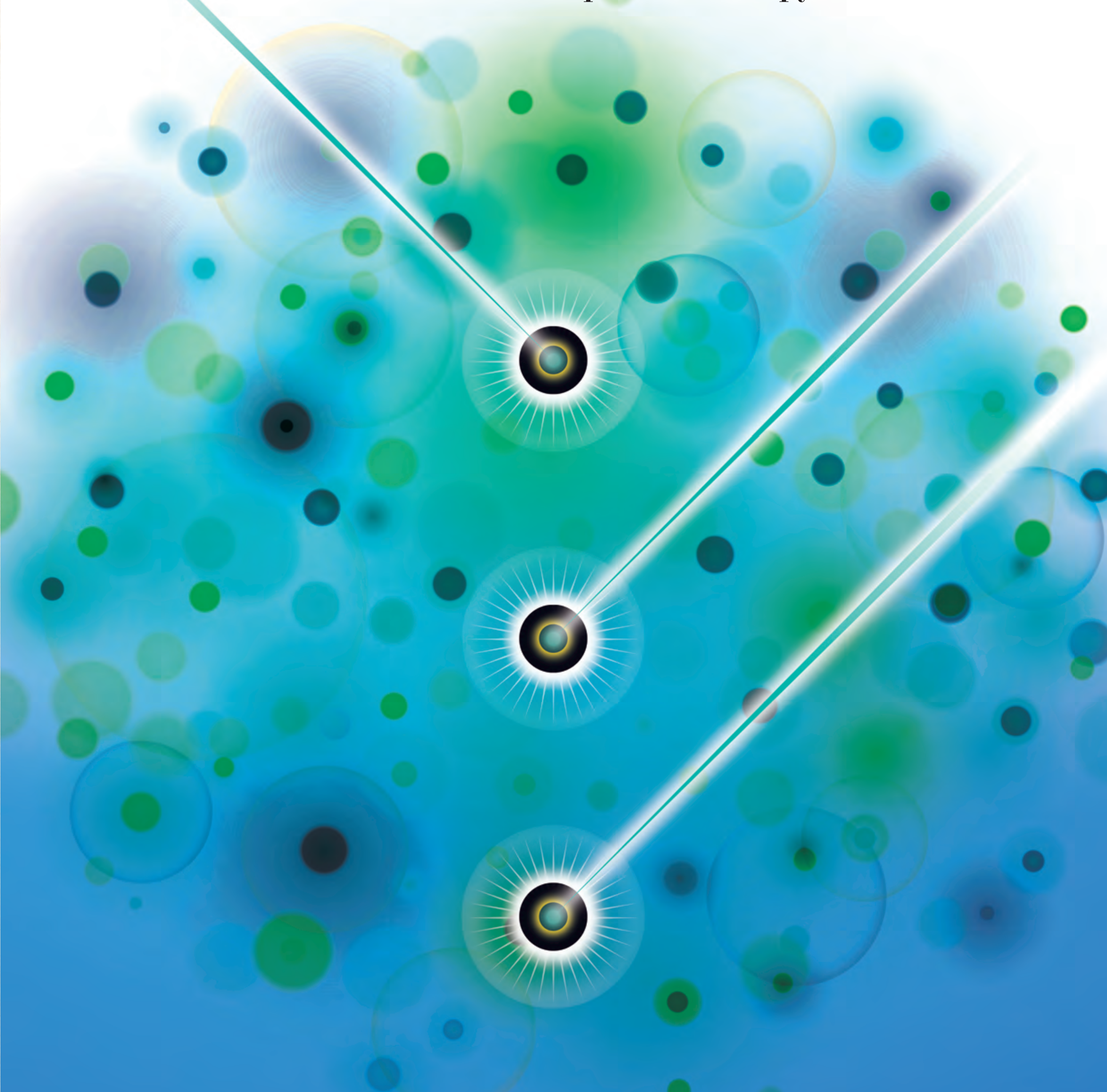
Synopsis

Pioneered by Japanese brainpower: New Horizons in Cancer Treatment

BNCT

Boron Neutron Capture Therapy



BNCT Promotion and Research Society

BNCT
Boron Neutron Capture Therapy

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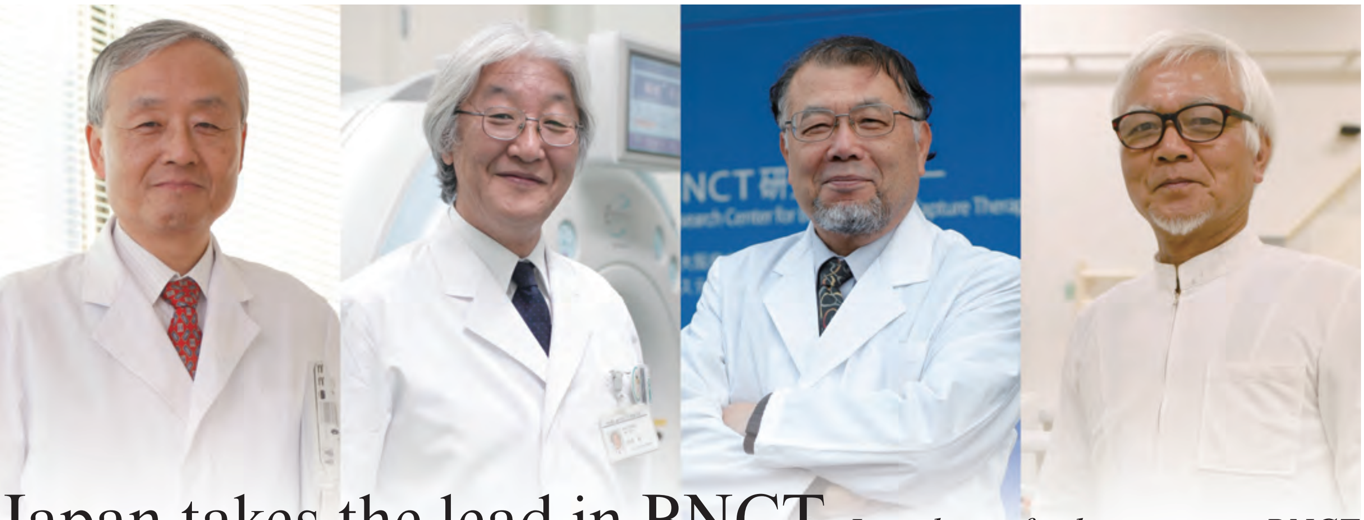
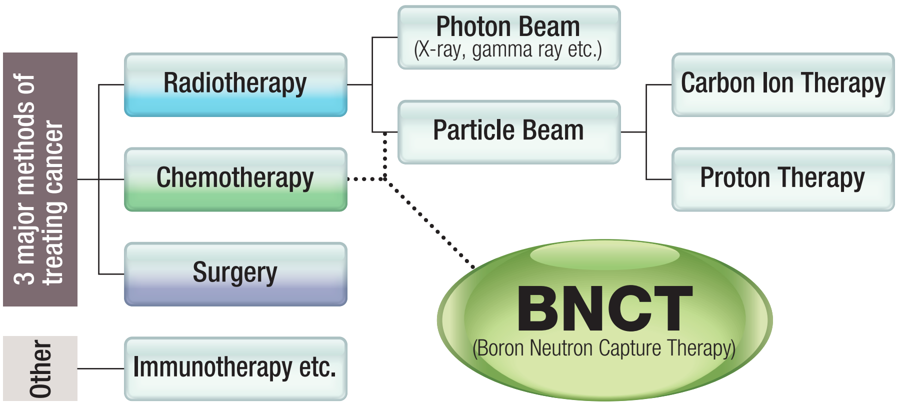


Japan takes the lead in BNCT *: In order to further improve BNCT*

BNCT first began in America with clinical studies as a possible treatment to selectively destroy cells. However, a number of problems could not be solved and the treatment failed to meet expectations. Since then, Japan has made great progress on its own in this field and this has led to the huge advances in BNCT today. Fundamental academic progress was necessary in areas such as the development of the source of an epithermal neutron, maintenance of facilities which are used for irradiation, etc., developing the selective accumulation of boron compounds in cancer cells and a precise understanding of this accumulation. We were able to solve these problems with the expertise shared with us from associated fields and experience accumulated to become the best in the world in BNCT treatment. To this end, BNCT is trying to become a new and ground-breaking force in cancer treatment.

A fourth option in cancer treatment **BNCT position in cancer therapies**

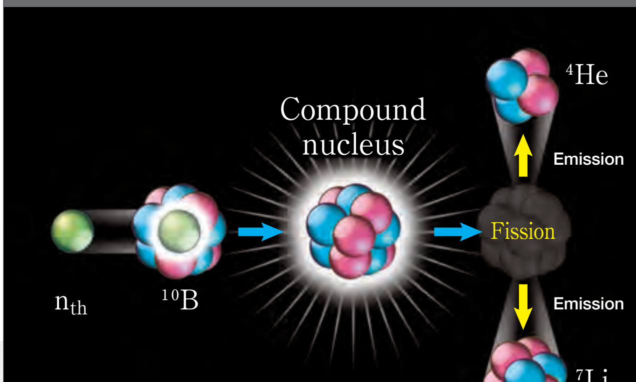
What kind of treatment is BNCT? Cancer treatments are broadly divided into three kinds; radiotherapy, chemotherapy, and surgery. Using the reaction between a neutron and boron to selectively destroy only cancer cells, BNCT is, in terms of effectiveness and safety, an epoch-making treatment that differs radically from conventional radiotherapy and one that promises to become a fourth option as a treatment for cancer.



The principles of applying "Neutron capture reaction"

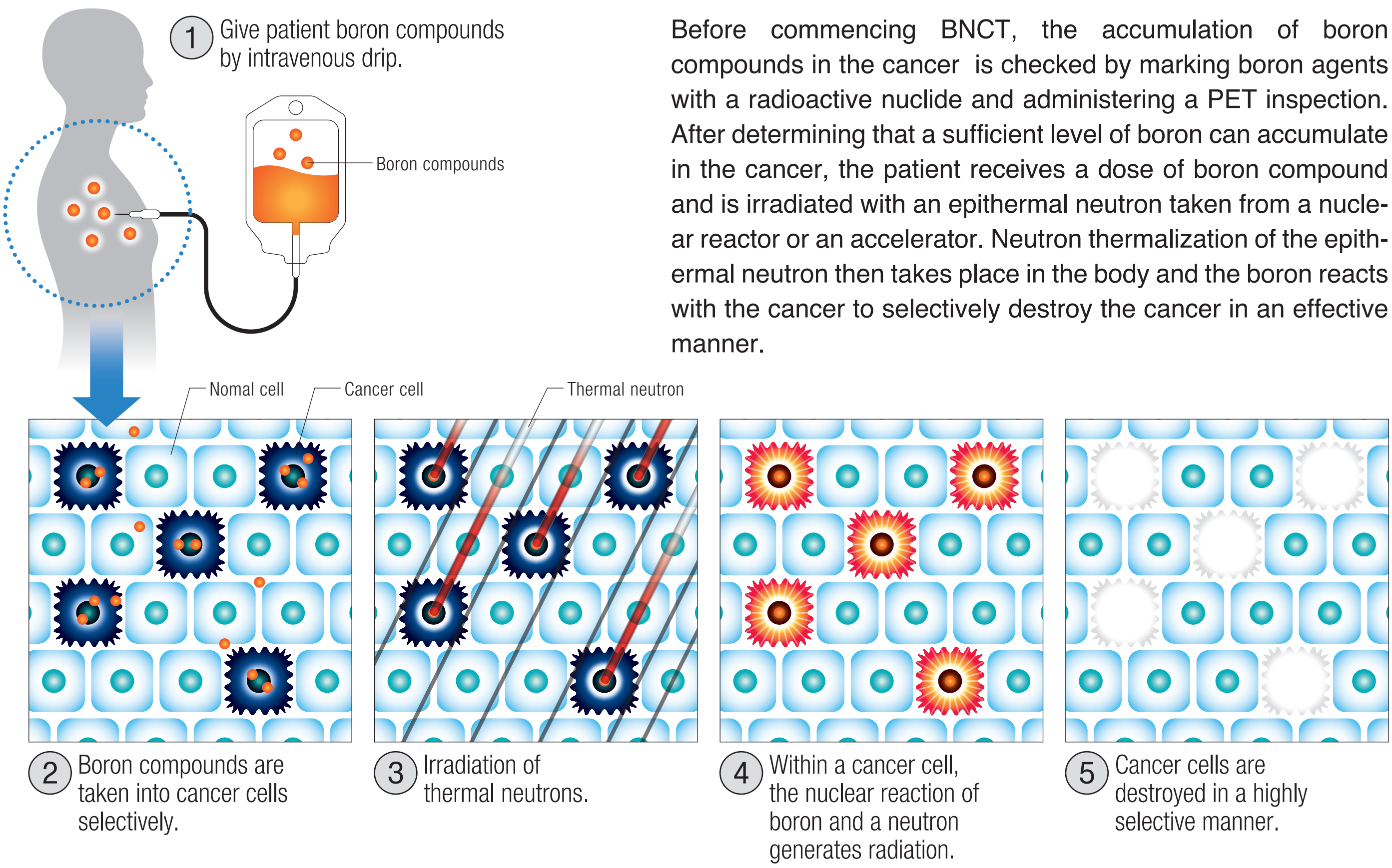
It was American physicist G.L. Locher who proposed the idea of using neutron capture reactions, in which a ^{4}He nucleus (alpha particle) and ^{7}Li nucleus are emitted when ^{10}B reacts with thermal neutrons, to destroy cancer cells in cancer treatment, four years after the discovery of the neutron in 1936. Thermal neutrons are captured by a variety of nuclei, but the probability of capture by a ^{10}B (expressed in terms of the capture cross-sectional area in : cm^{-2}) is much higher than that of capture by the atoms that constitute human tissue since its cross-section is about 2,000 times larger than that of nitrogen (^{14}N). Furthermore, the track ranges of the two emitted particles are extremely small and do not exceed the diameter of a typical cell. Based on these facts, if there were a ^{10}B-compound that accumulates at sufficient concentrations with a high level of selectivity for cancer cells and tissue, then it would be possible to selectively destroy cancer cells and tissue by irradiating the cancerous region with neutrons after administering that compound.

Nuclear fission process



The ^{10}B atoms that encountered and absorbed the thermal neutrons become compound nuclei and fission into ^{7}Li and ^{4}He. The ^{7}Li and ^{4}He are emitted in opposite directions, and the total distance traveled by both is 14μm, which corresponds to roughly the size of a cell.

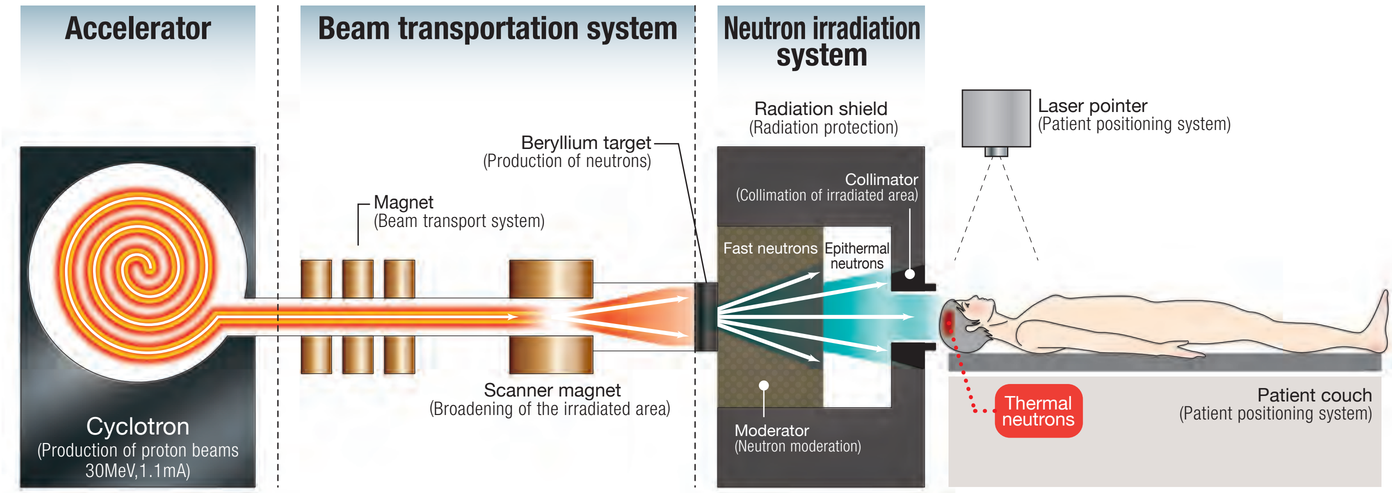
BNCT procedures



Before commencing BNCT, the accumulation of boron compounds in the cancer is checked by marking boron agents with a radioactive nuclide and administering a PET inspection. After determining that a sufficient level of boron can accumulate in the cancer, the patient receives a dose of boron compound and is irradiated with an epithermal neutron taken from a nuclear reactor or an accelerator. Neutron thermalization of the epithermal neutron then takes place in the body and the boron reacts with the cancer to selectively destroy the cancer in an effective manner.

The image shows neutron irradiation by an accelerator

(Source: the Sumitomo Heavy Industries, Ltd. Press Releases.)



The advantages of BNCT

BNCT is efficacious for very difficult to treat invasive cancer, rapidly spreading cancer, especially cancer which invades the nerve cells that do not respond to standard radiation therapy.

- The reaction of a neutron and boron destroys cancer cells selectively.
- Uses low energy thermal neutrons which do little damage to the healthy cells.
- Efficacious for invasive cancer, rapidly spreading cancer.
- Short treatment period (Number of irradiations: 1-2, 30-60 min./time.)
- Since an operation is unnecessary, it contributes to a patient's QOL.
- Anti-cancer drugs are not used so there are no side effects.

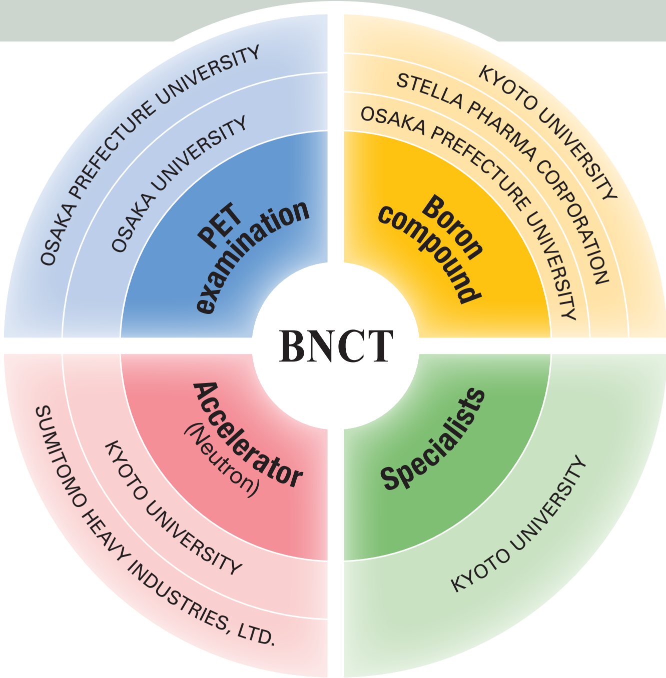
Cancers that can be treated with BNCT

- *Malignant brain tumors*
- *Head and neck cancers*
- *Malignant melanoma*
- *Malignant pleural mesothelioma etc.*

Industry/government/academia network in Kansai

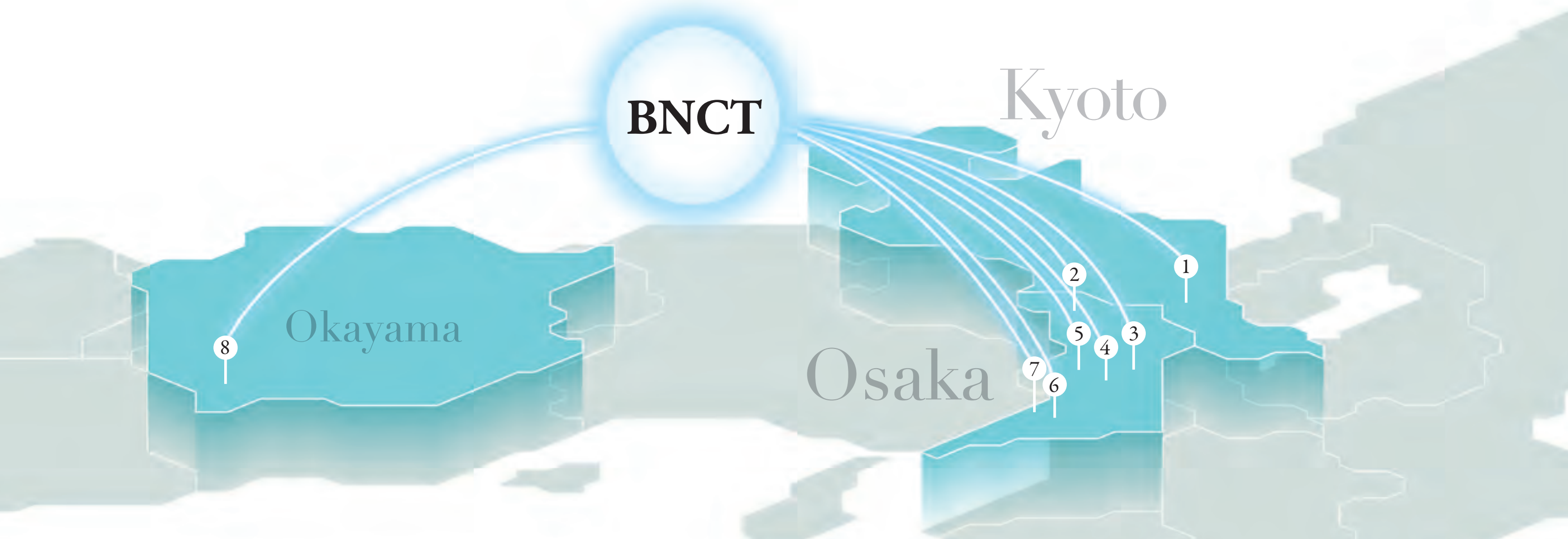
Requirements for BNCT

Four elements are indispensable in order to successfully implement BNCT.
Only the Osaka/Kansai Network, which centers around Kyoto University, Osaka University and Osaka Prefectural University, has all four of these elements.



The network towards BNCT utilization and growth

Industry, Academia and Government cooperate and target early utilization of BNCT.



❶ Kyoto University Hospital
(Training for specialists, Joint implementation of Clinical studies)

❷ Osaka University (Hospital / Dental hospital)
(Joint implementation of Clinical studies, PET examination, Boron medicine research, Training for specialists)

❸ Osaka Medical College Hospital
(Joint implementation of Clinical studies)

❹ Osaka Prefecture University
(Developing boron agents, Training for specialists)

STELLA PHARMA CORPORATION
(Joint-research - Developing boron agents with Osaka Prefecture Univ.)

❺ Medical Corporation Kinshukai, Hanwa Daini-Senboku Hospital
Hanwa Intelligent Medical Center *(PET examination)*

❻ Kyoto University Research Reactor Institute
(Clinical studies, Training for specialists, World's first prevalent type accelerator development)

Sumitomo Heavy Industries, Ltd.
(World's first prevalent type accelerator development)

❼ Rinku General Medical Center *(Joint implementation of Clinical studies)*

❽ Kawasaki Medical School Hospital
(Joint implementation of Clinical studies)

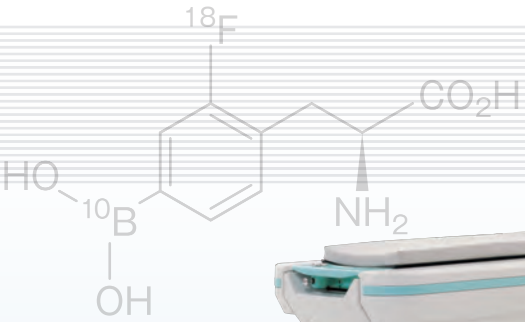
Other Organizations implementing Joint Clinical Studies

- Kinki University (Department of Medical Oncology, Faculty of Medicine)
- Wakayama Medical University (Department of Radiology)
- Hyogo Prefectural Amagasaki Hospital (Department of Pulmonary Internal Medicine)
- Hyogo College of Medicine (Division of Respiratory Medicine, Department of Internal Medicine)
- Okayama University (Department of Neurological Surgery, Faculty of Medicine)

＊There are other Organizations implementing Joint Clinical Studies but they are not listed here due to space limitations.

PET study

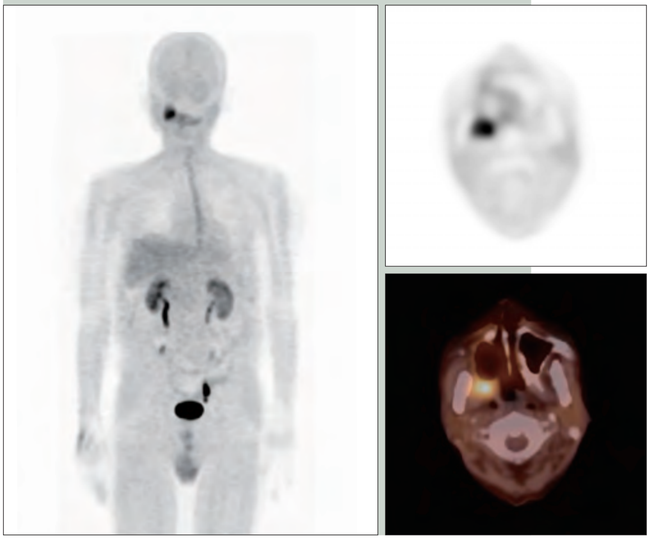
Imaging the state of boron accumulation in tumors and determining whether a given patient is a candidate for BNCT



Before treatment by BNCT,
it is necessary to verify that boron (^{10}B) has accumulated in the malignant tumor targeted for treatment but not in surrounding healthy tissue.
The amount of ^{10}B accumulation in the tumor directly affects the absorbed dose when irradiated with neutrons.
Additionally, verifying low accumulation in healthy tissue enables BNCT to be administered safely with minimal adverse effects.
Positron emission tomography (PET) can be used to measure the extent to which a certain compound has accumulated in a patient's internal organs.
PET testing consists of administering a minuscule amount of a radioactive compound or pharmaceutical and then imaging the patient's entire body.
By marking the carrier that transports boron (^{10}B) to the tumor with a radioactive nuclide and administering it to the patient, it is possible to quantitatively estimate the amount of boron in an individual patient's tumor and surrounding tissue.

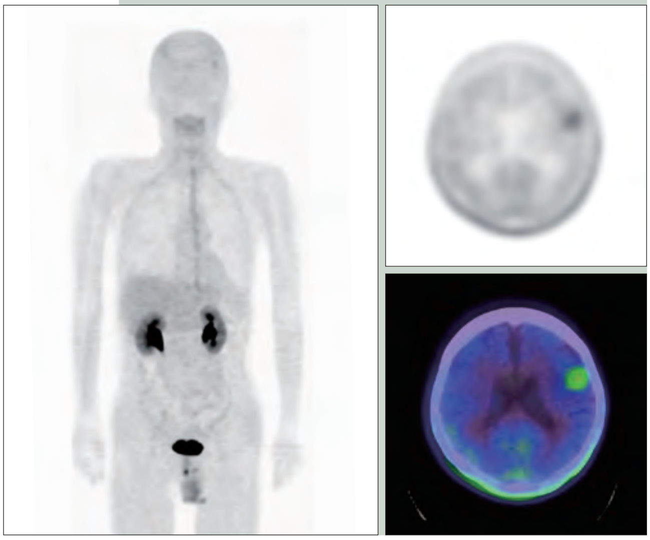
FBPA PET

A case showing high FBPA accumulation in a head and neck tumor



The patient, a 73-year-old male, was diagnosed as having maxillary sinus cancer on the right side of his face four years ago. After surgical removal of the tumor, he underwent radiation and chemotherapy, followed by BNCT. When a tumor mass returned in the area that had been treated, the patient underwent an FBPA PET test. A high accumulation of FBPA was confirmed in the recurrent tumor mass. The level of accumulation was about five times higher than in the surrounding healthy tissue, and he was diagnosed with a recurrence of the tumor and determined to be a candidate for BNCT. (This patient was referred by Dr. Itsurou Kato at Osaka University.)

A case with non-accumulation in a suspected brain tumor



The patient, a 63-year-old male, was diagnosed as having lung cancer one year ago and had the tumor surgically removed. Later, the patient developed a metastatic brain tumor in his left frontal lobe. After gamma knife treatment, imaging revealed that a ring-shaped tumor remained. An FBPA PET test indicated that accumulation in the tumor was only about two times that of the surrounding healthy tissue, prompting a determination that the patient was not a candidate for BNCT. (This patient was referred by Shin'ichi Miyatake at Osaka Medical College.)

Boron agents

Developing high-performance boron agents to selectively concentrate boron in tumor cells

In BNCT, development of a boron medicine is of primary importance. Many kinds of boron compounds have been designed on a molecular level, synthesized and subsequently evaluated. However, clinical studies have only been carried out on first generation BSH and second generation BPA. The third generation compounds to replace these have not yet been developed.

The simultaneous use of “BPA” + “BSH”

Currently, combination treatments are being developed to utilize the respective advantages of BPA and BSH. BPA has both high selectivity and concentration levels that allow it to display a superior rate of accumulation.

On the other hand, while BSH’s tumor selectivity (T/N ratio) and propensity to accumulate inside cells are low, reports indicate that it has a tendency to be distributed in the vicinity of tumor tissue.

Trends in the development of new ^{10}B compounds

Reports in scientific literature detail the synthesis of various boron compounds with the goal of developing effective new boron compounds. Most consist of oncotropic molecules that have been modified with ^{10}B. Drug delivery systems (DDSs) targeting the comparatively large gaps between capillaries that characterize tumor tissue are also under active development.

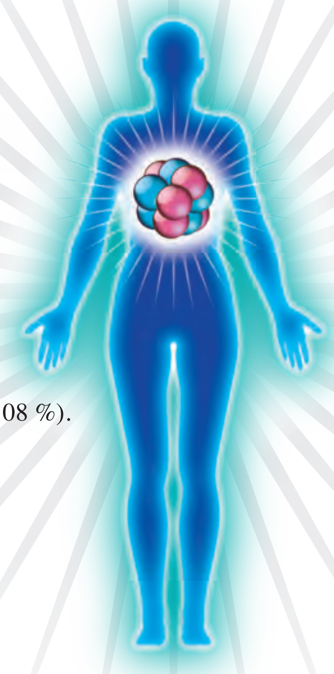
Research Center for Boron Neutron Capture Therapy:

A facility dedicated to developing boron compounds

The Research Center for Boron Neutron Capture Therapy was recently established on Osaka Prefecture University’s Nakamozu Campus. The facility, which is equipped with state-of-the-art equipment and systems, is hosting initiatives including trial projects

Neutron source

Imaging the state of boron accumulation in tumors and determining whether a given patient is a candidate for BNCT

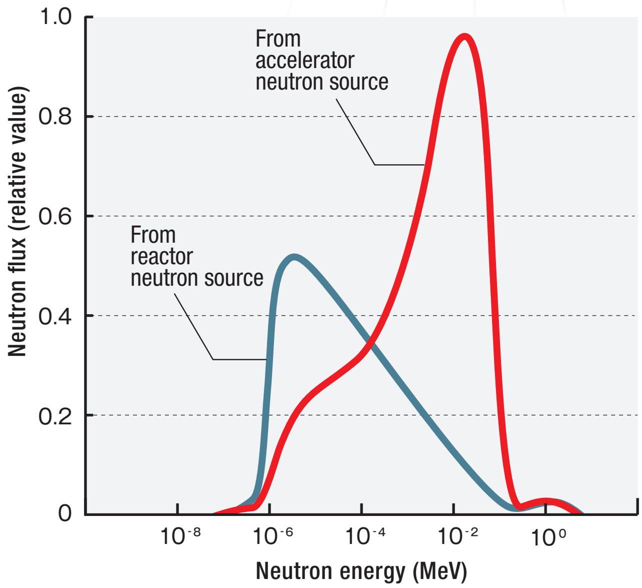


Requirements for BNCT

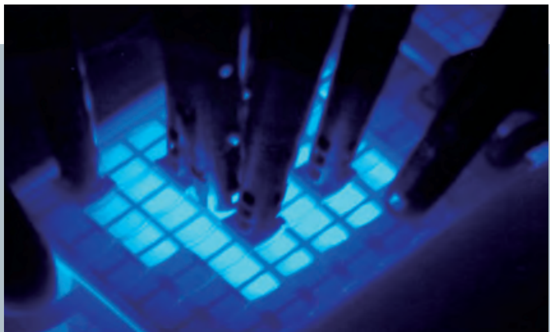
Neutrons are electrically neutral subatomic particles (that is, they have no electrical charge). When existing alone in a vacuum, neutrons decay into a proton and an electron at a half-life of 10.8 minutes.
All of the atomic nuclei are composed of neutrons and protons, which are usually approximately equal in number, although there can be up to a 30% difference.
The mass of a neutron is nearly equal to that of a proton (the differences between those are about 0.108 %).
A variety of reactions occur depending on the energy of the neutrons in question.
Consequently, fields where there are neutrons exhibit an extremely diverse range of radiation.
In addition to the epithermal neutrons that play the central role in BNCT, tissues in the bodies of patients placed in the BNCT irradiation field are exposed to radiation that has leaked from treatment equipment and radiation given off by neutrons.
Therefore, in addition to knowledge of radiation treatments, the technician administering BNCT needs specialist knowledge in the BNCT field.

A neutron source for BNCT

In its present form, BNCT is based on epithermal neutron irradiation. Currently, the only facilities used as sources of neutrons for BNCT in Japan are the Kyoto University Research Reactor (KUR) Heavy Water Neutron Irradiation Facility and the cyclotron accelerator system at the Kyoto University Research Reactor Institute. Both nuclear reactors and accelerators have deceleration systems capable of converting the generated neutrons into epithermal neutrons. The energy of epithermal neutrons is considered to range from 0.5 eV to 40 keV, taking into account the radiation weighting factor. To date, the KUR Joint-use Medical Treatment Group has verified the effectiveness of BNCT by offering the treatment to more than 500 patients using reactor neutrons and has also developed an accelerator neutron source for BNCT to facilitate wider use of the technique. In an effort to earn regulatory approval for the technique, the group began clinical trials on the treatment of recurrent glioma in October of 2012 and then on locally recurrent head and neck cancers in the spring of 2014.



Epithermal Neutron Energy Distribution
The mode energy values for epithermal neutrons produced in the reactor and accelerator are approximately 1 eV and 10 keV, respectively.



Photograph 1. Reactor Neutron Source

Photograph 2. Accelerator Neutron Source

Specialized training for BNCT staff : Objectives and issues

The central issue for the interim is fostering the development of medical physics specialists who would, along with medical doctors, guide neutron capture therapy based on their knowledge and experience in conventional radiation treatment. At the same time, BNCT's overall development also demands that personnel be trained to:

1. *Carry out medical and clinical research related to irradiation treatment*
2. *Carry out research in drug concentration (distribution) measurement*
3. *Carry out research in drug development*
4. *Carry out research and development work addressing the neutron irradiation field*

In addition to general knowledge in the areas of medical physics, radiation biology, radiation oncology, pharmaceutical science, and nuclear medicine, staff specializing in BNCT must exhibit specialized and basic knowledge of the following in their capacity as medical physics specialists.

1. Interactions of neutrons in the body

(nuclear transmutation, scattering, and capture reactions as well as methods of neutron spectra detections and of neutron-gamma discrimination detection)

2. Irradiation effects in the BNCT irradiation field

(radiation quality, dose evaluation, and tissue reactions)

3. Effective dose distribution optimization planning

(radiation quality, dose distribution, ^{10}B agent distribution, intra- and extra-cellular concentrations, and the cell cycle as well as dose-volume histogram (DVH) creation and the concepts of probability of tumor control and complication development)

4. Safe handling of, and protection from, leakage radiation, primarily in neutron form

Additionally, practical training in close partnership with BNCT work in the field is an important means of mastering this broad body of knowledge.

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