Boron Neutron Capture Therapy (BNCT)

Part IV: Local and Global Network Structure to Make Clinical BNCT a Success Story: BNCT Global

An optimal structure, as well as the management aspects, for an internationally organized, interdisciplinary highly profitable network

Introduction to Part IV

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 clinical 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 worldwide BNCT.

Part III "Worldwide network to make clinical BNCT a success: BNCT Global". Essential formal and regulatory requirements as a precondition for the clinical use of BNCT were presented. Organizational processes but especially management aspects were outlined. The focus was on regulatory aspects and requirements.

Aim of Part IV: "Local and global optimal network structures to make clinical BNCT a success story". The **BNCT Global** concept provides for a **lean** standardized basic structure and uniform organizational procedures for each individual center, which must be established before clinical work begins. Each center is an integral element of an international clinical BNCT network with several hundred **BNCT Therapy Centers** supported by the **BNCT Global Service Unit**. The importance of networked patient recruitment will be explained. A globally networked BNCT structure is necessary: only with such a structure a project of this kind can be realized within a manageable period of time.

Wanted:
Worldwide partners to be part of this international network!

Mandatory Requirements for clinical practice

The main differences and challenges between conventional therapies and BNCT are the following:

1. The treatment concept of BNCT varies fundamentally from conventional therapies. Current radio-oncological techniques optimize the dose distribution by applying the radiation of the beam as conformal as possible to the tumor (selective damage to the tumor by ballistic precision). On the contrary, BNCT can irradiate an extended area where microscopic disease is expected. The selective damage to the tumor cells is not achieved by the direct action of the primary beam but is obtained by the neutron capture reactions releasing high-LET particles where ^{10}B atoms are present. The therapeutic effect occurs only when the ^{10}B atoms, delivered to the tumor by a dedicated compound, are irradiated with thermal neutrons[1,2].
2. The binary nature of the principle of BNCT treatment requires investigation of a compound susceptible to targeting tumor cells but without, by itself, having its own therapeutic effect. Such a boron carrier must go through standard clinical testing like all other investigational drugs; however, conventional methods to test such compounds are not strictly applicable[3].
3. Standards for prescribing and reporting the irradiation dose are missing as are standards reporting on the concentration and distribution of boron and/or boron compounds. Very different methods with certainly different end points exist to measure the boron concentration and boron distribution. All such methods deliver valuable but often fundamentally differing information and cannot be easily compared. Also, not all of these methods are valuable for clinical decisions, for example, they are too demanding and take days to weeks until results are available [4].
4. BNCT uses an irradiation beam that is not established for clinical practice and that produces a complex dose distribution with high- and low-LET components.

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[1] Wittig A, Collette L, Moss R, Sauerwein WA (2009) Early clinical trial concept for boron neutron capture therapy: a critical assessment of the EORTC trial 11001. Appl Radiat Isot 67(7–8 Suppl):S59–S62

[2] Wittig A., Collette L., Appelman K., Bührmann S., Jäckel M.C., Jöckel Kh., Schmid K.W., Ortmann U., Moss R., Sauerwein W.A. (2009): EORTC trial 11001: distribution of two (10)B-compounds in patients with squamous cell carcinoma of head and neck, a translational research/phase 1 trial. J Cell Mol Med 13,1653-1665

[3] 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

[4] Wittig A., Sauerwein W. (2012): Boron analysis and boron imaging in BNCT. In: Sauerwein W., Wittig A., Moss R., Nakagawa Y.(eds) Neutron Capture Therapy. Principles and Applications. Springer. DOI 10.1007/978-3-642-31334-9, p.163-188

5. Hospital-based irradiation facilities have only recently become available and there is limited experience with their use.
6. Radiation facilities and beams used for BNCT to date differ considerably not only from facilities and beams used for conventional radiotherapy, but beams used for BNCT also differ among themselves. These differences complicate the conduct of multicenter trials, which will be necessary at a certain point in the developmental process of BNCT.
7. In spite of a large number of preclinical investigations, data often lack consistency and comparability. Early preclinical and clinical investigations were not conducted according to today's standards (e.g., GMP); therefore, results of such investigations must be interpreted with care, especially when used as basis for developing trial concepts.
8. To date, commercial companies show only a modest interest in drug development related to BNCT as the method is still far from being judged superior to current standard treatments. Drug development, however, usually conducted by the pharmaceutical industry needs specialized facilities and financial resources.
9. Underlying the special characteristics of the therapeutic principle, the design of clinical trials in BNCT is challenged by the highly complex and interdisciplinary nature of BNCT, which requires expertise in many fields such as neutron physics, mathematics, (boron) chemistry, radiobiology, radio-oncology, specialized analytical methods, and pharmacology. Such knowledge is usually available at selected academic institutions only. BNCT also needs expertise of specialists (e.g. neutron physicists) who are not used to working in the medical field or even in clinical trials.
10. As BNCT can be offered at selected institutions only, patients often travel long distances to be treated, which complicates the issue of timely, qualified, and well-documented recruitment but also follow-up of patients. Cooperation across state borders could be established in some clinical projects[5], which however require respecting national laws of all countries involved and also sometimes lead to linguistic barriers especially for patients.

These aspects make clinical trials in BNCT a challenging task for the clinicians and scientists involved, as well as for the regulatory authorities. Innovative clinical trial designs are necessary in conjunction with innovative organizational and administrative concepts and a strict quality assurance to meet these challenges. Additionally, in-depth training of all staff involved is required. Multidisciplinary and international cooperation is therefore necessary and highly desirable, as well as being more economically advantageous.

In recent years, efforts were already made to develop clinical trial strategies aiming to mature BNCT to a treatment modality. Here we will present a possible solution to cope with the described challenges: **BNCT Global.**

It is absolutely imperative that national and international rules are followed when establishing BNCT Therapy Centers, as already described in Part II and Part III.

We demonstrated the necessity to adapt existing rules and regulations for the purposes of BNCT, which might be accepted as a standard. This requires a great deal of human and financial resources and thus also a great deal of time. All these requirements, regulations, standardization, licensing etc. represent an immense challenge for the establishment of a clinical BNCT center.

[5] 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

The extensive time, personnel and financial expenditure required for a single BNCT Therapy 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 a common global project. Stand-alone solutions will not be able to develop BNCT into a world-wide accepted clinical therapy modality.

Every year there are more than 2,000,000 patients worldwide who would benefit greatly from BNCT. To this end, the establishment of a network of strategically distributed BNCT treatment centers is sensible and necessary.

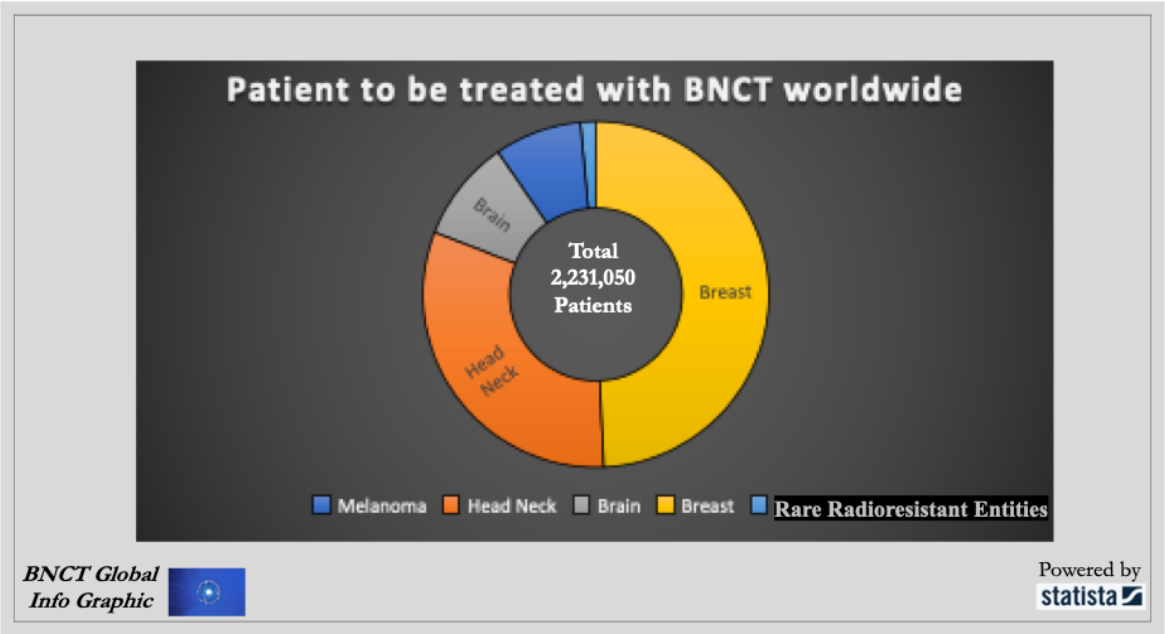

Fig 1: *More than 2 Million Patients can benefit from BNCT treatment: Palliative treatments, Re-irradiation in case of recurrences in pre-irradiated areas, tumor size reduction, therapy of radio-resistant tumors, curative treatments in only one fraction….*

This very large number of potential BNCT patients requires responsible and reliable care to provide the most appropriate therapy. But first, a number of national and international procedures and approval steps are necessary. In this context, it is important to point out again and again that proof of quality, safety, effectiveness, etc. must be provided with high level of evidence in order to establish a project of this magnitude with global impact.

Establishing a sustainable, science based clinical BNCT that functions as a business case requires the efforts of the entire, worldwide BNCT community. It is particularly important to bring together all the preliminary work and fundamental findings that have been made so far. All efforts and resources should be focused on building an international clinical BNCT network: **BNCT Global**.

The Concept of BNCT Global

Basic Structure of an International Clinical BNCT Network

Important issues of structure, organization, quality management and the tasks for carrying out the treatment are described om zhis section.

From a principle point of view, the application of BNCT to human patients requires multi-institutional and multidisciplinary cooperation. 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 can only be handled through contractual agreements, which must define unambiguously the responsibilities and tasks of all partners.

BNCT Global is designed as an international network of BNCT facilities with one (or more) research-oriented reference center(s) or headquarters, providing services to clinically oriented institutions focused on patient care.

Up to now, all BNCT centers are some "stand alone" solutions and have to find their way through the jungle of bureaucracies on their own and set up the entire organization themselves. **BNCT Global** will streamline processes and reduce the effort required to achieve goals by eliminating paperwork for all treatment centers at once, creating clear organizational structures, that work everywhere, and providing centralized services of the highest quality that were previously decentralized and provided at high costs. Such centralized services include the provision of treatment protocols, a central database, therapy planning, purchase of consumables (especially the boron compounds) and technical support for therapy planning, dosimetry, accounting, maintenance, etc.

There will be two types of BNCT facilities:

1. **BNCT Therapy Centers exclusively for patient treatment:** They are intended for the treatment of patients from abroad, who are travelling for this purpose. In this context, the availability of good transport connections and accommodation for patients and accompanying persons is particularly important. Such a center can serve a region of about 5 – 15 million people**.** It should cooperate with a local hospital, but not necessarily be located on its premises.

2. **BNCT Reference Center:** It has to be linked to a hospital with a strong academic background, a well-established reputation in oncology, and competent pharmacy licensed to handle experimental drugs. It will have staff members from several (non-medical) disciplines for research activities optimizing BNCT. It will intensively relieve the BNCT Therapy Centers in its daily work. However, the integration of such a treatment center into an existing large clinical center/university hospital is extremely complex in terms of planning and approval and therefore time consuming.

Specifications of a peripheral facility exclusively for the treatment of patients: BNCT Therapy Center

The **BNCT Therapy Center is** planned from the beginning in close partnership with a local hospital. These BNCT facilities are built and organized in a standardized way, with all software and hardware components available for a perfectly equipped, functional and profitable BNCT treatment unit. This **BNCT Therapy Center** will concentrate exclusively on the treatment of patients, as it is also part of a national and global network. Overarching administrative functions such as financing, reimbursement, regulatory aspects, etc. are handled by the **BNCT Global Service Unit** as well as special services supporting the treatment of an individual patient. This ensures the highest possible profitability. The functions that have to be covered (at least) are summarized in figure 2.

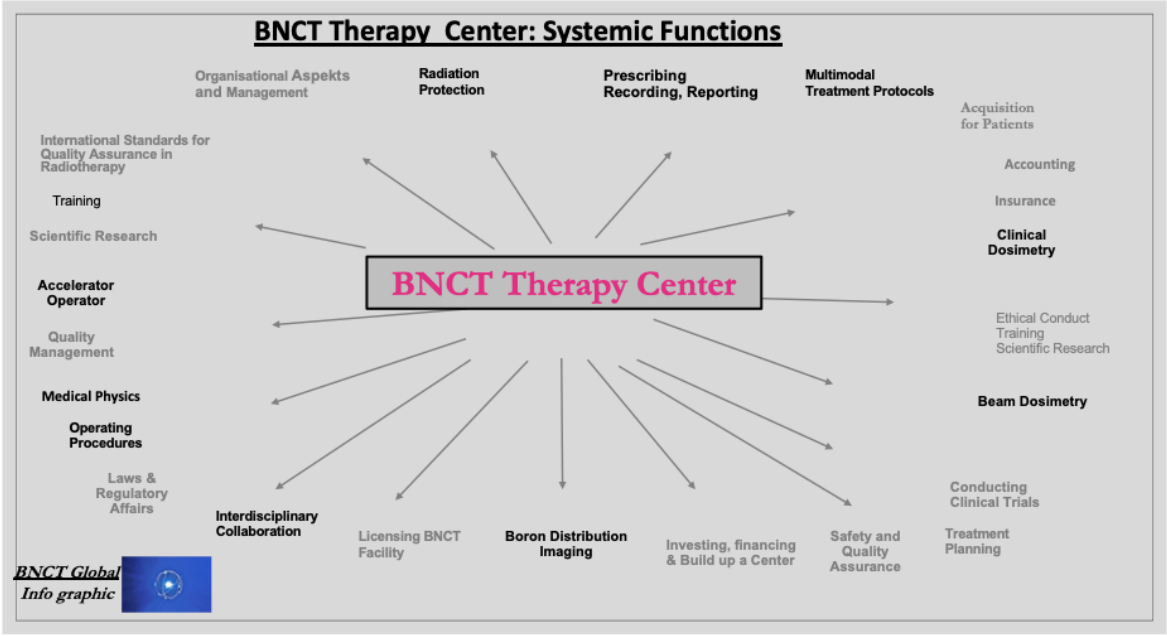

Fig 2: *For each **BNCT Therapy Center** the presented functions must be covered. Some of these functions can only be performed in the local center (black letters). But others (gray letters) can be performed or at least supported by the **BNCT Global Support Unit** and the **BNCT Reference Center**.*

The footprint of the accelerator and the beam delivery system (target, moderator, collimator etc.) will be small. Technical solutions are available that do not need more than approximately 6 x 8 m^2 for the accelerator. Accelerator and target will be separated: one room for the accelerator with a low radiation level and a small compartment with thicker walls for the target. The beamline will be horizontal and end with a collimator, which protrudes into the irradiation room to ensure easy positioning of the patient. There will be a possibility to shield the activated beam delivery system from the irradiation room after treatment to facilitate radiation protection of the staff. The beam intensity will be high enough to treat a patient in less than 30 minutes.

Directly in front of the irradiation room there will be a preparation area where positioning of the patient is prepared. The table or chair on which the patient is positioned for irradiation must be movable in order to transport the patient from the preparation area to the irradiation room. A room for applying the drug and an examination room complement the clinical area.

An important issue is the need to measure the boron concentration in blood prior and during the treatment. There are several methods available. In the past, most centers used ICP-OES, which cannot

however differentiate between B-10 and B-11. A better and faster method is Prompt Gamma Ray Spectroscopy.

A small waiting area for patients and their relatives will be placed in the direct neighborhood of the irradiation area. Office space and social rooms for the staff complete the **BNCT Therapy Center**.

The BNCT facilities are built in a standardized way: Room equipment, room layout, security structures, laboratories and technical rooms etc.

A good cooperation between the local **BNCT Therapy Center** and the neighboring radiotherapy / oncology centers is essential for **good clinical practice (GCP),** evidence-based medicine, acquisition of patients and economic success. The pre-selection and aftercare of patients by cooperating radiotherapy centers/oncology centers is a crucial factor in the development of an absolutely necessary national structure of BNCT services.

Specifications of a research-intensive and research managing **BNCT Reference Center**

The **BNCT Reference Center** has to be integrated into the network with a radiation therapy department of an academic hospital, that is surrounded by an active multidisciplinary research landscape.

The irradiation equipment will have the same accelerator as is available at the peripheral **BNCT Therapy Centers.** In addition to 2 treatment rooms with horizontal beam lines, an optimal design will include one room with a vertical beamline. The patient preparation areas, waiting rooms will be the same as in the facilities dedicated for treatments only. Three treatment rooms should be available to allow research activities in parallel with patient treatments.

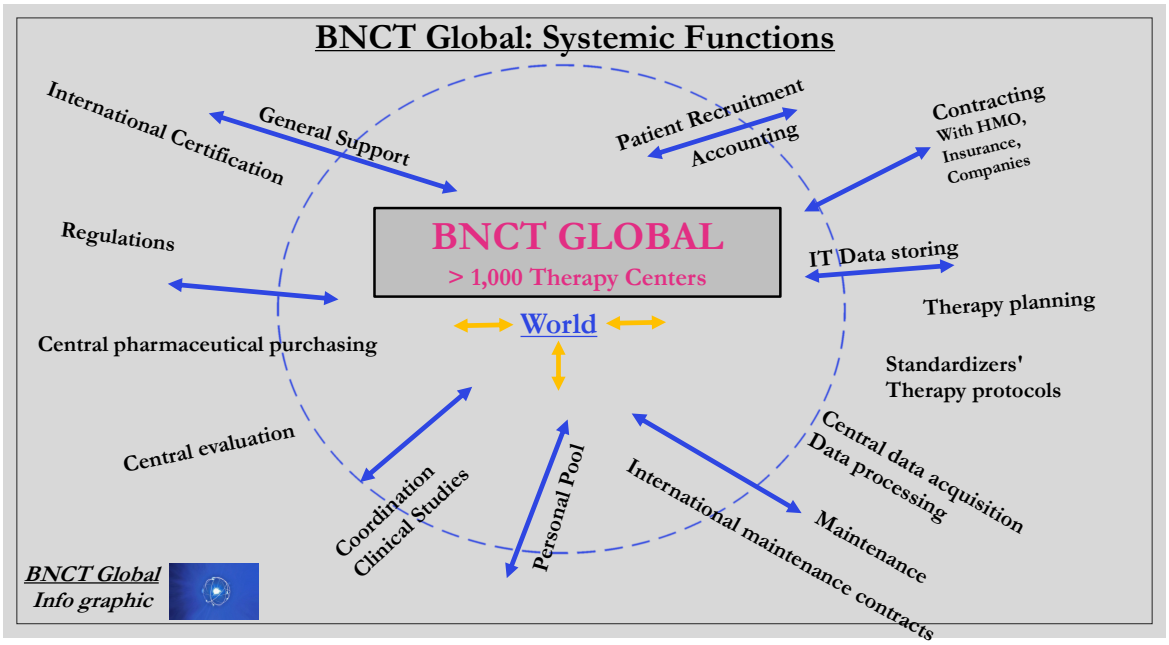

***Fig 3: BNCT Global** will take over essential tasks for the local **BNCT Therapy Centers**: Centralized purchasing of drugs, hardware configurations, standardization, insurance, regulations with the various national regulatory authorities, contracting with national Health Maintenance Organizations (HMO) and insurance companies, patient recruitment, accounting, training of staff, etc.*

The leading radiation oncologist has to be trained in conventional radiation oncology techniques. Experience in charged particle therapy would be useful but is not mandatory. However, he/she needs to have deep knowledge in BNCT and experience in translational research. This chairperson must have practiced leading multidisciplinary research teams and he/she must fulfill all the requirements to be allowed to perform and supervise clinical trials with ionizing radiation. Similarly, high demands must be made on the senior medical physicist, who needs in addition to a deep knowledge in conventional radiotherapy, must have a profound expertise in neutron physics and dosimetry as well as in Monte Carlo simulation. Both must have good leadership qualities.

The staffing of the **BNCT Reference Center** must be in line with the increased requirements resulting from the research and central support functions. In addition to the clinical personnel for the care of patients on site (MDs, radiographers, nurses), resources must be provided to support and relieve the peripheral facilities. This concerns medical physicists who prepare the radiation plans for the peripheral facilities, technicians and engineers for service and replacement, in case of illness, related to failures in the dependent facilities.

Networking between **BNCT Reference Center** and **BNCT Therapy Center**

An essential interface between the **BNCT Reference Center** and the **BNCT Therapy Centers** is the **BNCT Global Service Unit,** that is part of **BNCT Global.** In order to operate the peripheral treatment units safely with only a small number of staff, continuous support from the central **BNCT Reference Center** and the **BNCT Global Service Unit** is required.

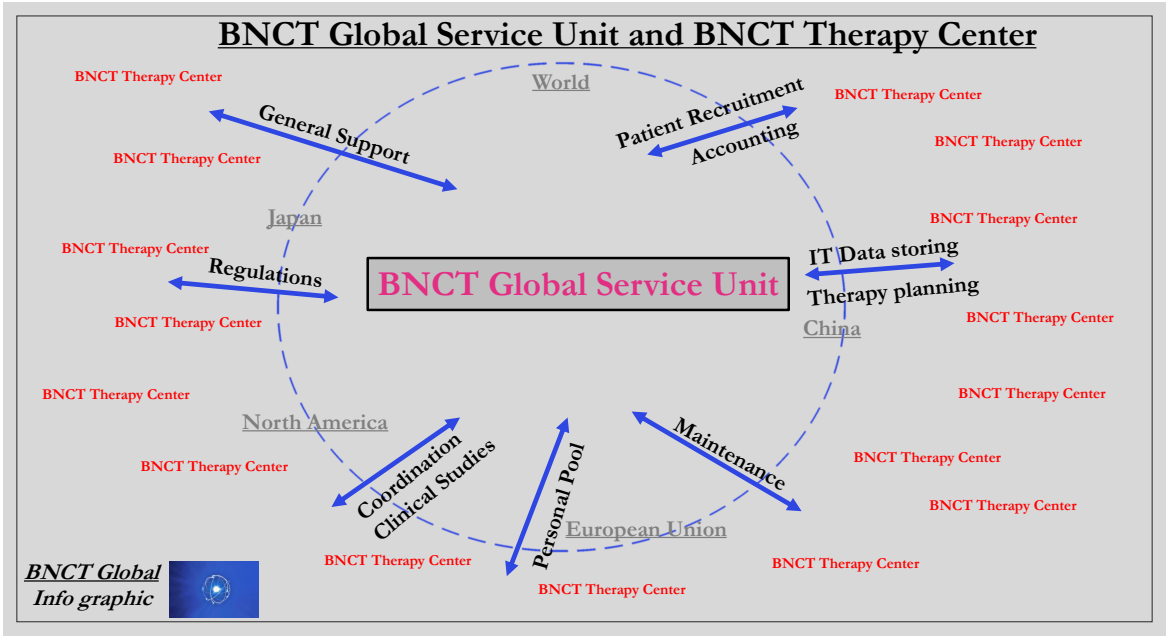

Fig 4: BNCT global Service Unit *will take over specialized functions for the local centers: maintenance, therapy planning, coordination of clinical studies, service functions, general support, personal pool (!) etc.*

Treatment protocols will be provided to all treating facilities as a standard for patient care. A central register of patient files will allow a fast evaluation of results and will play a central role in quality management.

All time-consuming work, that requires special knowledge and for which no direct contact with the patient is necessary, is centralized. This is obvious for administrative purposes such as exchange with national authorities, billing, personnel planning, material procurement and so on. Such centralized services will be extended to treatment planning. A dedicated central unit will compute all treatment plans, reducing the workload of the medical physicists at the **BNCT Therapy Centers** to quality control, radiation protection and direct involvement into the treatment of individual patients.

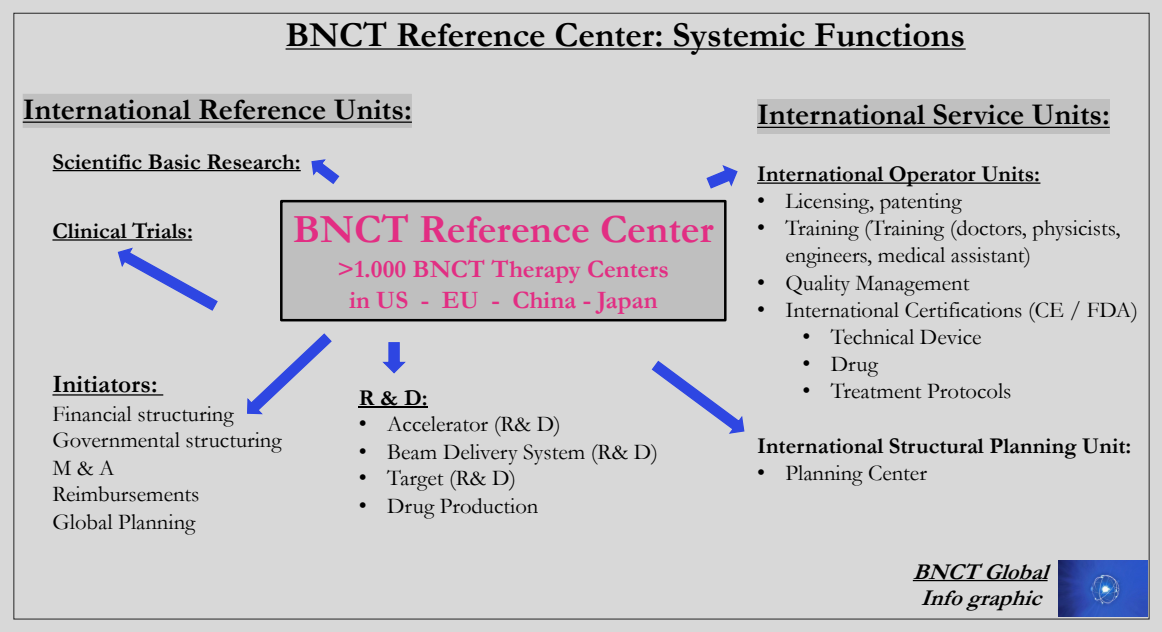

Fig 5: *The **BNCT Reference Center** is responsible for the entire field of scientific research, clinical studies and global management. R & D for all areas from pharmaceuticals to hardware are coordinated centrally.*

The **BNCT Global Service Unit** will have dedicated IT staff, data manager as well as a strong collaboration with epidemiologists and statisticians. Audits at the peripheral units will have to be organized from here. The staff number needed for this purpose will depend on the number of centers, but for 3 centers, for example one auditor will be necessary.

BNCT Global provides a platform:

- to coordinate basic research for technical, physical and biochemical developments and the translational research needed to bring the innovations to our patients.
- to carry out R & D for accelerator, beam delivery systems, target and drug development are combined and coordinated at this level.
- to perform the complex clinical research, which often has very different formal requirements at national level, is centrally coordinated and controlled to ensure a high level of quality.
- to initiate new **BNCT Therapy Centers**.
- to educate new staff and organize the continued training at this level.
- to coordinate possible financial structuring, up to PPP financing structures, as well as the supra-regional problem of revenue structures.
- to coordinate certification units, the certifications, QM units, treatment protocol as well as service units on the different levels.
- to consider that for the medical personnel, there will be a wide range of new functions to fill, including completely new ones. An interesting article by Gordon at al. "Shaping the physician

of the future" describes a future in a different field (Figure 6), but one that we have to face especially when implementing the complex BNCT as a clinical modality[6].

- **and finally, the driving force for these changes is the increasing digitalization, handling of enormous quantities of Data and the use of artificial intelligence (AI).**

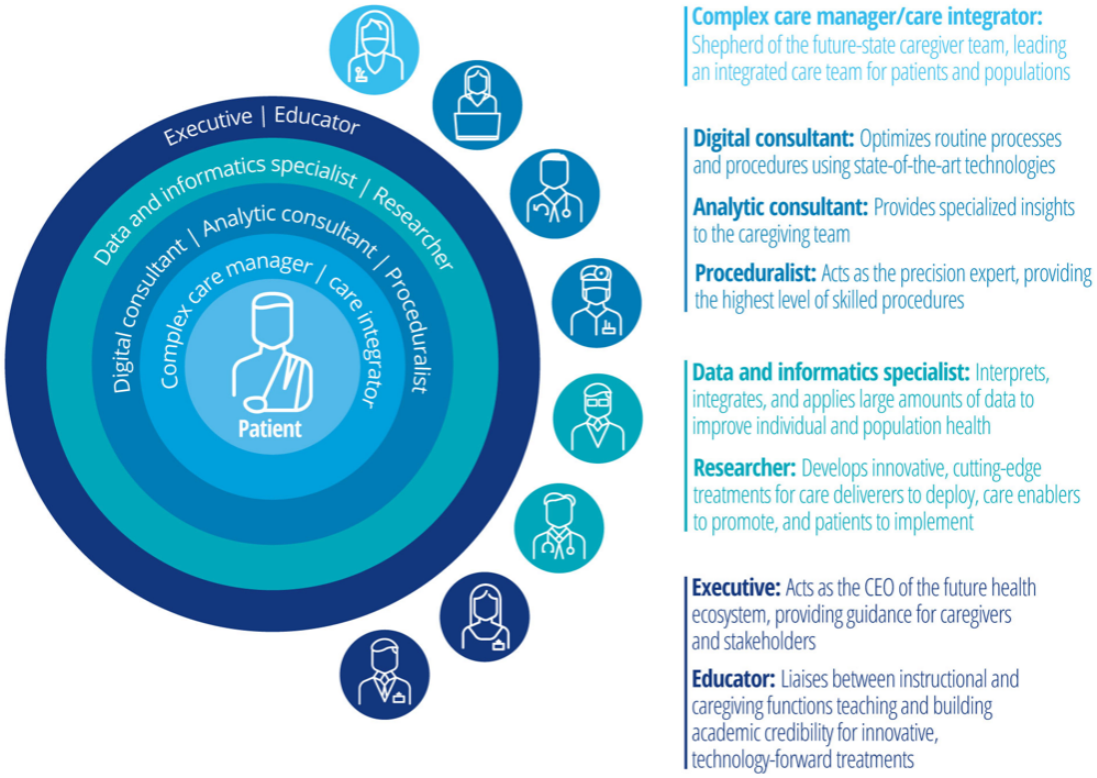

Fig 6: *Tasks for physicians in the future. We need to prepare our employees at BNCT Global for such activities. Special thanks to Deloitte Development LLC for granting permission to use this graphic here.*

Patient Recruitment

Every year, there are more than 2,000,000 patients around the world, who might benefit from BNCT. For this purpose, the establishment of a network of **BNCT Therapy Centers**, strategically distributed, is sensible and necessary. However, especially in the initial phase a careful selection of patients is necessary. A pre-selection will be made by the participating hospitals and doctors, who will also provide follow-up treatment and aftercare. Clear selection criteria are defined to avoid time-consuming presentations of patients who are not suitable for a BNCT.

[6] https://www2.deloitte.com/us/en/pages/life-sciences-and-health-care/articles/physician-of-the-future.html

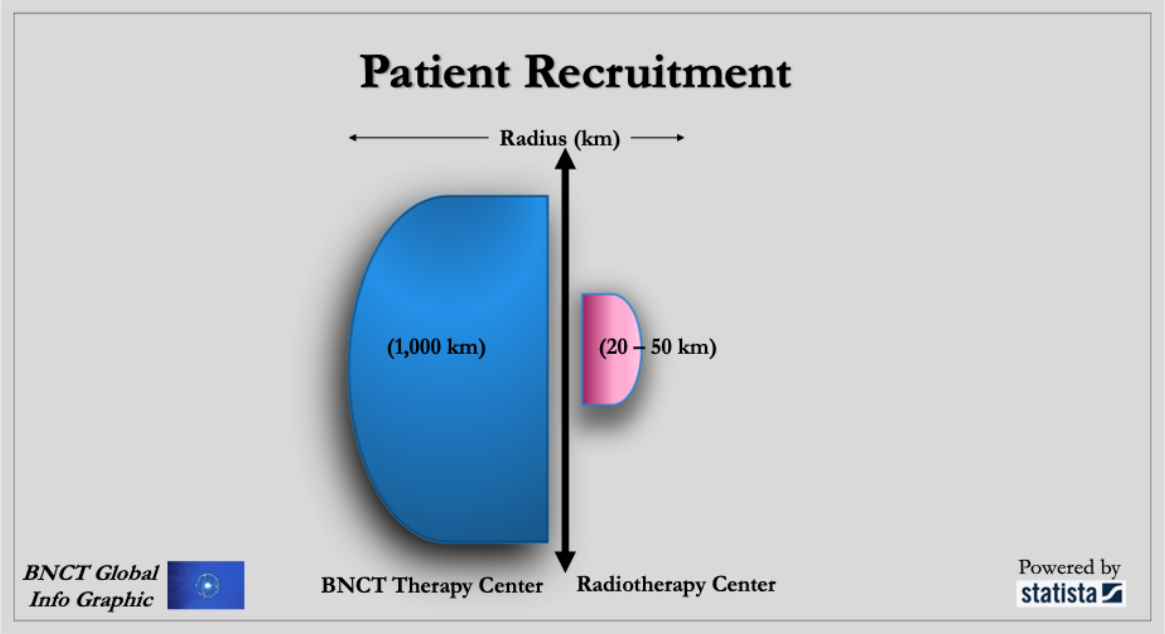

***Fig 7**: The catchment area for patients to undergo BNCT, with a radius of up to 1,000 km, is much larger than that of a conventional radiation therapy center. This has considerable consequences for recruitment costs, marketing costs, utilization of the center, etc.*

The catchment area of a BNCT facility can cover a radius of 1,000 km (Figure 7). Such kind of a **BNCT patient tourism** is easier to organize as compared to conventional radiotherapy, because only one fraction will be applied and the time the patient has to spend at the therapy center will be short. Experience exist in such organizational set-up from EORTC BNCT trials[7,8,9,10], but also in long lasting collaboration with the proton center in Nice (France)[11] and iThemba LABS (Somerset West, South Africa) for fast neutron therapy of German patients.

[7] 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

[8] Sauerwein W. (2000): Therapeutic strategies for Boron Neutron Capture Therapy (BNCT). In: 5th Framework Programme Quality of life and management of living resources. (eds: Benediktsson I., Joliff-Botrell G., Weiland S.) Book of Abstracts KA3 – Cell Factory funded projects. European Commission, Research Directorate- General (April 2000) p.81-82

[9] Sauerwein W., Moss R.L., Rassow J., Stecher-Rasmussesn F., Hideghéty K., Paquis P., Goetz C., Gabeld D. and the EORTC BNCT Study Group (2000): The European BNCT Centre in Petten: Organisational Structure. In: From Medical Biotechnology to Clinical Practice. Report of a workshop organized under the aegis of the External Advisory Group (EAG) of the Cell Factory Key Action. (rapporteurs: M. Carrondo, B. Diderichsen, A. Bernard and E. Balzi), p. 26-30. Quality of Life Programme European Commission Research Directorate General, Brussels June 2000

[10] Hideghéty K., Sauerwein W., Pahlke-Berkowitz B., Meusers P., Moss R., Heijmans J., Fankhauser H. (2000): Psychological consideration of clinical trial execution in non-medical environment in interdisciplinary, cross-cultural, trans-European set up. Int.J.Rad.Biol.Phys. 46, p. 757

[11] Sauerwein W., Chauvel P. (1994): Protonentherapie von Patienten aus Essen in Nizza: Grenzüberschreitende Nutzung kostenintensiver Therapieanlagen. Zbl. Rad. 150, S. 248

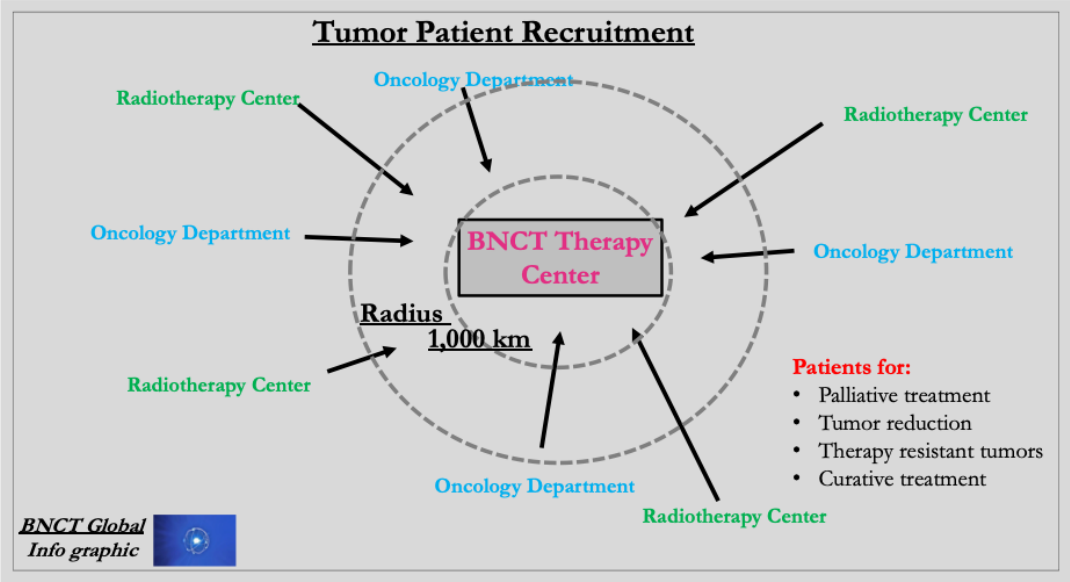

***Fig 8**: Patients for the **BNCT Therapy Center** are referred by radiotherapy clinics and oncology departments. The necessary logistics are organized by the **BNCT Global Service Unit**, if necessary, even across national borders.*

Next steps:

Thanks to **RENOVATE**, many discussions have begun worldwide to bundle together and organize the available resources, coordinate planning, design the necessary clinical studies, etc. Right from the start, it is important to motivate, organize and coordinate all the necessary interdisciplinary partners for this great project. For this reason, we are looking for partners, employees and sponsors for this big project.

Wanted: Worldwide partners to be part of this international network!

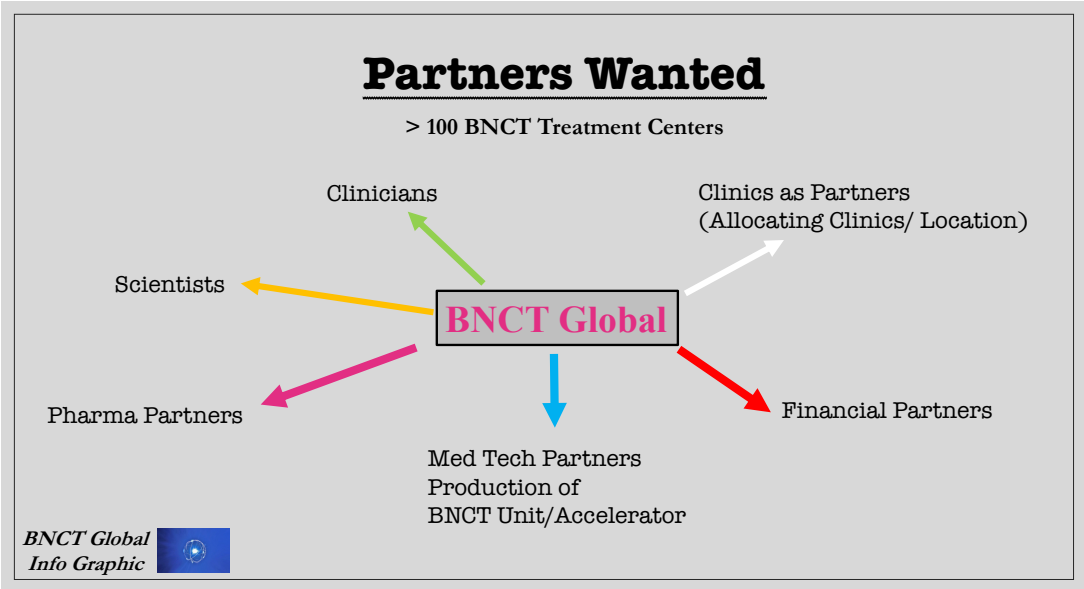

***Fig 9:** For this worldwide network of BNCT centers professional partners (Med Tech, Pharma, Financial Partners), scientists, doctors, etc. are sought.*

The Global BNCT Community will have to work on this **To Do list**:

- **Clinical Trial Protocol**
- **Development of Standards**
- **Training and Education**
- **Collaborating with the existing BNCT Therapy Centers worldwide**
- **Establishing of BNCT Reference Center(s)**
- **Establishing of additional BNCT Therapy Centers**

Only with a concentrated and focused worldwide effort by all partners will it be possible to get this project up and running. In the coming months we ask for your help, ideas, assistance in finding partners in the different areas.

Conclusions: A worldwide network will make BNCT a success story

The worldwide Network to make Clinical BNCT a Success: **BNCT Global** is started. The mandatory requirements, optimal, basic and global structures and management aspects for an internationally organized, interdisciplinary network were described. A stand-alone solution is not conceivable.

The **BNCT Global** concept provides for a basic structure and uniform optimal organizational procedures, which must be established before the start of clinical work, for each individual center. Each center is an integral element of an international clinical BNCT network with several hundred **BNCT Therapy Centers** supported by the **BNCT Global Service Unit**. A networked **patient recruitment** is defined.

Conclusion: Global networking BNCT structures are the solution: only with this structure can such a project be realized in manageable time periods. Such a project can only be financed in the described optimal structures.

Wanted: Worldwide partners to be part of this international network.

Ready for a Business Case?

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

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

We will focus on this topic **Proof of a business case** in next (and last) Part V.

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Essen/Germany, August 19, 2020

Upcoming Events and Publications

- Special issue of the journal **Cells**: Articles already available free of charge!
  https://www.mdpi.com/journal/cells/special_issues/cells_BNCT

- **BNCT Meeting at PTCOG**: Scheduled at September 11 (13:00 MEST)

  https://www.ptcog2020online.org

- **Neutron Capture Therapy – Principles and Applications (second edition)**. W. Sauerwein, K. Ono, A. Wittig, R. Moss, Y. Nakagawa (Eds.): will be published by Springer in 2020.

- **2021:** International Atomic Energy Agency (IAEA) **Updated TECDOC 1223**.