Boron Neutron Capture Therapy (BNCT)

Part III: Worldwide Network to Make Clinical BNCT a Success: BNCT Global

Mandatory requirements, basic structures and regulatory aspects for an international organized, interdisciplinary network

Introduction to Part III:

In **Part I "Principles and Challenges of BNCT",** we discussed BNCT: its progression and key milestones, with shifting paradigms: hospital-based accelerators for BNCT, State of the Art worldwide and the urgent need for BNCT. The result of the Part I study was: More than two million patients per year have a potential benefit from BNCT. For treating such a number of patients, several hundreds of BNCT centers are necessary, which would treat up to 1500 patients each per year.

Part II "Clinical Experiences and Mandatory Requirements for Clinical Practice" focused on some important aspects necessary to make BNCT a licnical modality: The most important prerequisites for globally applied BNCT are clinically validated data obtained through well designed, controlled clinical trials. We tried to briefly summarize some important aspects concerning clinical trials that will have to be designed following the goal that should be reached. Clinical trials for obtaining reimbursement were described. Regulatory Affairs and Licensing for a BNCT Facility were addressed. BNCT Global is an international network of BNCT facilities with one (or several) research-oriented Reference Centers or headquarters offering services to the clinically oriented facilities that are focusing on treating patients. 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.

Aim of Part III: A Global BNCT network is being designed from the ground up to support local BNCT facilities within a nearby hospital. Mandatory Requirements for clinical BNCT – basic structure of an internationally organized, interdisciplinary network that fulfils these conditions will be introduced. Some important regulatory aspects are highlighted.

Mandatory Requirements for a clinical BNCT Treatment Center

The BNCT concept sounds simple.
It can be realized.

But the following steps are indispensable prerequisites

Regulatory Affairs and Licensing for a BNCT Facility

For performing BNCT, an approval must be obtained from the national Ministry of Health or equivalent. As there are usually no regulations or guidelines dedicated to BNCT, it is necessary to prepare a complete, multifunctional portfolio of approvals, documentations and infrastructural requirements in order to have a sound basis for obtaining permissions and special licenses to perform BNCT.

Issues that usually have to be resolved are listed briefly below and are applicable to all BNCT Centers worldwide:

- Infrastructure related: the building must fulfil legal requirements that differ from one country to another. Radiation protection aspects, comfort of the patients as well as of the staff and practical aspects are playing a role. BNCT Global offers a basic model that can be easily adapted for special requirements but does not necessitate a completely new planning for a new BNCT facility to be constructed
- Accelerator related: licensing of the accelerator as a medical device; licensing of the entire facility and gaining local approval on safety aspects and radiation protection
- Treatment planning software related: licensing of the software as medical device, establishing quality assurance procedures for controlling if the calculated data really leads to the expected distribution of neutrons (for example be using an active phantom)
- Drug related: Currently, outside of Japan, there is no drug commercially available for BNCT. Special permissions are needed, and a dedicated infrastructure has to be installed
- Protocol related: reconciling the different points of view of different ethics committees in different countries gaining approval of the study protocol by different review boards and handling a non-registered drug to be used in the study protocol following the relevant guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)[1], as published by the European Medicines Agency (EMA)[2]
- Patient related: obtaining reimbursement for patients and building up the local infrastructure for patient care, travel and nursing, including all anticipated emergencies
- Personnel and institutional related: licensing of physicians to treat patients; 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
- Management related: the multidisciplinary context of BNCT and its application as a medical modality needs an effective coordination and leadership that on one hand has all aspects of a hospital under control and on the other hand knows the complex multidisciplinary needs that are special to BNCT.

There is a tendency for underestimating the importance and the efforts needed of these managerial issues when preparing BNCT.

An updated description of all these regulations for countries inside and outside the EU cannot be presented here. Over the last decade the regulations concerning drugs, medical devices, radiation protection and requirements for the qualification of the personnel have become more complex and more specific in all relevant countries (Europe, North America, China, Japan). Nevertheless, none of these regulations is dedicated to BNCT and the regulatory authorities will have to apply a mix of rules made for “simple” drugs with some specific effect by their own, for nuclear research reactors and hospitals. None of these

[1] https://www.ich.org/

[2] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000429.jsp&mid=WC0b01ac0580029590

regulations, except the rules for hospitals, can really be applied for BNCT. The discussion with the regulatory authorities in all the countries mentioned above is overdue, even if there is no real interest from the administrations to discuss potential problems as long as there is no real application for a real center and a real application. There is a high risk that very similar rules will be applied in a different way producing a financial burden that will vary considerably from one center to another. **To limit this challenge, BNCT Global intends to create simultaneously a series of BNCT centers offering the regulatory authorities a clear and comparable structure and allowing to apply straight forward licensing procedures.**

Laws and Regulations

BNCT is not yet an established modality for patient treatment. All BNCT applications in the near future have to be done in the framework of clinical trials. All clinical trials must comply with international guidelines such as the guidelines of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the Rules Governing Medicinal Products in the European Union[3], i.e. the Regulation (EU) 2017/745 on Medical Devices, which will have to be fully applied by 26 May 2021[4]; as well as all other applicable directives and national laws. In the US the regulatory guidance of the US Food and Drug Administration will have to be followed[5]. Well-regulated conventional approaches concern either a new medical device or a new drug. In BNCT both are coming together, and this will make the bureaucratic burden heavy, because such a complexity is not foreseen by the rules to be applied.

Other regulations that will play an important role concern radiation protection. We will come back on this aspect in a dedicated paragraph. Here, we only look at the rules that have to be applied for establishing a new treatment modality when clinical trials play an important role.

Clinical trials are closely supervised by appropriate regulatory authorities. According to our experience, it is very useful to include regulatory authorities early on in the discussion of the trial concept and continuously during the process of writing the trial protocol and conducting the trial, especially if transnational scientific cooperation is an aim to be established. The time period needed until regulatory and administrative rules are set must not be underestimated and can be shortened through continuous cooperation with the regulatory authorities. It is highly recommended to register trials at ClinicalTrials.gov, which is the largest clinical trials registry and searchable database of clinical trials run by the United States National Library of Medicine at the National Institutes of Health. In most countries such registration is even mandatory.

Treatment Planning

The treatment planning software needs dedicated licensing. There are different aspects that have to be considered:

- *Computational Aspects of Treatment Planning:* Patient Geometric Modeling Approaches, Neutron Beam Source Definition, Dose Calculations, Planning System Quality Assurance and Verification, Planning System Calibration and Validation, Treatment Planning System soft- and hardware.

[3] https://ec.europa.eu/health/documents/eudralex_en

[4] https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trials-guidance-documents

- *Clinical Aspects:* The Treatment Planning Process, Patient Data Acquisition, Image Processing, Target Volume Definition, Model Construction, Beam Selection, Plan Evaluation and Optimization, Dose Prescription.

Some Considerations Related to Staff Responsibilities and Liabilities

The medically responsible clinican will prepare all relevant clinical data for treatment planning, as well as approving the final treatment plan; decide on the timing and the amount of boron compound to be administered to the patient; take the blood samples from the patients, for example, for boron concentration measurements using prompt gamma analysis or ICP-OES; be responsible for the positioning of the patient for the irradiation; accept responsibility for the starting time and duration period of the irradiation of the patient; start the irradiation and take the overall responsibility for the well-being of the patient whilst at the BNCT facility (including concomitant disease and arising acute symptoms). He bears the overall responsibility and liability.

The role of the **medical physicist** is to assure quality and safety of the medical use of ionizing radiation. The medical physicist supports the physician in his/her task to treat patients by providing all necessary physical and technical data to perform a safe and precise treatment and to control all technical equipment involved in the patient treatment. (For the EU, some aspects of the work are described in Council Directive 2013/59/EURATOM[6]). The major tasks of the medical physicist are to define, describe and perform step by step the dosimetry needed to fulfil the requirements of the treatment protocol; to define, describe and perform the quality assurance for all medical physics aspects of the treatment; to be present at all treatments of patients; to be responsible for treatment planning calculations; to perform the quality control calculations with the treatment planning system; to calculate the actual dose given to the patient on the basis of the boron concentration in blood taken before and after the irradiation and to document all actions and data obtained from the measurements and calculations, which have to be archived following the national rules.

Here we will not go into further details concerning other important employees such as radiographers, nurses and all the other staff members who make the functioning hospital; but here is the place to point out the importance of **staff training**. The demand for qualified employees will be difficult to meet. Most of the staff necessary to treat a patient with BNCT require special training and licenses. We have to create short-term training centers that are able to train these people comprehensively.

Radiation Protection

The treatment of a patient and the potential exposure of personnel to ionizing radiaion require by the national Nuclear Energy Law that the license holder must ensure that radiation protection and monitoring of all personnel, including external staff, is provided and that the correct radiation protection measures are taken and followed.

During BNCT, both the patient and the supporting treatment tools, such as mask and therapy table, become radioactive. As such, measurements of the patient and surroundings should be taken at regular intervals after treatment, checked and documented in an appropriate format. To improve radiological protection of the patient and staff, the radiation beam should be regularly and fully characterized (using activation foils, ionization chambers, TLDs).

[6] https://eur-lex.europa.eu/legal-content/DE/ALL/?uri=CELEX%3A32013L0059

Radiation protection includes the issuing of personal dosimeters to all staff, finger or ring dosimeters to the radiotherapists and pen dosimeters to participants classified as visitors, for example, nurse(s) and relatives of the patient. Furthermore, it is necessary to measure and record all material in and out of the radiation room and to perform activation measurements on all materials used in patient treatment. The patient is an exceptional case and it is not required that a personal dosimeter is issued to the patient. However, following treatment, the patient should be monitored for radioactivity. It is advisable to form a local radiation protection committee for BNCT. The committee has the primary task to review and advise regularly on the radiation protection methods used for BNCT.

Insurances

Special care has to be paid to establish insurance cover for, at least, the following aspects: radiation incidents; insurance for patients in clinical trials; liability for staff interacting with patients/being involved in patient treatment; liability for further specialists needed who are not staff from the BNCT Center; accident cover for staff during traveling between hospital and BNCT center if not on the same campus and accident cover for patients between hospital and BNCT Center.

Ethical Conduct

Each clinical trial must follow ethical rules (e.g. Declaration of Helsinki) and must be approved by an ethics committee before permission is granted to run the trial. To be ethical, detailed informed consent is necessary from each patient before he/she is included in the trial.
Patients included in BNCT clinical trials are often in exceptional circumstances (life-threatening disease, sometimes terminal phase of life, patients participating for altruistic reasons), which can lead to ethical questions that have been answered in the past quite differently by research groups/ethics committees. Such questions can arise, especially as BNCT is still an experimental treatment option and in some concepts contains procedures that can cause severe side effects, e.g. special surgical procedures, liver transplantation, re-irradiation, and heavily treated pre-treated patients.
There are also ethical concerns associated with conducting very early-phase clinical trials, including the risk-benefit ratio and the lack of treatment intent. The risk for patients can be reduced by very limited drug exposure that is below the non-observable adverse effect level (NOAEL = Highest Dose Administered Without any Toxicity), whereas the critical proof of principle and data on pharmacokinetics and distribution can still be gained. Such data help the design of more elaborated trials that are based on early clinical data rather than on animal models[7]. It is the responsibility of each clinical research group and each individual investigator in cooperation with the local ethics committee to plan and conduct such trials following international standards and in the best possible and most responsible way to ensure that the rights and safety of trial subjects are protected. This also includes careful documentation of all procedures, careful follow-up of patients even if they live at distance, and timely publication of results.

These often very complex issues should be structured and coordinated by the central Reference BNCT Center.

[7] 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. DOI 10.1007/978-3-642-31334-9, p.369-376

Quality Assurance for an Accelerator Generated Neutron Beam

Most experience concerning quality assurance for BNCT has been made at nuclear research reactors[8,9]. Some of the challenges that had to be overcome and were related to the necessity of treating patients in non-hospital environments and the need to license the BNCT facility at a nuclear research reactor as a medical device are not important here as accelerator-based facilities will be built in a medical environment from the outset. However, the stability and constant quality of a neutron beam generated by an accelerator is more difficult to maintain. Dedicated radiotherapy quality assurance programs are required for performance and safety of radiation units, including testing of performance characteristics on a regular basis (quality control). Consequently, as part of the licensing procedure, QA procedures are needed wherein the testing of certain performance characteristics, including all dosimetry aspects, as well as treatment planning, is written down as standard operating procedures or similarly accepted procedures.

International Standards for Quality Assurance in Radiotherapy

The performance of BNCT requires the application of national and international rules of safety and quality assurance, for radiation protection and for radiotherapy. The application of established standards and rules for radiotherapy to BNCT, however, is challenging. An effort was made in Europe by establishing recommendations for the physical dosimetry of BNCT[10] that was developed for a beam produced by a fission reactor and now has to be adapted to the needs of accelerator generated neutron beams. However, up to now, there are no international standards dedicated to BNCT. It is therefore a highly important task to transfer – as far as possible – analogous rules from conventional radiotherapy to BNCT. A first step in this direction is the ongoing revision of TECDOC-1223[11]. Nevertheless, in the end, arrangements must be found with the national authorities that prove themselves in practice. We try to list here some international standards that will have to be applied.

For Safety

IEC 60601-2-1:2009+AMD1:2014 CSV Consolidated version. Medical electrical equipment - Part 2-1: Particular requirements for the basic safety and essential performance of electron accelerators in the range 1 MeV to 50 MeV.[12]. This particular standard establishes requirements to be complied with by manufacturers in the design and construction of **electron** accelerators for use in radiotherapy; it does not attempt to define their optimum performance requirements. Its purpose is to identify those features of design that are regarded, at the present time, as essential for the safe operation of such medical electrical equipment. It places limits on the degradation of medical electrical equipment performance beyond which it can be presumed that a fault condition exists and where an interlock then operates to prevent continued operation of the medical electrical equipment. IAEA TECDOC-1891 "Regulatory Control of the Safety of Ion Radiotherapy Facilities "[13] will be another guideline for

[8] RASSOW J., STECHER-RASMUSSEN F., VOORBRAAK W., MOSS R., VROEGINDEWEIJ C., HIDEGHÉTY K., SAUERWEIN W., (2001): 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, 99-108

[9] SAUERWEIN W., MOSS R. (eds) 2009: Requirements for Boron Neutron Capture Therapy (BNCT) at a Nuclear Research Reactor. EUR 2383 EN. Luxembourg: Office for Official Publications of the European Commission. EUR - Scientific and Technical Research series - ISSN 1018-5593 ISBN 978-92-79-12431-0 DOI 10.2790/11743

[10] Daquino GD, and Voorbraak, WP, (2008) A Review of the Recommendations for the Physical Dosimetry of Boron Neutron Capture Therapy (BNCT), EUR 23632 EN, ISBN 978-92-79-10868-6, European Communities

[11] IAEA-TECDOC-1223 "Current status of neutron capture therapy", International Atomic Energy Agency, Vienna, 2001

[12] https://webstore.iec.ch/publication/2616

[13] IAEA-TECDOC-1891: Regulatory Control of the Safety of Ion Radiotherapy Facilities. INTERNATIONAL ATOMIC ENERGY AGENCY, VIENNA, 2020

establishing safety and performance procedures at BNCT facilities. Furthermore, experiences made in hadron therapy centers can be helpful[14].

For Performance

Acceptance tests: IEC 60976: 2007 Medical electrical equipment – Medical electron accelerators – Functional performance characteristics. IEC 60976[15] applies to medical electron accelerators when used, for therapy purposes, in human medical practice. It describes measurements and test procedures to be performed by the manufacturer at the design and construction stage of a medical electron accelerator but does not specify acceptance tests to be performed after installation at the purchaser's site. An important aspect has been introduced by IEC 60976 that recognized that inaccuracies in the test methods must be allowed for when assessing performance. It is assumed in this standard that the irradiation facility has an isocentric gantry, which is not the case in BNCT. It is, however, explicitly mentioned that where the equipment is non-isocentric, the description of performance and test methods may need to be suitably adapted.
Consistency tests: IEC/TR 60977:2008. Medical electrical equipment – Medical electron accelerators – Guidelines for functional performance characteristics[16]. IEC/TR 60977 applies to medical electron accelerators when used, for therapy purposes, in human medical practice. It includes the addition of performance guidelines relating to several relatively new technologies introduced within the last few years, including dynamic beam delivery techniques, such as moving beam radiotherapy, intensity-modulated radiation therapy, image-guided radiotherapy and programmable wedge fields, as well as stereotactic radiotherapy/stereotactic radiosurgery and the use of certain electronic imaging devices but of course does not mention BNCT.
Data Transfer and Data Handling, Coordinates and Scales: IEC 6121:2011 Radiotherapy equipment – Coordinates, movements and scales . IEC 61217[17] applies to equipment and data related to the process of tele-radiotherapy, including patient image data used in relation with radiotherapy treatment planning systems, radiotherapy simulators, isocentric gamma beam therapy equipment, isocentric medical electron accelerators and non-isocentric equipment when relevant. The problems raised by this international standard are of high importance for BNCT, especially when the preparation of the treatment with CT, MRI, treatment simulators etc. is performed outside the BNCT facility in a referring hospital.

Radiotherapy Treatment Planning Systems (RTPS): IEC 62083:2009. "Medical electrical equipment – Requirements for the safety of radiotherapy treatment planning systems"[18]. EC 62083:2009 applies to the design, manufacture and some installation aspects of a radiotherapy treatment planning systems: for use in radiotherapy treatment planning in human medical practice; that imports data either through input by the operator or directly from other devices; that outputs data either in printed form for review or directly to other devices. It applies to RTPS that are intended to be: for normal use, under the authority of appropriately licensed or qualified persons, by operators having the required skills and training; maintained in accordance with the recommendations given in the instructions for use, and used within the environmental and electrical supply conditions specified in the technical description.

[14] R. Filippini, P. Urschütz (2019) Risk Management for a Particle Therapy Accelerator: The MedAustron Experience. In book: Safety and Reliability – Safe Societies in a Changing World, pp.1879-1886. DOI: 10.1201/9781351174664-235
[15] https://webstore.iec.ch/searchform&q=IEC%2060601-2-1
[16] IEC 60976 International Standard (2008) Medical electrical equipment - Medical electron accelerators - Functional performance characteristics. International Electrotechnical Commission, Central Office Geneva http://www.iec.ch
[17] IEC/TR 60977 Technical Report (2011) Medical electrical equipment - Medical electron accelerators - Guidelines for functional performance characteristics. International Electrotechnical Commission, Central Office Geneva http://www.iec.ch
[18] https://webstore.iec.ch/publication/6447

Treatment Room: IEC/TR 61859 Ed. 1.0:1997 "Guidelines for radiotherapy treatment rooms design"[19]. This old and withdrawn (2018) technical report applies only to those aspects of the installation ensuring the safety of the patient, the operator and other persons during the radiotherapy equipment use. The installations considered are those in which are located radiotherapy equipment delivering ionizing radiation used for therapeutic purpose; some aspects have to be considered when designing the radiation room for BNCT, however, the specific aspects related to a high intensity low energy neutron beam are not covered by an available standard.

Standard Operating Procedures: It is highly recommended if not mandatory that **standard operation procedures (SOP)**, which describe step by step all relevant procedures concerning the performance of BNCT and the execution of the clinical trial, must be written. They will follow the guidelines of good clinical practice[20] [21]. All SOPs should be collected in one dossier that has to be available at any time for each staff member.

Quality Control (QC): QC programs, especially for medical electron accelerators, are adopted internationally, such as the IEC publications quoted above. BNCT must follow the same or similar procedures. Furthermore, in following such procedures, this will increase the confidence and reassurance of radiation measurements at the BNCT facility and hence the accuracy of the dose given to the patient. With respect to quality control procedures related to the beam calibration and patient dosimetry (functional performance characteristics), it can be stated that despite the relatively more complex dosimetry of BNCT, many performance and safety characteristics associated with medical electron accelerators show dependencies on irradiation and operational parameters that are also relevant for BNCT accelerator based facilities. Rassow[8] showed in detail the comparison between the performance and safety characteristics of medical electron accelerators and a BNCT facility and in particular for dose delivery, as well as against stray radiation.

Quality management (QM): It is of the utmost importance that, as well as designing an optimal physical facility, special attention must be given to a managerial 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[22]. This latter aspect will become an important issue when multicenter clinical trials are performed.

Drug Development/Pharmaceuticals of a BNCT Center

The available boron-containing compounds for BNCT are experimental drugs and cannot be used without special permission of the national agency responsible for new drugs in medicine. To handle such issues, the participation of experienced pharmacists and of a well-equipped pharmacy licensed for preparing the drugs is mandatory. The pharmacy organizes

[19] IEC 62083 Ed. 1.0 International Standard (2000) Medical electrical equipment – Requirements for the safety of radiotherapy treatment planning systems. International Electrotechnical Commission, Central Office c e Geneva http://www.iec.ch

[20] European Medicines Agency (EMEA) (2002) Guideline for good clinical practice, ICH harmonized tripartite guideline (CPMP/ICH/135/95). http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000429.jsp&mid=WC0b01ac0580029590

[21] IEC/TR 61859 Ed. 1.0 Technical Report (1997) Guidelines for radiotherapy treatment rooms design. International Electrotechnical Commission, Central Office c e Geneva http://www.iec.ch

[22] https://www.iso.org/iso-9001-quality-management.html

the drug supply. Supplying companies must produce the compound according to **good manufacturing practice (GMP)**, which will include a drug master file and written procedures for preparation and quality control of the final product and its intermediates. All actions have to be documented following the legal requirements.

Despite the decades of effort from chemists, only two compounds showing some tumor specificity are actually available for clinical use: the boron cluster sodium borocaptate (BSH) and the amino acid analogue boronophenylalanine (BPA). The latter one is available on the market in Japan since May 20th, 2020 under the name Steboronine®. However, even for these two compounds, not all the requisite data exist, and were not always collected in a controlled and reliable way. This situation is mainly due to the fact that all major research activities in the field were made by academic institutions to answer a scientific question but not by pharmaceutical industries with the goal to collect data for regulatory authorities for licensing a new drug. Starting in 1995, the European Organization for Research and Treatment of Cancer (EORTC) made a first approach to design clinical trials with the goal to follow the principles of classical trial design for drug development intended to collect clinical data for regulatory authorities[23,24].

Missing information with respect to the quality control of the drugs used for animal experiments but also in some pioneering clinical trials are a major concern when interpreting some of the observations reported in the past. We therefore gave a detailed description of the quality control procedures used for both drugs in the frame of the EORTC trials 11001 and 11011[25].

Conclusion I: Interim results for the mandatory Requirements

BNCT is thwart with danger and has the potential, if incorrectly applied, to be damaging to the patient. BNCT needs nuclear technologies, which are known to convey fear to some people. Both aspects cause possible additional safety-related issues.

It is therefore absolutely imperative that national and international rules are followed when establishing BNCT Treatment Centers.

A major effort will be necessary to adapt existing rules and regulations to the purposes of BNCT.

This will require a great deal of human and financial resources and, consequently, a great deal of time. These requirements, regulations, standardization, licensing etc. represent an immense challenge for the establishment of a clinical BNCT center. In addition, it is of utmost importance that, as well as designing an optimal physical facility, special attention is given to a managerial structure that provides safety, beyond normal rules.

[23] Sauerwein W., Moss R., Rassow J., Stecher-Rasmussen F., Hideghéty K., Wolbers J.G. Sack H. (1999): Organisation and management of the first clinical trial of BNCT in Europe (EORTC Protocol 11961). Strahlenther. Onkol. 175, 108-111

[24] Sauerwein W., Zurlo A. on behalf of the EORTC Boron Neutron Capture Therapy Group (2002):The EORTC Boron Neutron Capture Therapy (BNCT) Group : achievements and future projects. EJC 38, S31-S34

[25] Sauerwein W., Bet P., Wittig A. (2012): Drugs for BNCT: BSH and BPA. 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, ISBN 978-3-642-31334-9 (eBook) DOI 10.1007/978-3-642-31334-9, p. 117-160

These requirements, regulations, standardization, licensing etc. described in this Part III represent an immense challenge for the establishment of a clinical BNCT center.

The immense time, personnel and financial expenditure required for a single BNCT Treatment Center cannot lead to an economically successful result. For this show of strength, it is essential that the worldwide BNCT community work together and focus on global solutions: A global network is mandatory.

Ready for a Business Case?

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

1. Basic research for the essential individual factors of this procedure (mostly done)
2. Studies at clinical level (partly, most of it is still missing)
3. Mandatory requirements for clinical BNCT – structure of an internationally organized, interdisciplinary network that fulfills these conditions (these conditions must be met in an essential way)
4. Requirements for an internationally organized, interdisciplinary network of a working business structure
   Proof of a business case

We will focus on these topics in the next Part.

Prof. Wolfgang Sauerwein
Deutsche Gesellschaft für Bor-Neutroneneinfangtherapie
Universitätsklinikum Essen
Hufelandstr. 55
45147 Essen Germany
wolfgang.sauerwein@dgbnct.de

Essen/Germany, July 25, 2020

Upcoming Events and Publications:

1. July 27 – 31, 2020 **International Atomic Energy Agency (IAEA) Technical Meeting on Advances in BNCT**. The Purpose of these WebEx events is to collect the opinion of the community as to which parts of the existing TECDOC-1223 are still current and satisfactory, which parts need modification, and what topics are missing and need to be added to any revision of the TECDOC due to changes in the field in the last two decades.

2. 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.

3. 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. Five papers already available online: https://www.mdpi.com/journal/cells/special_issues/cells_BNCT
   If there are still manuscripts that are in preparation but have not yet been submitted, please contact me directly.