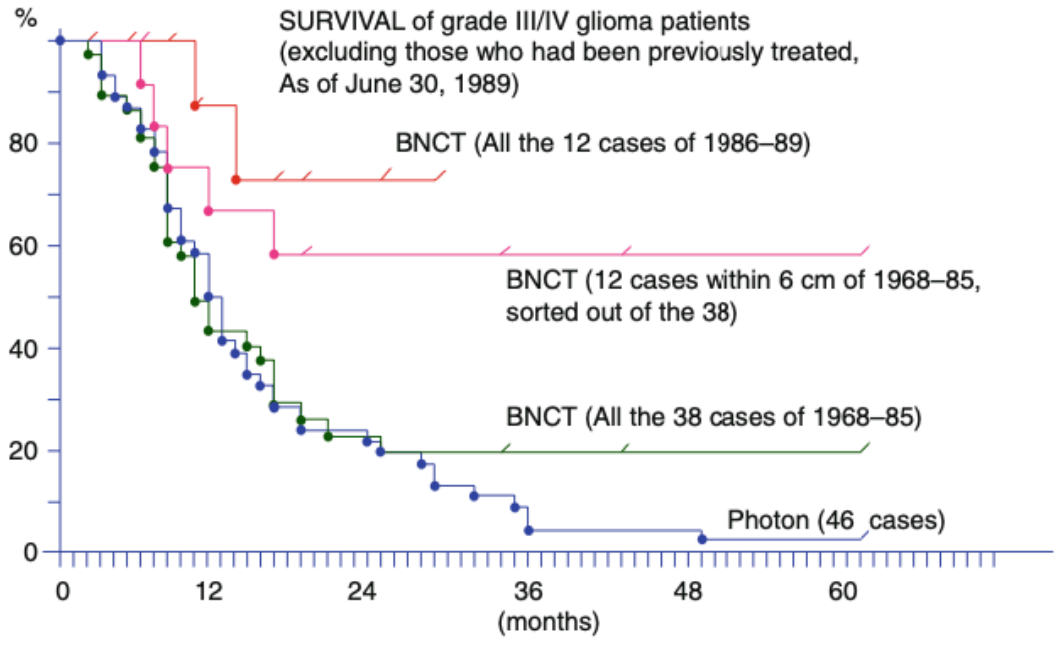

FIG 3 *Hatanaka reported exciting results, the 5-year survival rate being 58 % in a small group of highly selected patients suffering from malignant glioma grades 3 and 4.*

Of particular importance was the discovery, investigation and verification of the transport mechanism through the cell membrane of the boron compound, p-(dihydroxyboryl)-phenylalane (BPA). The results of

[4] Hatanaka H (1990) Clinical results of boron neutron capture therapy. Basic Life Sci 54(15):15–21

this study showed that BPA is transported by the L system and that transport can be further stimulated by amino acids pre-accumulated in the cell by either the L or A amino acid transport system. [5]

Up to now, radiation therapy (RT) is one of the most powerful tools to treat any kind of cancer. However, even when using the most precise techniques that are available today, a large volume of tissue will be irradiated in which both tumor cells and normal cells will be damaged. Furthermore, prior to reaching the targeted volume, radiation traverses normal tissues leading again to undesirable biological effects. In addition, the target has to be identified by diagnostic procedures, but these procedures, even the most advanced ones, only give a virtual "image" of the tumor, resulting in different values of size and extension depending on the imaging modality that is chosen. Finally – and this is a very crucial aspect – a medical doctor has to define the volume that will be irradiated. Based on experience, available technologies and established routines, this target volume will be different from one clinician to another. Furthermore, time is another parameter displaying additional uncertainties. Even the best imaging modality can only show the situation at the time of imaging and, not for example, the next day, when the situation might be completely different. Although the magnitude of each factor varies with treatment technique, they appear to be an inherent characteristic of current advanced RT techniques. Expensive and labor-intensive equipment such as MRI guided radiotherapy or proton therapy are means for mitigating these factors but they most likely cannot eliminate them. This implies that unless some entirely new way of delivering RT is developed, any improvements in the efficacy of RT will be incremental rather than substantive. An approach is needed in which the target is determined and labeled at the biological level. In such a way, the treatment is designed to target only labeled diseased cells wherever they may reside, sparing even normal cells in the immediate proximity to the disease.

BNCT has the potential to be such a radiotherapy of the future for the following reasons:

- it combines a radiation and an activating agent, which is harmless except in the presence of the radiation.
- the radiation dose is low, except in the presence of the agent.
- **only boron targeted tumor cells receive a lethal dose.**

If one agrees that these basic principles themselves are valid, the specific approach has not yet been realized in the sense of evidence-based medicine. There are several reasons:

- Up to now, thermal neutron beams fulfilling the physical requirements for BNCT were only available at a few nuclear research reactors, usually located far away from hospitals. As a result, a clinical trial could never be performed that included a statistically relevant number of patients to prove efficacy.
- Furthermore, at the few places where patients could be treated, this was never supported by the pharmaceutical industry, due to a lack of patient numbers, which did not trigger a market for drug production. Due to this non-existing market, a professionally run, a drug development program was never started. Even the two drugs that were used for patient treatments to-date have never undergone a systematic development and hence there are still a multitude of open questions concerning pharmacokinetics and pharmacodynamics, optimal delivery procedures etc. More effective drugs dedicated to specific cancer entities are necessary.

[5] Wittig A, Sauerwein WA, Coderre JA (2000) Mechanisms of transport of p boronophenylalanine through the cell membrane in vitro. Radiat Res 153:173–180

- The concept of the absorbed dose, that is used in conventional radiotherapy is based on a homogenous distribution of the deposited energy in the observed volume, and therefore cannot be applied for BNCT due to its extremely high inhomogeneity in irradiating only the tumor cells. A new concept for prescribing and reporting this innovative radiation therapy is needed.
- A globally coordinated development is necessary for the safe and successful handling of BNCT. Some of the burning challenges (without claim to be complete) are: reliable and accurate treatment planning systems; reliable, precise and standardized measurements of boron-10 in patients and tissue samples (i.e. blood); imaging showing the drug distribution in a patient; trial design for binary treatments that are accepted by the regulatory authorities, etc.

These very different challenges can only be investigated and solved by interdisciplinary research efforts on an international level.

For the future development of BNCT, the data published in 2019 by Koivunoro H et al. [6] are most significant. Patients suffering from inoperable head and neck squamous cell cancer, recurrent after full dose radio- chemotherapy entered a prospective clinical trial. These types of cases, which are not curable with currant, clinically available therapies were treated with BNCT.
Forty patients received BNCT once (on 1 day), and 39 twice. Forty-seven (68%;) of the 69 evaluable patients responded; 25 (36%) had a complete response, 22 (32%) a partial response, 17 (25%) a stable disease lasting for a median of 4.2 months, and 5 (7%) progressed. The patients treated with BNCT twice responded more often than those treated once. The median follow-up time after BNCT was 7.8 years. The 2-year locoregional progression-free survival rate was 38% and the overall survival rate 21%. A high minimum tumor dose and a small volume were independently associated with long survival in a multivariable analysis.

	CR (n, %)	PR (n, %)	SD (n, %)	PD (n, %)
All evaluable patients, n=69	25 (36%)	22 (32 %)	17 (25 %)	5 (7 %)
BNCT given once, n = 31	6 (19 %)	11 (36 %)	10 (32 %)	4 (13 %)
BNCT given twice, n = 38	19(50 %)	11 (29 %)	7 (18 %)	1 (3 %)

Table 1: Abbreviation: CR = complete response: PR = partial response: SD = stable disease: PD = progressive disease; BNCT = boron neutron capture therapy.[7]

Most patients responded to BNCT. Three patients, who were suffering from a disease incurable with currently available therapeutic modalities were alive without head and neck cancer 5.5, 7.8, and 10.3 years after the date of BNCT.

2. Shifting paradigms: hospital-based accelerators for BNCT

Until recently, only research reactors were available for BNCT, usually located far away from the treating hospital and generally available for patient care only for limited periods of time. It was hardly possible to treat such large patient cohorts that could provide statistically relevant data on the success of this therapy became possible. The lack of neutron sources for BNCT in hospitals has hindered the development of this

[6] 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
[7] see 6

modality. Recently, this problem could be solved by advances in accelerator technologies. Accelerators and beam delivery systems based on different technical solutions are now commercially available for BNCT at prices below the costs for a proton facility and therefore achievable for large hospitals interested in advanced oncology. Currently, there are already 3 accelerator-based BNCT facilities in hospitals in Japan treating patients. Further installations are under construction in China, and Finland.

3. Cancers to be treated with BNCT

What kind of cancer can be treated more efficient with BNCT compared to the most modern radiotherapy methods?

- These are local and regional tumors that grow and invade the normal surrounding tissue, which is the case with most solid malignant tumors.
- A special indication will be recurrent tumors that have already received a full dose from conventional radiotherapy.
- Based on the results of the Helsinki Groupe, hand neck cancer seems to be an excellent indication, that might be extended from such salvage therapy of recurrences to primary treatment.
- The efforts performed over recent decades were often targeting highly malignant brain tumors, which still seem to be a reasonable approach.
- In addition, there are rare cancers that actually have a very low chance to be cured, for example, some salivary gland cancers very resistant to conventional radiotherapy and not responding to chemotherapy, some rare sarcoma such as angiosarcoma of the skin, but also malignant melanoma of the mucosa or malignant meningioma.

BNCT is performed in one, or at most two fractions. This is an important issue for elderly patients, very often suffering from other diseases and unable to tolerate therapies that lasts 6 weeks or longer. This hypo-fraction aspect of BNCT makes it highly interesting to countries where patients may need to travel long distances to a cancer center. It also opens up the possibility of “patient tourism”, the short time needed for the treatment and hospitalization will allow patients to be received from further away at one dedicated center. Treatment can be performed at the BNCT center, patient recruitment and follow up can be done at the participating regional or local cancer center**.**

BNCT has the potential to be a highly effective cancer treatment applied once without long term hospitalization and therefore protecting a high quality of life and reducing costs of hospitalization.

As early as 2012, when the last major summary on the clinical relevance of BNCT was published, clear ideas/proposals were already available.[8]

It can be expected that as soon as the results of the Japanese-controlled BNCT clinical trials, performed under the auspices of the Pharmaceuticals and Medical Devices Agency (PMDA, the Japanese FDA), become available, there will be a rapidly growing interest in BNCT from clinicians and health care providers around the world. Already now, the US National Cancer Institute (NCI) has created a working group for BNCT. The same has happened inside the PTCOG (Particle Therapy Co-Operative Group). The IAEA (International Atomic Energy Agency) is preparing a Technical Meeting with the intention to replace the 20 years old TECDOC related to BNCT (IAEA TECDOC 1223).

[8] See [1]

The fact that a growing market for BNCT is emerging is triggering the development of new drugs to treat diseases other than brain tumors, head and neck cancer or melanoma, which have been the main indications for BNCT in the past.

4. BNCT world-wide

Currently, the medical community outside Japan shows little interest in BNCT. This is mainly because radiation oncologists are not trained in the complex physics of neutron beams. Furthermore, most clinicians are not used to interact with non-medical disciplines, which is a prerequisite for BNCT. In addition, the mainstream in radiation oncology over the last four decades has been focused on ballistic precision, interested in hitting a defined, complex target volume very accurately. No emphasis was placed on the examination of specific biological reactions to different radiation qualities and certainly not on the use of neutrons in tumor therapy.

Sophisticated BNCT treatment protocols (see for example NIH/USA: clinicalTrials.gov) have provided many new insights into possible forms of applications.

However, there is up to now no institution worldwide that is prepared and able to coordinate the complex translational research activities necessary for the success of BNCT in a limited period of time.

Last year in particular, clinicians and scientists from around the world joined forces to establish a coordinated, feasible, scientifically sound, interdisciplinary cooperation. Now, there is a strong need for an interdisciplinary clinical research-based international **Reference Center**, which will support local BNCT hospitals that are focused on patient treatments.

5. Need for BNCT

5.1 Expected patient numbers

In this paragraph we will try to give a rough estimate of the number of patients who can benefit from BNCT. For this purpose, we will first restrict the potential indications to those for which results have been reported. Considering melanoma, head and neck cancer, brain malignancies we obtain, based on data published by IARC[9], NCI[10], WHO[11], the patient numbers summarized in table 1.

We also included in this table breast cancer, the most common cancer in women worldwide. A recent population-based analysis estimates that overall 8 % of the treated patients will suffer a loco-regional recurrence[12] and hence become a candidate for BNCT.

[9] IARC - International Agency for Research on Cancer https://www.who.int/ionizing_radiation/research/iarc/en/
[10] National Cancer Institute 2019 https://seer.cancer.gov/statfacts/more.html
[11] World Health Organisation **WHO** https://www.who.int/cancer/country-profiles/en/
[12] Holleczek, B., Stegmaier, C., Radosa, J.C. *et al.* Risk of loco-regional recurrence and distant metastases of patients with invasive breast cancer up to ten years after diagnosis – results from a registry-based study from Germany. *BMC Cancer* **19,** 520 (2019) doi:10.1186/s12885-019-5710-5

	Global	US	China	Europe	Japan [13]
Melanoma	282,000	96,000	8,000	120,000	1,818
Head Neck	1,091,000	82,000	605,000	84,000	40,107
Brain	330,000	24,000	101,000	9,000	6,319
Recurrent Breast	136,160	21,440	21,760	22,000	5,288
Total/Region		**223,440**	**735,760**	**235,000**	**53,532**
Total/Worldwide		**1,247,732 Patients per year**			

Table 2: *Summarizing total number of patients for BNCT treatment*

At this point it should be reminded that there are several other, candidate indications:
First of all, any locally recurrent malignancy after having had a full dose of radiation will be an excellent indication for BNCT. Some rare diseases that are very difficult to control with other available treatment modalities should also be mentioned. For example, malignant or anaplastic meningioma WHO III (about 370 new cases per year in the USA[14]), or angiosarcoma (about 1 % of all sarcoma[15]) and malignant melanoma of the mucosa (in the US, its rate is 2.2 mucosal melanoma cases per million per year[16]).

5.2 BNCT centers to be created

Using the numbers above and assuming that in one facility 10 patients can be treated per working day or 1.500 per year, there would be a need for a few hundred facilities in the US, in China, in Japan and in the EU. In other words, there is a much higher need for BNCT centers as compared to the need for proton facilities.

More importantly is the fact, that BNCT is designed to treat situations that actually cannot be treated successfully elsewhere, which means that an evidence of the benefit realized by BNCT can be established at short term (in contrast to charged particle therapies).

On the one hand, BNCT is a complex area of research involving multiple disciplines, while on the other hand, BNCT is a clinical application that can be performed easily with trained staff. There is only one application and sometimes a second fraction after some weeks. The beam line is (compared to charged particles) very simple, no gantry is needed and by selecting an optimal accelerator/target solution, maintenance is not as complex as compared with other modalities.

A decisive prerequisite is the fact that it is not the regional center that cares for the local patients, but the BNCT center recruits its patients in a radius of up to 1,000 km.

[13] Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries Freddie Bray BSc, MSc, PhD, Jacques Ferlay ME et al. 12 September 2018, IARC https://doi.org/10.3322/caac.21492
[14] see [9]
[15] Ann Diagn Pathol. 2011 Apr;15(2):93-7. doi: 10.1016/j.anndiagpath.2010.07.012.
[16] McLaughlin CC, Wu XC, Jemal A, Martin HJ, Roche LM, Chen VW. Incidence of noncutaneous melanomas in the U. S. Cancer. 2005; 103:1000–7.

Therefore, there is a strong need for an intensive clinical research-based **International Reference Center**, which will support peripheral, local BNCT hospitals for patient treatments worldwide.

6. Next milestone

The key factor for success and failure in BNCT is first of all the collaboration between very different disciplines, ranging from nuclear physics to surgery, from chemistry to radiation oncology, and from mathematics to radiation biology.

Such a diverse collection of intellect requires dedicated structure to coordinate and develop the synergies needed to move forward. A second important aspect is the availability of a reliable hospital-based neutron source. This technical challenge now seems to be realized and in the near future, a real progress in BNCT can be reached, if the open scientific issues are now investigated in a common well-coordinated effort.

The drug aspect, which in the past often has been perceived as the bottleneck of BNCT, is less important. Real progress in this area will only be possible when the pharmaceutical industry can be involved in a drug development program. A prerequisite for such expensive campaigns is the existence of a market for the drugs to be developed. Such a market now is appearing when BNCT facilities become available in a large number.

The first step is to establish an **International Reference Center for BNCT** will be established. This Center would be able to coordinate all the different clinical and non-clinical disciplines that are needed to perform the translational research that is required in order to introduce successfully, over a limited period of time, BNCT as an innovative treatment modality into clinical practice.

This **International Reference Center for BNCT** will be organized as an international clinical research unit, including a patient data center open to all BNCT performing facilities. It has to be a **reference and a partner for regulatory authorities worldwide** (who actually have major difficulties to handle BNCT, especially potential new drugs), and last but not least , it will be **a training center for clinicians, technicians, and scientists to be prepared for their own local BNCT centers.** This center will be in close exchange with other already existing BNCT facilities, which up to now, do not have such a **strong scientific backup**.

Invitation: Constructive criticism, additions etc. are expressly desired

Essen/Germany, and Okayama/Japan March 2020

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Upcoming events

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. A **special edition** 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
3. July 27-30, 2020, **IAEA/**International Atomic Energy Agency is organizing a Technical Meeting on BNCT to replace the **IAEA-TECDOC-1223 (**CURRENT STATUS OF NEUTRON CAPTURE THERAPY, VIENNA, 2001, ISSN 1011–4289
4. **RISE / RENOVATE Consortium**: The DGBNCT (**German Society for Boron Neutron Capture Therapy**) is actually preparing to submit a staff exchange project between academic institutions and industries interested in BNCT in the frame of the RISE Program (Research and Innovation Staff Exchange) of the European Commission. This ambitious program currently includes 40 partners around the world.

End of **Part I**. (**Part II** will be distributed soon)