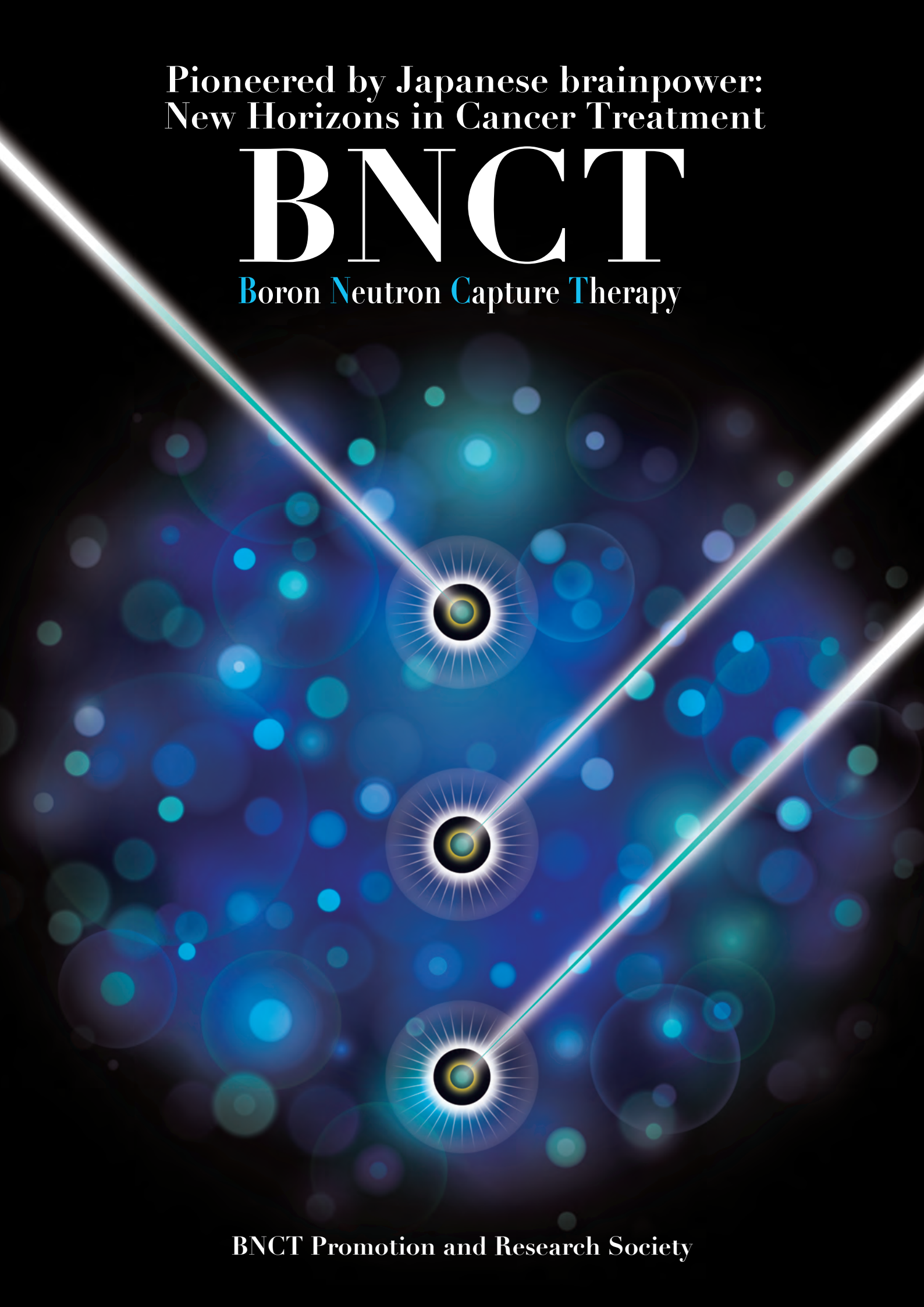
Pioneered by Japanese brainpower:
New Horizons in Cancer Treatment

BNCT

Boron Neutron Capture Therapy



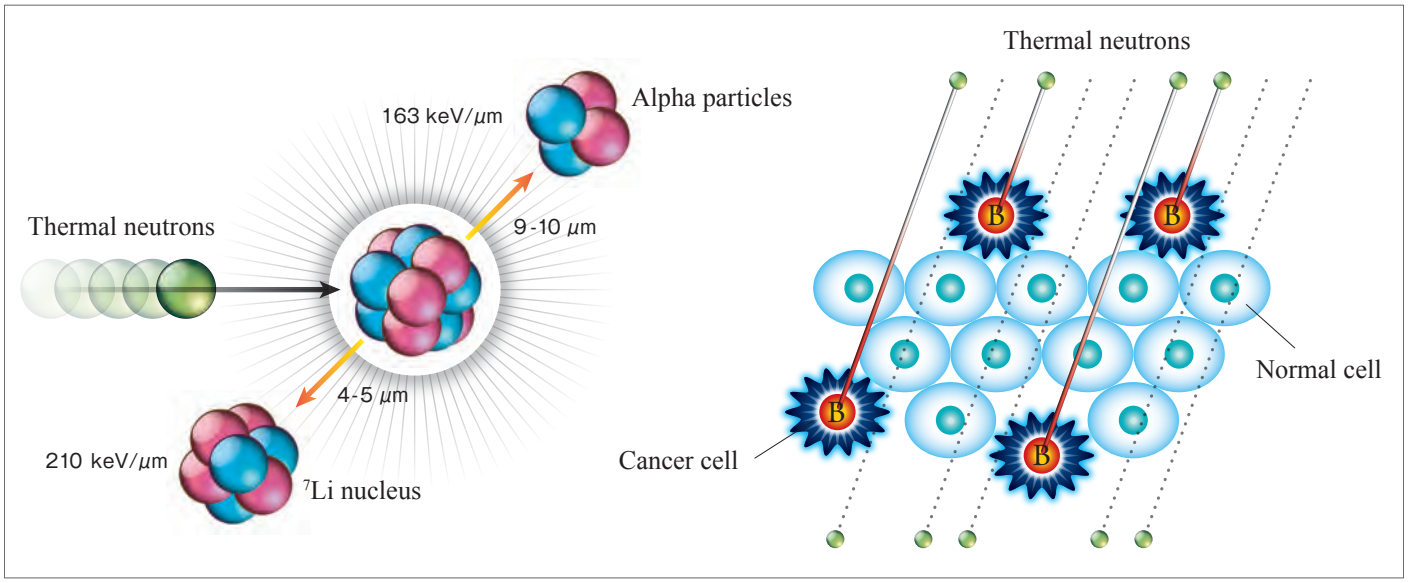
BNCT Promotion and Research Society

The birth of BNCT

Boron neutron capture therapy, or BNCT, is a treatment technique that allows selective irradiation at the cellular level. The first clinical studies, which began in the U.S., failed to yield good results, but Japan continued the process where the American researchers left off, driving progress to the present day.

Proposal of BNCT

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 short 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 cancerousregion with neutrons after administering that compound. However, while the probability of this reaction is close to 2,000 times higher than that of the reaction with nitrogen, the extremely high density of nitrogen atoms in tissue makes it necessary for the boron to accumulate in the cancers at levels on the order of several mM.




James Chadwick

Discovery of the neutron

The neutron was discovered by Professor James Chadwick of Cambridge University in 1932. In a famous episode, the husband-and-wife team of Frederic and Irene Joliot-Curie had noted a phenomenon that was tantamount to discovering the neutron when they found that an unknown form of radiation with an extremely high level of penetration was emitted when paraffin was irradiated with protons. However, they lost the honor of discovering the neutron and winning the Nobel Prize when they misinterpreted their results.

World's first clinical research (U.S.)

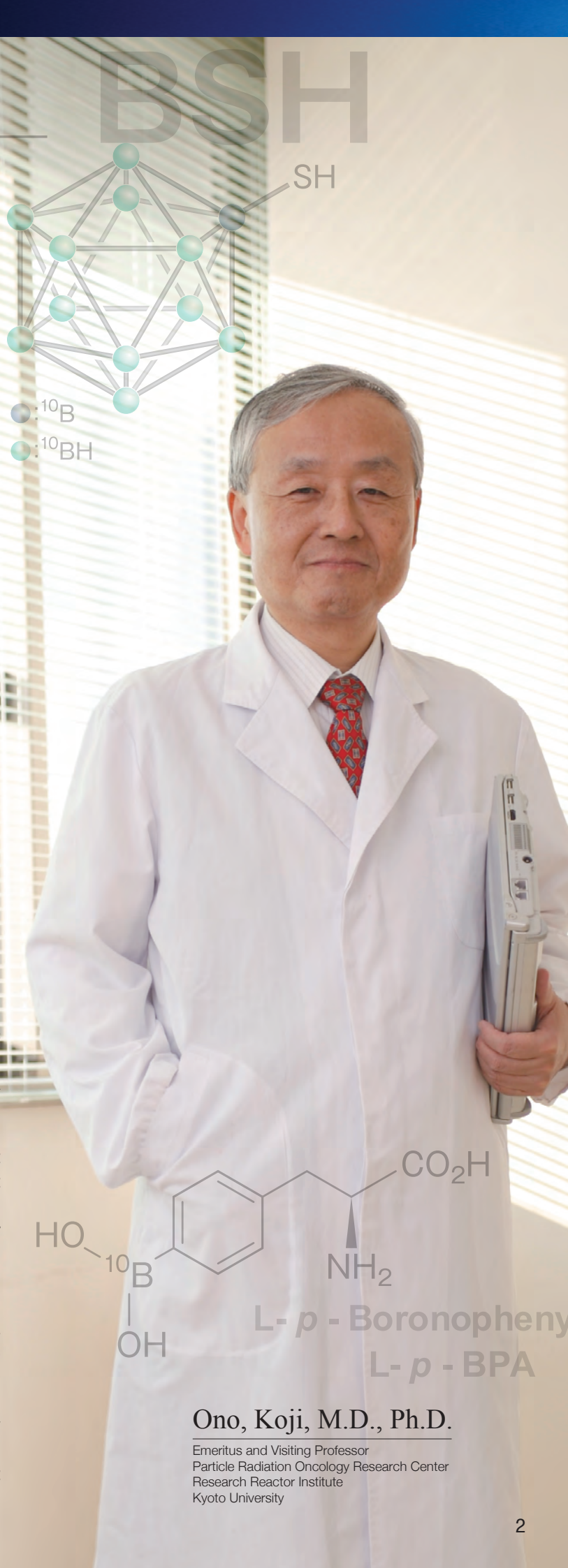
A neutron source with a high fluence rate is essential if the approach is to be applied to cancer treatment. Consequently, any application of the idea had to wait for the emergence of nuclear reactors. Reactors at Brookhaven National Laboratory (BNL) and the Massachusetts Institute of Technology (MIT) were utilized in the first clinical research. Professors L.E. Farr and W.H. Sweet carried out clinical research targeting malignant brain tumors over the 10-year period beginning in 1951, but the clinical results were poor, with average survival times of less than six months. Concluding that the principal reasons for these outcomes were insufficient selectivity in the accumulation of boron compounds in tumors and the poor quality of the neutron beam, the researchers were forced to focus on resolving these difficulties. BNCT research in America was suspended and Japan subsequently picked up where the. Americans left off.

BSH : *The first clinically effective boron compound*

At the end of the 1950s, irradiation experiments using small animals as basic research began at the Japan Research Reactor No.1 (JRR-1) and the Hitachi Training Reactor (HTR). In 1968, a team led by Hiroshi Hatanaka began administering BNCT to patients with malignant brain tumors using a new boron compound ($Na_2B_{12}H_{11}SH$, commonly known as BSH). The HTR and the Musashi Institute of Technology Reactor (MuITR), which was modified for medical use, were used as neutron sources, and a high-purity thermal neutron irradiation field developed at the heavy-water facility of the Kyoto University Research Reactor (KUR) was also used in 1974. Since the ability of the neutron beam (consisting of thermal neutrons) to penetrate deep tissue was limited, irradiation was performed during a craniotomy (in a process known as intraoperative irradiation). The compound BSH, of which each molecule has 12 ^{10}B atoms, is easy to use since it excels in its ability to transport ^{10}B and offers high water solubility. Whereas BSH is prevented from penetrating brain tissue by the blood-brain barrier in normal brains, the failure of this barrier function allows it to penetrate, and accumulate in, malignant brain tumors, resulting in a large concentration difference. However, the compound's properties are not such that cancer cells actively accumulate it. Although the results obtained by Hatanaka were favorable and suggested the efficacy of BNCT, he was unable to convince neurosurgeons and radiation oncologists of the usefulness of this treatment.

BPA: *A boron compound that accelerated new developments in BNCT*

Yutaka Mishima, formerly a professor of dermatology at Kobe University, conducted many years of research in an effort to treat malignant melanoma (skin cancer) exhibiting X-ray resistance with BNCT. He focused on L-*para*Boronophenylalanine (L-BPA, referred to as "BPA" below) as an analog of tyrosine, which is a precursor of melanin, and conducted basic research to apply BPA in BNCT as melanoma-specific boron compound. As a result, there was a large difference in BPA concentration between malignant melanoma cells and normal cells. Through subsequent research using FBPA PET imaging, it was discovered that the compound accumulated not only in malignant melanoma, but also in various malignant tumors. It is thought that this fact is accounted for by the increased level of amino acid transport in malignant tumor cells, and today the effects of BPA-BNCT on numerous types of tumors are being studied. BPA was first used clinically in BNCT to treat a malignant melanoma in 1987 by Mishima and his team. The compound was first used in BNCT to treat a patient with recurrent malignant glioma in February 1994 using the KUR. This trial preceded a similar study at Brookhaven National Laboratory in the U.S. by about seven months.
BPA differs significantly from BSH in that it is selectively absorbed by cancer cells, and it is fair to say that BNCT could first be called a technique for selective cancer cell treatment with the advent of BPA.



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Basic, clinical research and technological develop

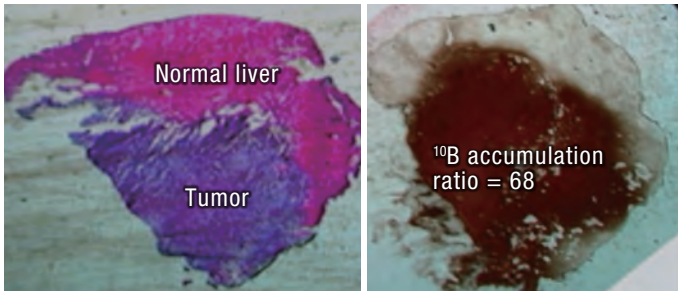
Development of Compound Biological Effectiveness (CBE) factor and basic technologies in Japan

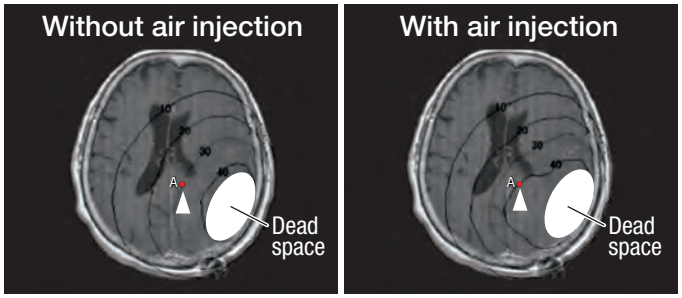
Along with the development of new boron compounds, important issues for BNCT include basic research to expand the application of existing compounds to common cancers and develop targeting techniques for using them effectively. Boron compounds exhibit a complex microscopic distribution, and the boron accumulation and dose vary with the types of cells that constitute normal tissue. Present research into the biological effects of radiation has not revealed how damage to individual types of cells contributes to overall tissue damage. Consequently, it is standard practice in BNCT to calculate a virtual dose based on the concentration of boron in the blood and the neutron fluence to the tissue, and then the X-ray equivalent dose is calculated by multiplying the virtual dose by a conversion coefficient. This coefficient indicates the effective relative biological effectiveness (RBE) of BPA or BSH, and it is known as the compound biological effectiveness (CBE) factor. Since the CBE factor changes depending on the kind of boron compound used and the type of tissue evaluated, it is determined by means of animal experiments. Japanese researchers have determined CBE factors of BPA for the skin and hepatocytes and of BSH for hepatocytes. This data has enabled BNCT to be used to treat malignant melanoma and liver cancer.

In order to facilitate the selective accumulation of boron compounds in tumors, KUR researchers devised the idea of applying the IVR procedure. It succeeded in selectively confining BSH to an experimental liver cancer using the IVR procedure, and a boron concentration ratio of about 70 was attained. In BNCT treatment of head and neck cancers, researchers are attempting to inject boron compounds into tumor arteries to facilitate super-selective drug delivery.

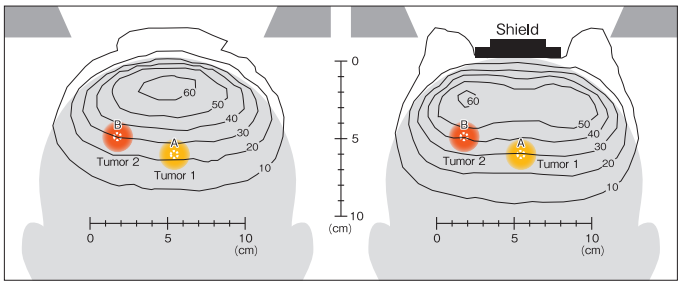
Unlike X-rays and heavy charged particle radiation, neutrons disperse like mist in the body upon irradiation. Consequently, their depth distribution can be improved by using techniques that seem counterintuitive from experience with X-rays and other kinds of radiation.

Radiation type	Tumor	Brain	Skin	Mucous membrane	Lung	Hepatocyte
$^{10}B(n,\alpha)^{7}Li$						
BPA	3.8	1.35	2.5	4.9	2.3	4.3
BSH	2.5	0.37	0.8	0.3	?	0.9





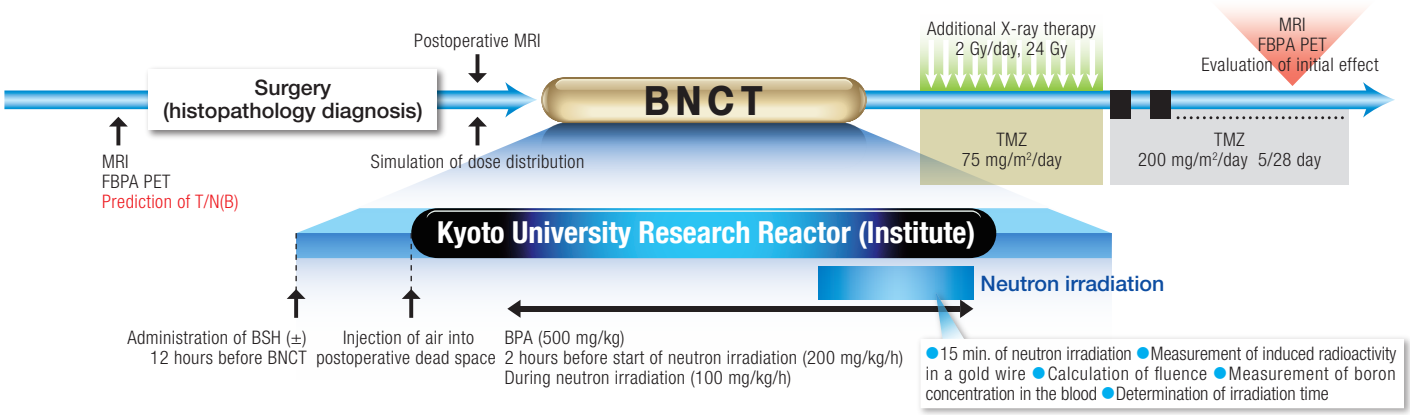
By non-invasive injection of air into the dead space left after tumor resection, the depth distribution of neutrons can be improved, allowing BNCT to be used to treat deep tumors as well. When the size of the dead space is large, this technique is extremely effective (see figure below). The dose at point A has been increased from 30 Gy-eq to 40 Gy-eq.



It is clear that by shielding the central part of the neutron irradiation field, it is possible to improve the relative depth distribution of neutrons (compare the doses at points A and B with and without the center shield).

Our BNCT procedure (using a malignant brain tumor as an example)

The following figure illustrates the standard BNCT procedure for use in treating a malignant brain tumor, including prior medical examination, image inspection using CT and MRI, and confirmation of diagnosis by using FBPA PET.



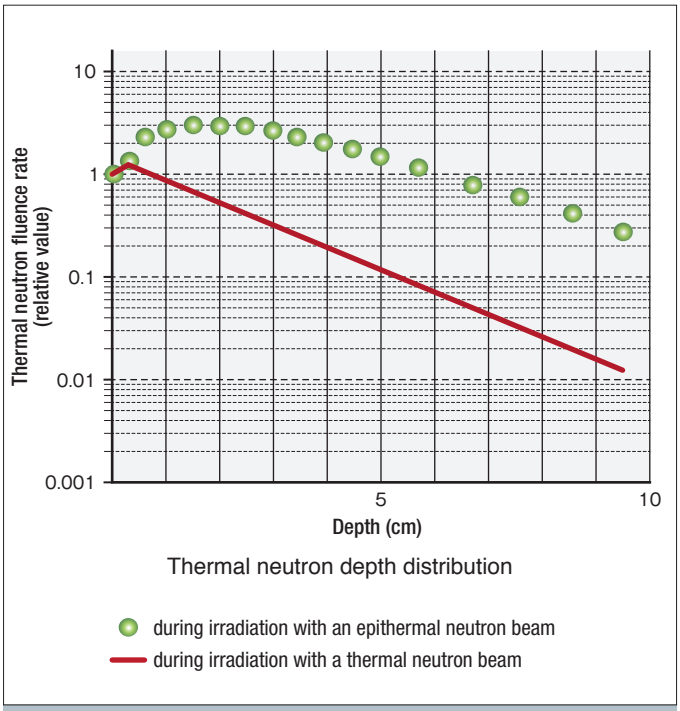
ment in Japan lead BNCT research in the world.

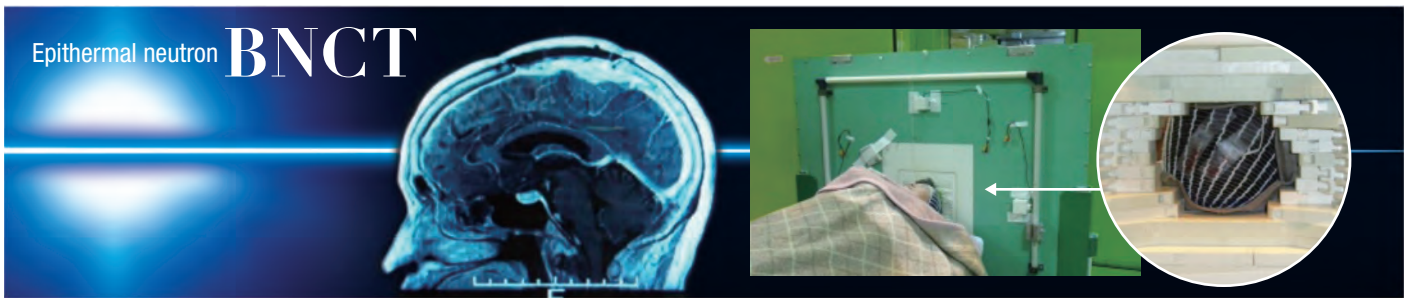
Improved thermal neutron beam facility

In addition to insufficient selective accumulation of boron compounds in tumors, the poor clinical results in the U.S. can be attributed to the low quality of the neutron beam that was used, that is, the mixing of an excessive level of gamma rays with a neutron beam. In Japan, an improved neutron beam port was used in clinical research. In particular, a heavy water facility capable of extracting thermal neutrons at a high level of purity was added to KUR. While this facility was not specialized for BNCT, it provided a high level of thermal neutron purity with a Cd ratio of 5,000 and a thermal neutron fluence rate of 6×10^9 n/cm^2•s. A facility of the highest caliber, it was used in 1974 for the first BNCT at KUR.

From using thermal neutrons to using epithermal neutrons (described in detail elsewhere in this pamphlet)

Research into BNCT became active again during the second half of the 1980s, especially basic research targeting malignant glioma, particularly glioblastoma. Epithermal neutrons lose their energy by degrees as they react with various atoms in the body and change into thermal neutrons. The depth distribution of thermal neutrons generated inside the body reaches its maximum value at a depth of 2 to 3 cm, about 3 times the value at the surface.
Furthermore, the attenuation of thermal neutrons in tissue is relatively gradual. Consequently, by using an epithermal neutron beam, no craniotomy is needed for neutron irradiation at the research reactor site when BNCT is applied to malignant brain tumors. In the autumn of 1994, BNCT was performed without a craniotomy at BNL's research reactor in the U.S. using an epithermal neutron beam. In Japan, KUR's attached heavy-water thermal neutron facility was modified so that it could also use epithermal neutrons from 1995 to 1996. However, the fixation on use of a thermal neutron beam was strong among researchers who studied BNCT, and large-scale use of epithermal neutron beams had to wait for the arrival of this century. In Japan, the modifications at KUR were followed by similar changes at facilities operated by the former Japan Atomic Energy Research Institute.





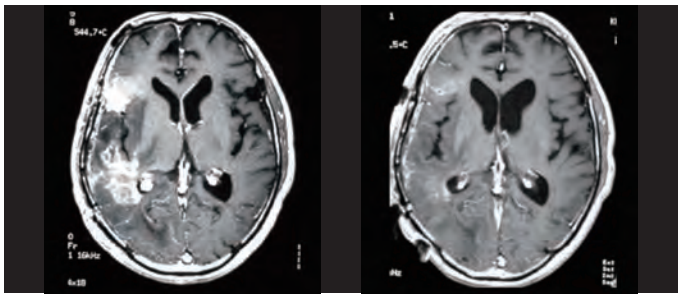
Appearance of FBPA PET (described in detail elsewhere in this pamphlet)

Since BNCT can be expected to yield clear effects with good accumulation of a boron compound, efficient treatment could be attained if such cancer patients could be selected by prior inspection.
Fortunately, BPA can be labeled using ^{18}F, a positron-emitting radionuclide, and its accumulation in tumors confirmed by means of PET. Furthermore, the accumulation ratio in actual BNCT can be predicted by the ratio of ^{18}F radioactivity in the tumor and that in normal tissue (blood). The world's first BNCT procedure based on this prior inspection using FBPA PET was performed using KUR in February 1994, and it yielded the expected results.

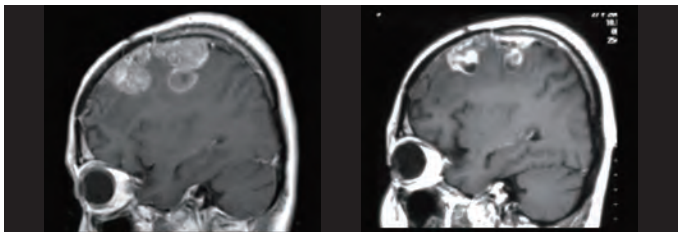
Pioneering and excellent clinical results in Japan

Malignant brain tumors

There are high expectations concerning BNCT research targeting treatment of malignant brain tumors, particularly malignant glioma.
Since BNCT allows a large radiation dose to be administered at once, there are cases in which the tumor reacts (as evidenced by the degeneration and disappearance of the lesions in MRI) much more quickly (in about two days), unlike in X-ray therapy. (Photo: A case at Osaka Medical College.)

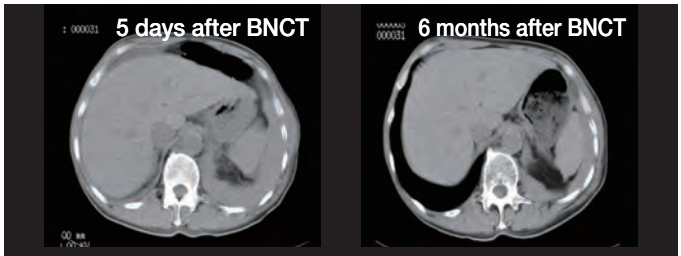


Apart from the above example, there have been malignant meningioma cases in which good tumor response has been achieved. This pathological type of tumor is refractory to X-ray therapy. (Photo: A case at Osaka Medical College.)



Malignant pleural mesothelioma (MPM)

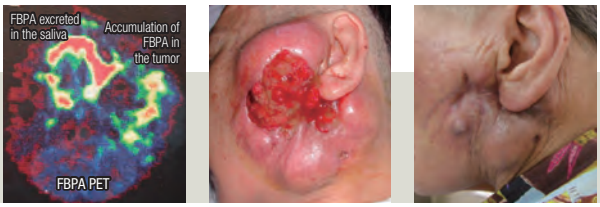
Because the cancer has spread along the pleura in cases of MPM, the tumor presents a complicated, three-dimensional geometry. Consequently, it is impossible to irradiate the tumor with a controlled dose while avoiding the lungs, which are covered with tumors, even using today's high-precision radiation treatment technologies. Experts hope that treatment techniques such as BNCT to offer a high level of tumor selectivity that will provide superior effectiveness in MPM.

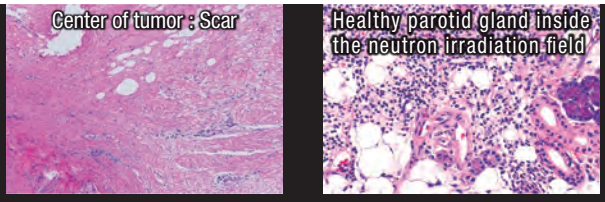


This is the world' s first MPM to be treated with BNCT. The treatment proved to be remarkably effective. (Photo: A case at Hyogo Prefectural Amagasaki Hospital.) The patient had suffered from severe chest pain and needed to use morphine every day, but the pain disappeared completely several days after BNCT. Regression of the tumor was confirmed by CT six months later, and the patient lived for 10 months, far beyond initial expectation of less than three months.

Head and neck cancers

The standard treatment regimen for head and neck cancers combines surgery, X-ray therapy, and chemotherapy. BNCT is expected by radiation oncologists to serve as a technique that makes possible repeated radiation therapy for recurrent patients because re-irradiation by X-rays is not allowed due to the tolerance dose of normal tissue consumed during previous X-ray therapy.
The world's first use of BNCT to treat a head and neck cancer was a case of recurrent cancer of the parotid gland. After two BNCT treatments, the tumor had completely regressed, and the patient's skin reaction did not reach to the level of dry desquamation. (Photo: A case at Osaka University.) It is not possible with other treatment modalities to avoid damage such as thin and blistered skin while irradiating enough of a control dose to the tumor lying just under the skin. The responses observed in this case showed BNCT's high degree of tumor selectivity and its superiority.

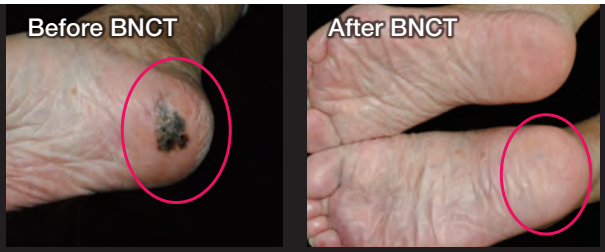




In one case where surgery was conducted after BNCT, the complete degeneration of the tumor was confirmed by histopathological examination, while the parotid gland and fat cells remained without destruction (despite lying inside the neutron irradiation field). (Photo: A case at Kawasaki Medical School.) It is a case that confirms the selective effects of BNCT at the microscopic level.

Malignant melanoma of the skin

BPA was developed clinically as a boron compound for use with malignant melanoma of the skin, and its tendency to accumulate at high concentrations in melanoma lesions has been confirmed. While surgical removal has proven adequate for treating small lesions, BNCT using BPA is an effective new treatment in cases where the area of removal is large or where removal would lower the patient's quality of life.



The black spot lesion had completely degenerated, and normal skin regenerated at a high level of quality. (Photo: A case of malignant melanoma at Kawasaki Medical School.)

Experiments and preliminary clinical trials of BNCT for other types of tumors

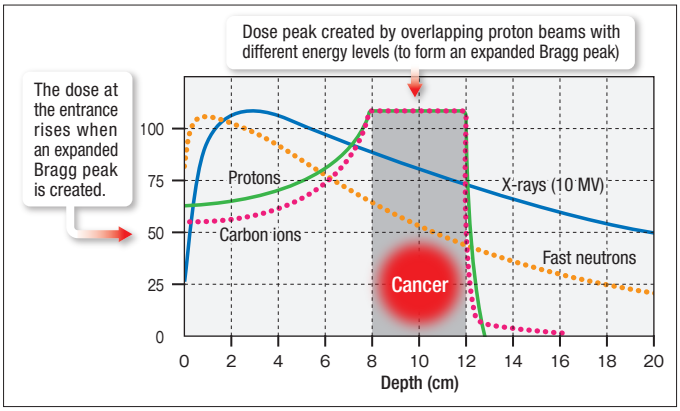
Neither X-ray therapy nor other types of particle therapy are applicable to multiple liver cancer, and there is no treatment that offers the possibility of a permanent cure. Since it is necessary to irradiate the entire liver, we believed that this type of cancer would be a good candidate for BNCT, which can be expected to selectively destroy such tumors, and we attempted clinical BNCT in several cases based on the results of BSH tumor trapping experiments as described above. We were able to confirm a certain level of effectiveness, but it remained insufficient. We are currently waiting for a new technique to be developed. Similarly, by using BPA we attempted BNCT for patients with carcinomatous pleurisy, in which the cancer has spread throughout the pleura, and obtained comparatively favorable results. In many cases, Paget disease, a type of skin cancer, spreads over a large area, and surgical removal would lower quality of life (as is the case with malignant melanoma). We have experienced several cases that show the usefulness of BNCT for this disease. Otherwise, BNCT has been successful when cancer has metastasized to the lymph nodes and accompanied by strong symptoms in patients who have previously undergone X-ray therapy in the same region of the body.

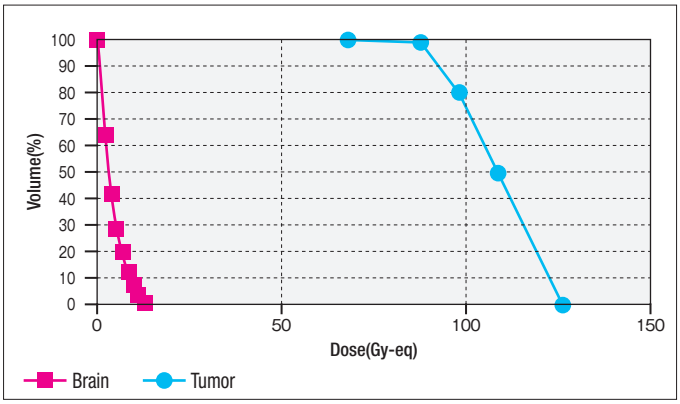
Characteristics and role of BNCT in cancer radiotherapy

Cancer radiotherapy with different high-level selectivity

Recently, high-precision radiotherapy has been praised for the ability to selectively target tumors with pinpoint precision, allowing them to be selectively targeted and irradiated while leaving normal tissue unexposed. This characterization constitutes a misapprehension and is not at all correct. Proton therapy and carbon ion therapy that use the Bragg peak expose normal tissue to large doses of radiation before the particles reach the tumor, as shown in the figure. Moreover, normal tissue (cells) surrounding the tumor and inside the tumor receive the same dose as the tumor itself.

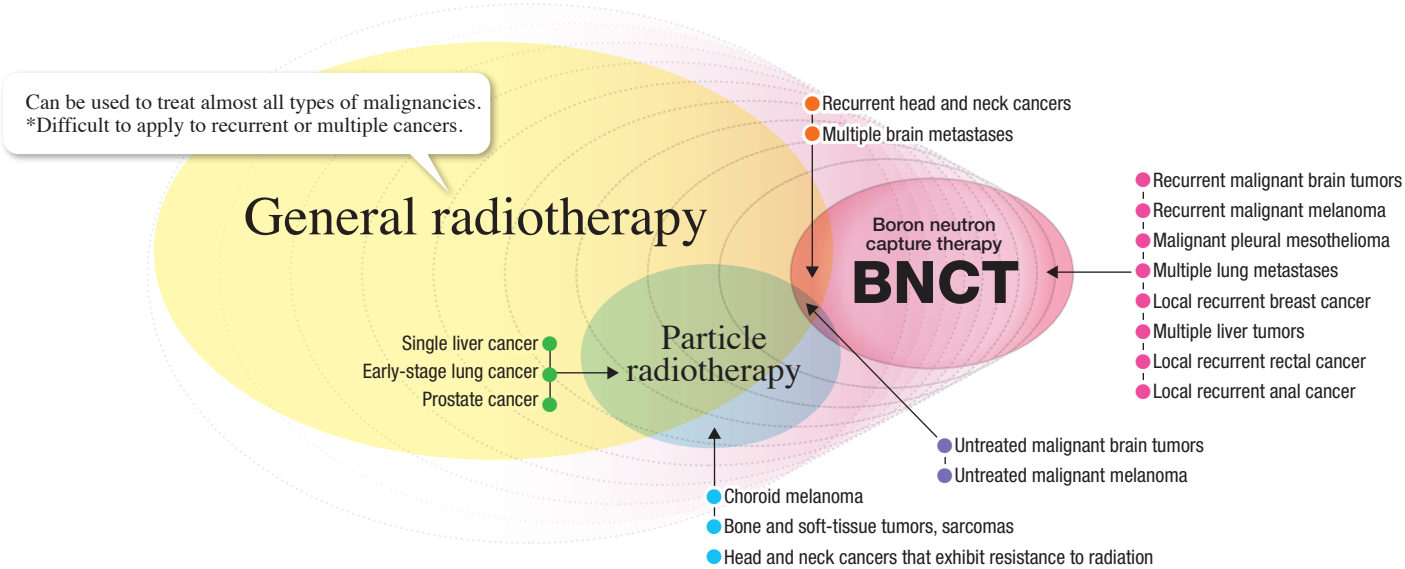
By contrast, BNCT, which allows selective irradiation of cells, differs radically from these approaches. Even normal cells inside the GTV (Gross tumor volume) receive a dose that differs completely from tumor cells. The difference is clear when illustrated with DVH (Dose volume histograms) (see figure): observe that the curves for the normal tissue dose and the tumor (cell) dose do not intersect anywhere. Except for BNCT, there is no treatment in which the DVH curves are completely dissociated from one another. BNCT can administer a dose of radiation to tumors (cells) selectively, making it appropriate to call the technique pinpoint radiotherapy.

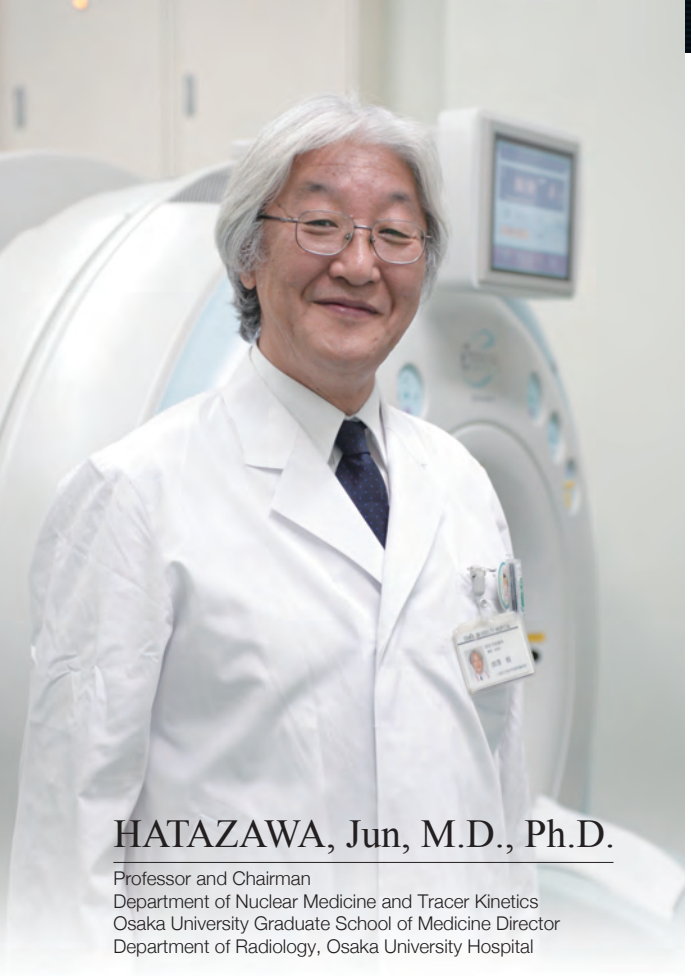




Roles and applications of BNCT in cancer radiotherapy

X-ray therapy, which offers coverage for a broad range of cancer types and stages, plays a major role in cancer radiotherapy, and this fact is unlikely to change in the future. It is thought that the application of both proton therapy and carbon ion therapy overlaps considerably with X-ray therapy. By contrast, insofar as it allows cells to be selectively irradiated, BNCT has an advantage in that it can be used to treat cancers and stages to which X-ray therapy, proton therapy, and carbon ion therapy are ill suited due to the principles on which they are based. If boron compounds that accumulate even more selectively in tumors can be developed in the future and the limits on treatment depth resolved, the time may come when BNCT can be used to treat as broad a range of cancers as X-ray therapy. The following figure illustrates likely applications and distinctions from other radiotherapy approaches.





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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.

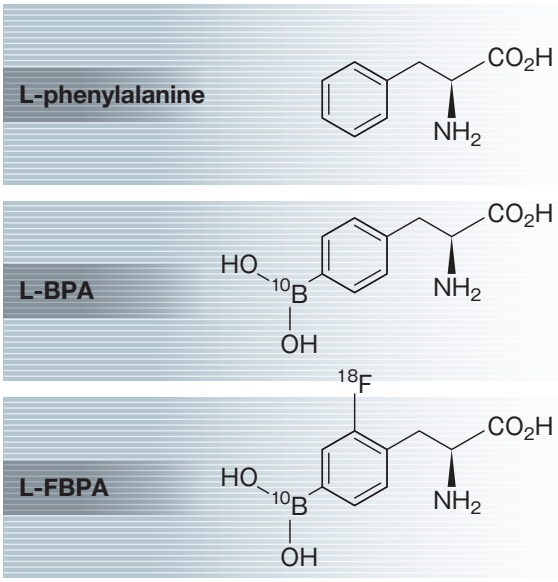
Positron emission tomography (PET) can be used to measure the extent to which a certain compound has accumulated in a patient's internal organs. PET testing consists of administering a minuscule amount of a radioactive compound or pharmaceutical and then imaging the patient's entire body. By marking 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.

Borono-phenylalanine, a boron compound with a high propensity to accumulate in tumors

Phenylalanine, an aromatic amino acid, is metabolized more quickly in tumor cells that are growing rapidly. Since the compound cannot be synthesized inside cells, it is absorbed in large volumes from the blood.

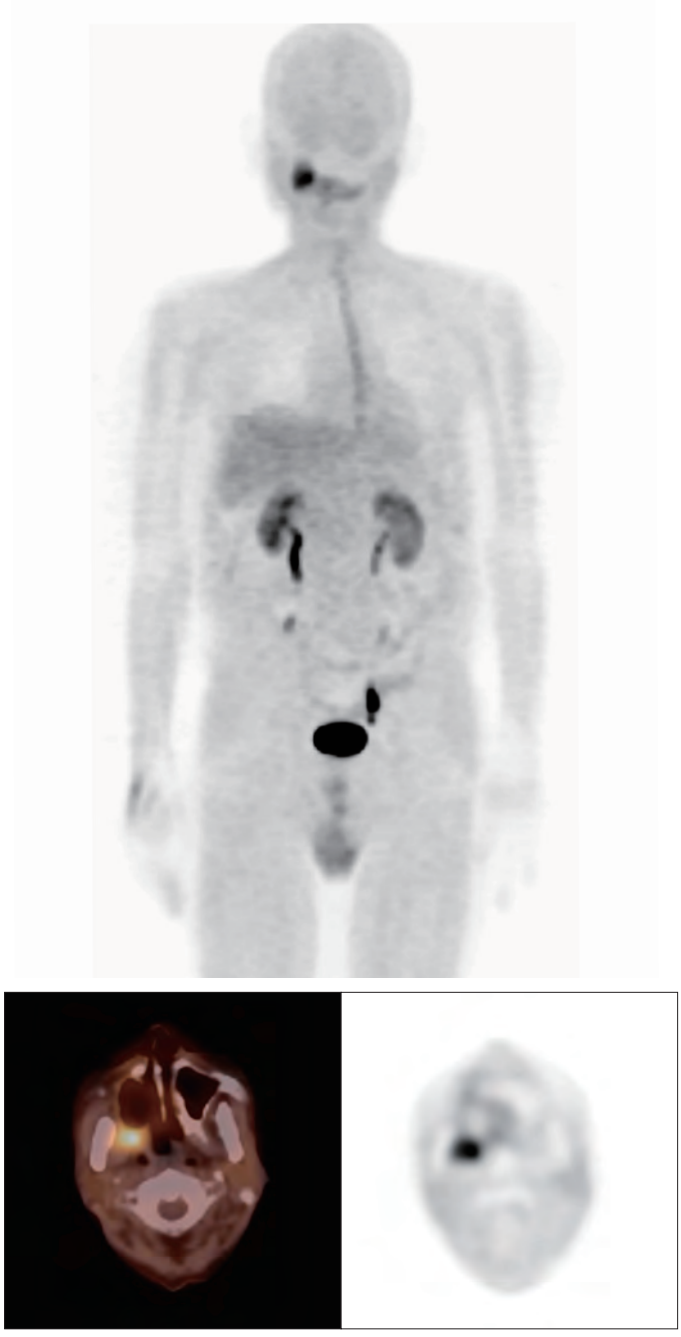
Borono-phenylalanine (BPA), derived by marking phenylalanine with ^{10}B boron, is also taken up in large volumes by tumors. In BNCT, BPA is used as the principal boron carrier.

The compound ^{18}F-fluoro-borono-phenylalanine (FBPA), derived by labeling BPA with the radioactive nuclide ^{18}F, is used to image the distribution of BPA in the body using PET. Like BPA, FBPA also has a high propensity to accumulate in tumors.



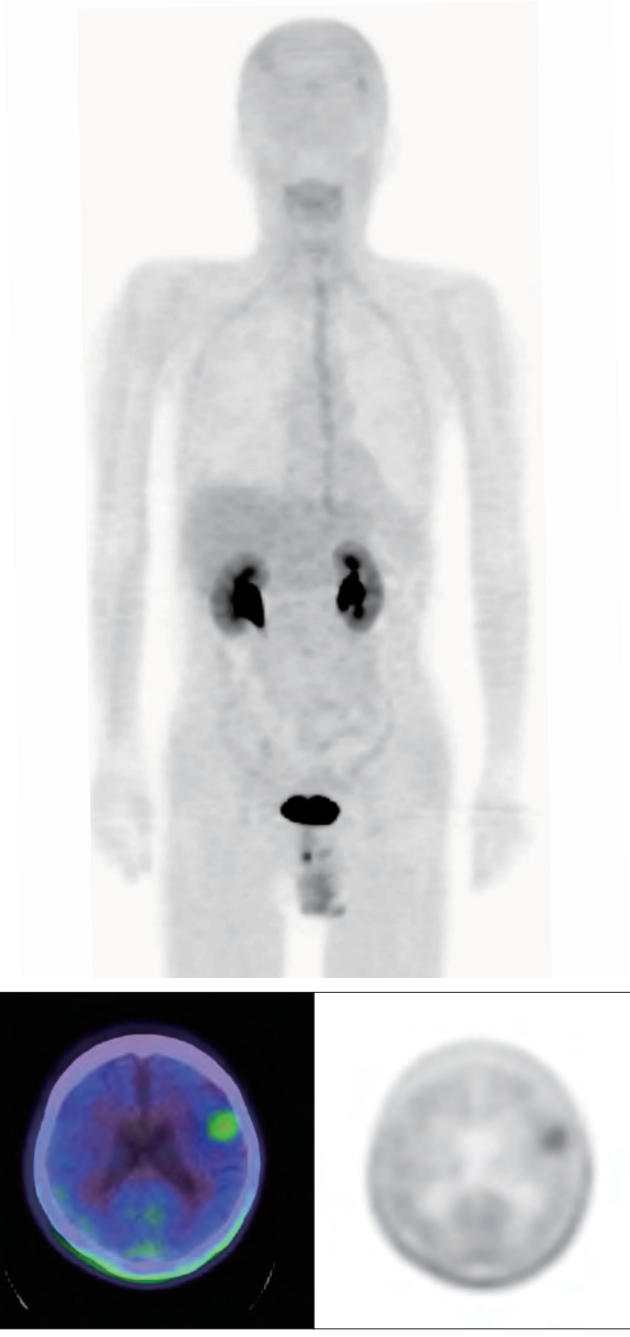
FBPA PET

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.)

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Boron agents

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

Boron-10 and the manufacture of high-purity, enriched boron-10

Boron is a chemical element with atomic number 5 in group 13 and period 2 of the periodic chart. Although it is common in the form of boric acid in rock, groundwater, surface water, and plants, it is not present in the human body. Natural boron exists in two isotopes with mass numbers of 10 (^{10}B) and 11 (^{11}B) in a proportion of about 1:4, and only ^{10}B is capable of absorbing (capturing) thermal neutrons. Consequently, high-purity ^{10}B (enriched ^{10}B) is necessary as a raw material in order to manufacture the boron agents that are used in BNCT. Currently, only a small number of countries, including Japan and the U.S., have plants capable of manufacturing enriched ^{10}B by sorting ^{10}B and ^{11}B in natural boron compounds and supplying it in large quantities.
Pharmaceutical-grade boron compounds are manufactured using this enriched ^{10}B in Japan, the Czech Republic, and other countries.

^{10}B manufacturing plant
(courtesy of Stella Chemifa Corporation)

High-purity boron compounds for use in BNCT

1 Properties required of ^{10}B compounds and boron agents

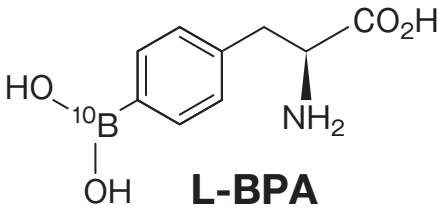
Boron compounds for use in BNCT must exhibit the following principal properties:

- they must accumulate selectively (the ratio of the concentration in tumor cells to the concentration in normal cells [T/N] must be greater than or equal to 3) and in large volumes (at a ^{10}B concentration of 20 to 40 ppm),
- they must not have any pharmaceutical effects themselves and must function only as a boron delivery molecule (in this property, they differ substantially from normal drugs),
- they must not be metabolized but must instead remain in tumor tissue for a certain period of time,
- they must exhibit low toxicity since they are administered directly into the blood.

Additionally, research to date has pointed to the importance of properties such as the balance of hydrophobic and hydrophilic tendencies and the proportion of each molecule's chemical makeup accounted for by the element boron. Currently, two boron compounds are being used in clinical research into BNCT: BPA, which has the structure of an amino acid, and BSH, which has a cluster-like structure.

2 L-BPA (L-p-boronophenylalanine [paraboronophenylalanine])

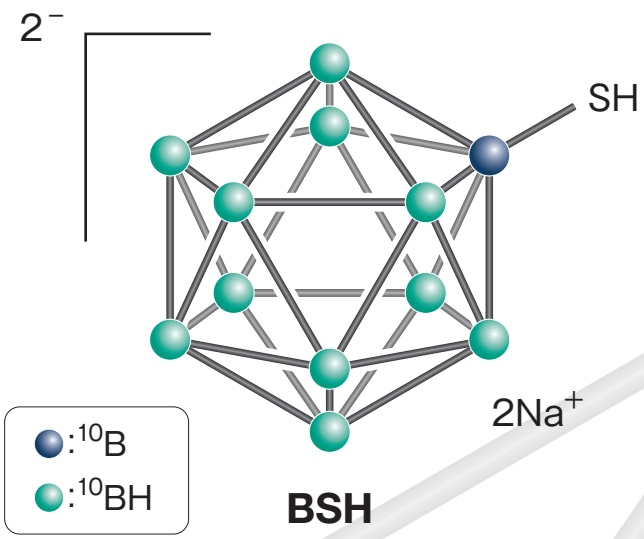
L-BPA was initially used in BNCT for melanoma due to its similarity to L-phenylalanine, which is the substance from which melanin biosynthesis begins. Later, researchers realized that it has an exceptionally high propensity to accumulate in other tumors as well, and today it is used in BNCT for brain tumors and head and neck cancer. Additionally, because its high degree of hydrophobicity means that it almost never dissolves in water under neutral conditions, it is combined with a water-soluble substance such as D-fructose to form a water-soluble complex that is then used as a boron agent.



L-BPA

3 BSH (disodium mercaptoundecahydro-dodecaborate)

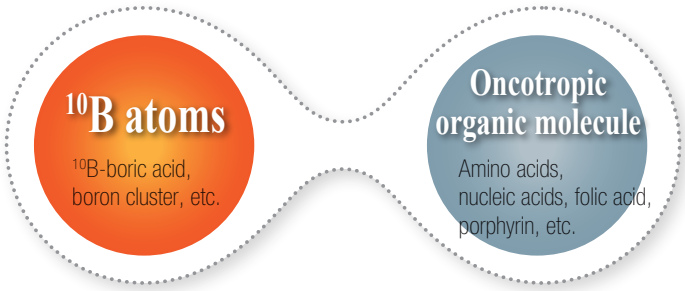
Another boron compound that is used in clinical research is BSH, which consists of a series of boron clusters with a unique 20-facet structure. BSH, a water-soluble ionic molecule with 12 boron atoms, reacts efficiently with neutrons and, because it can pass through the blood-brain barrier, was initially used to treat brain tumors. While BSH's tumor selectivity (T/N ratio) and propensity to accumulate inside cells are low, reports indicate that it has exhibits a tendency to be distributed in the vicinity of tumor tissue. Currently, combination treatments are being developed to take advantage of the respective advantages of BPA and BSH.



BSH

4 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.

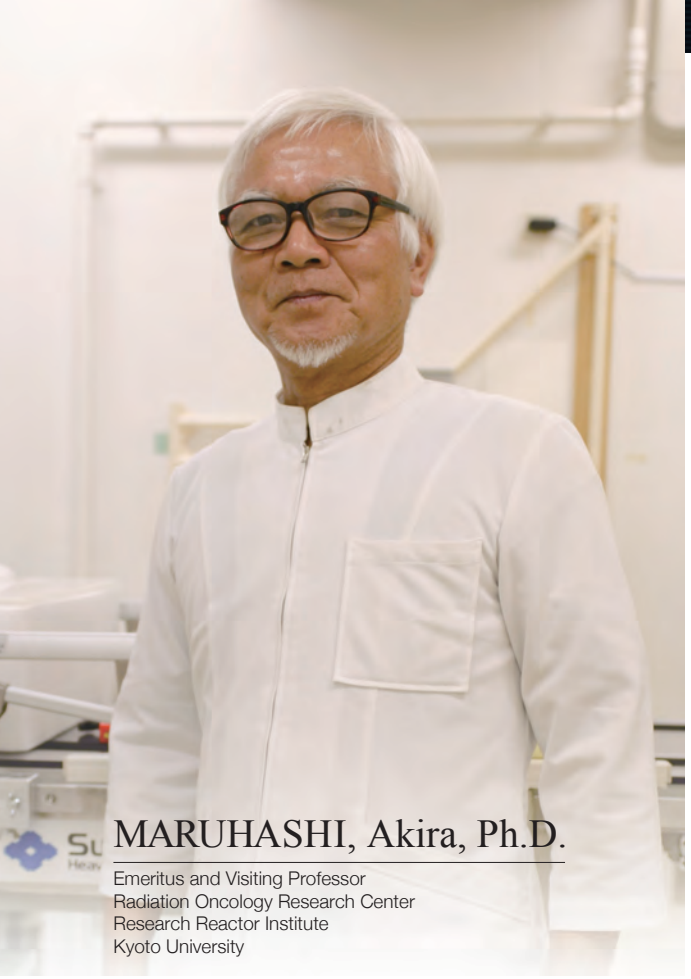


Structure of oncotropic ^{10}B molecules

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 centering on the development of new boron compounds and associated human resources development programs.



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Neutrons and their reactions

Neutrons, their properties, and their interactions with matter

Neutrons and their characteristics

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 %). Depending on their particular combination of nuclear particles, atomic nuclei are either stable (giving rise to a stable isotope [SI]) or unstable (giving rise to a radioisotope [RI]).

Neutrons can be characterized by the manner in which they interact with other types of matter. The interactions of neutrons at or below 20 to 30 MeV, the range of energy levels that are used in medical treatment, can be classified using the following conceptual categories:

1. Elastic scattering reactions (n, n)
2. Inelastic scattering reactions (n, n′)
3. Neutron capture reactions (n, γ)
4. Nuclear transmutation reactions (n, x)

These interactions occur with qualitative (in terms of reaction content) and quantitative (in terms of reaction probability) differences depending on the energy of the neutrons in question and the type of matter with which they are interacting.

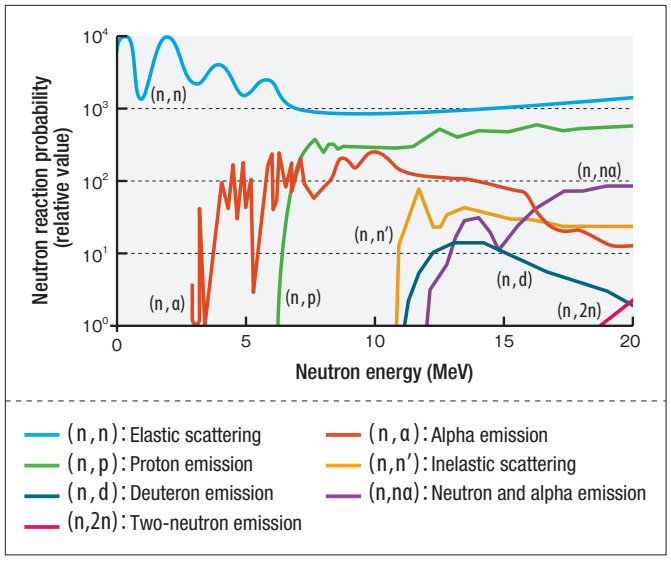


Figure 1. (for example)
Various Nuclear Reactions between ^{16}O and Neutrons

As illustrated in Figure 1, 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.

Let's take a closer look at the following reactions while paying special attention to their relationships with BNCT:

1 Elastic scattering reactions (n, n)

Elastic scattering refers to a scattering phenomenon involving neutrons and atomic nuclei in which momentum and kinetic energy are conserved. These reactions include potential scattering and resonance scattering, in which compound nuclei are formed. In the case of the latter, the wave character of the neutrons, based on the de Broglie wavelength, is involved in causing a resonant reaction. This reaction is dominant for many elements with neutrons at or below 10 MeV. Although elastic scattering reactions with hydrogen are primarily used in fast neutron therapy, this reaction is undesirable in BNCT since it is mostly unrelated to ^{10}B concentrations and has similar effects on tumor tissue and healthy tissue.

2 Inelastic scattering reactions (n,n')

In inelastic scattering, momentum is conserved, but kinetic energy is not. These reactions are excited state reactions in which the internal energy of colliding atomic nuclei increases, and with high-atomic-number substances, they mostly occur with neutrons of MeV-order or greater energy. While they can be useful insofar as they make it possible to shield neutrons of MeV-order or greater energy from high-atomic-number substances, they have no direct medical use.

3 Neutron capture reactions (n,γ)

Unlike inelastic scattering reactions, colliding neutrons are absorbed by atomic nuclei in neutron capture reactions. Consequently, each nucleus becomes an isotope with a mass number that is one greater. In most elements, the binding energy of nuclear particles is about 8 MeV. The formed nuclei enter an excited state of about that level of energy, which then decays upon emitting gamma rays according to the excitation level. This reaction involves only the emission of gamma rays and is not desirable for BNCT, but it is used as a technique for prompt gamma-ray analysis (PGA) since ^{10}B concentrations in blood or other biological specimens must be measured to obtain basic data for treatment. This reaction can also be described as one type of nuclear transmutation reaction (4).

4 Nuclear transmutation reactions (n,x)

In a nuclear transmutation reaction, of which they are a variety of types, a compound nucleus formed by colliding neutrons and an isotope is split into a combination of isotopes that differ from the pre-reaction state. Of these, the most important reactions for BNCT are ^{10}B (n, α) ^{7}Li and ^{14}N (n, p) ^{14}C.

It is from the former that the name for BNCT is derived. Figure 2 diagrams the process by which the epithermal neutrons that are used in BNCT, which have energy of about 0.5 eV to 40 keV (the typical energy of a thermal neutron is 0.0254 eV), are irradiated, encounter boron-10 (^{10}B) in the body, and decay into ^{7}Li while emitting alpha particles.

The latter reaction of ^{14}N (n, p) ^{14}C gives off protons with energy of 0.58 MeV, which gives them a high cell-killing potential. Since large numbers of nitrogen atoms are present in both tumor cells and healthy cells, the reaction has a not insignificant impact on both. In particular, it is important to emphasize this latter reaction for its relationship with the development of issues (complications) in normal tissue.

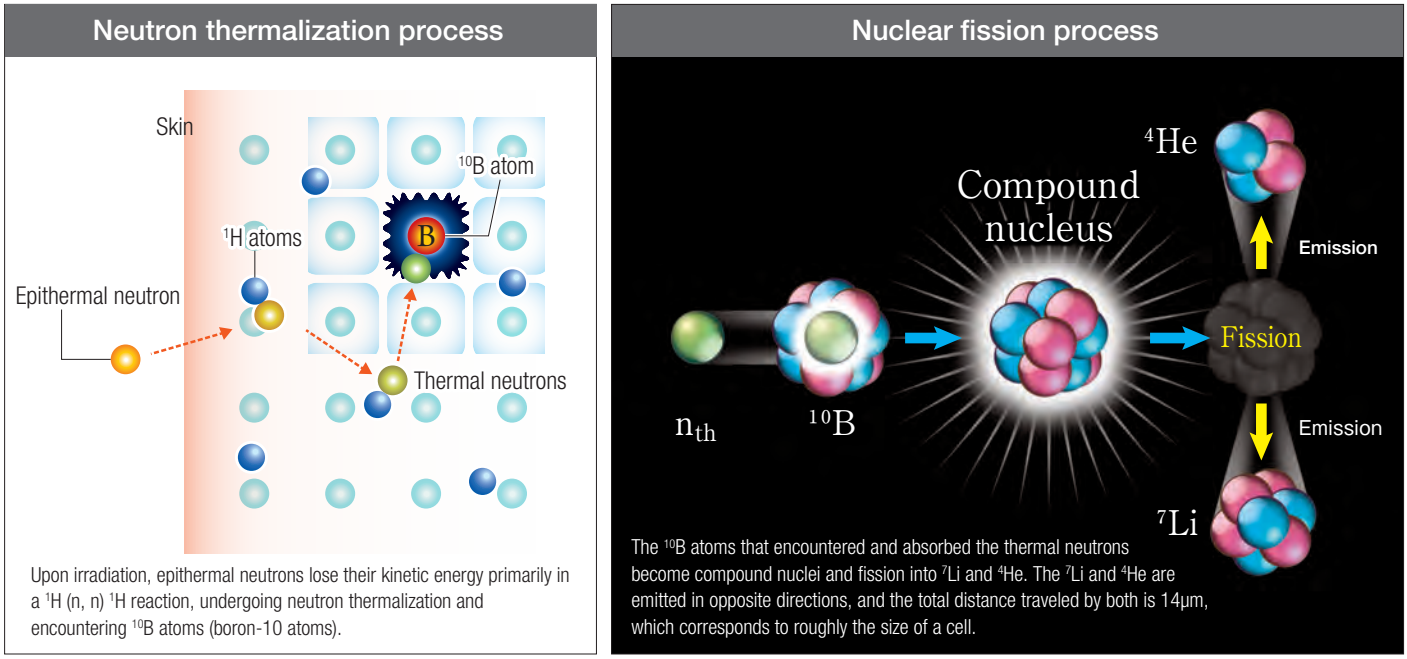


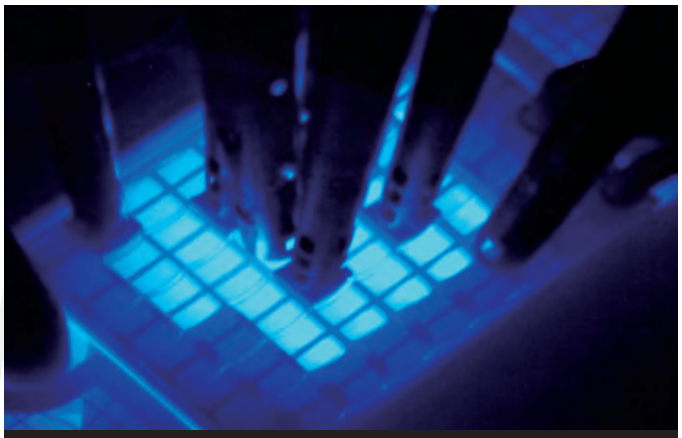
Figure 2. Epithermal Neutron Scattering Process and ^{10}B Nuclear Fission Process

Neutron source

Developing a neutron source and controlling the complex mix of radiation doses that exist in the irradiation 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, shown in Photographs 1 and 2. Both nuclear reactors and accelerators have deceleration systems capable of converting the generated fast neutrons into epithermal neutrons. Figure 3 illustrates the energy distribution for the epithermal neutrons produced by these systems. 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 by using this accelerator–moderator system.



Photograph 1. Reactor Neutron Source

- 5 MW
- Number of nuclear fissions: Approximately 10^{17} per second (Reactor core: 60 cm^3)
- Epithermal neutron flux used at radiation port: Approximately 5×10^8 $s^{-1}cm^{-2}$
- Average energy of generated neutrons: Approximately 1.5 MeV

Photograph 2. Accelerator Neutron Source

- 30 MeV, 1 mA protons
- Number of neutrons generated: Approximately 10^{15} per second (Target: Be; diameter: approximately 16 cm)
- Epithermal neutron flux used at radiation port: Approximately 1×10^9 $s^{-1}cm^{-2}$
- Average energy of generated neutrons: Approximately 10 MeV

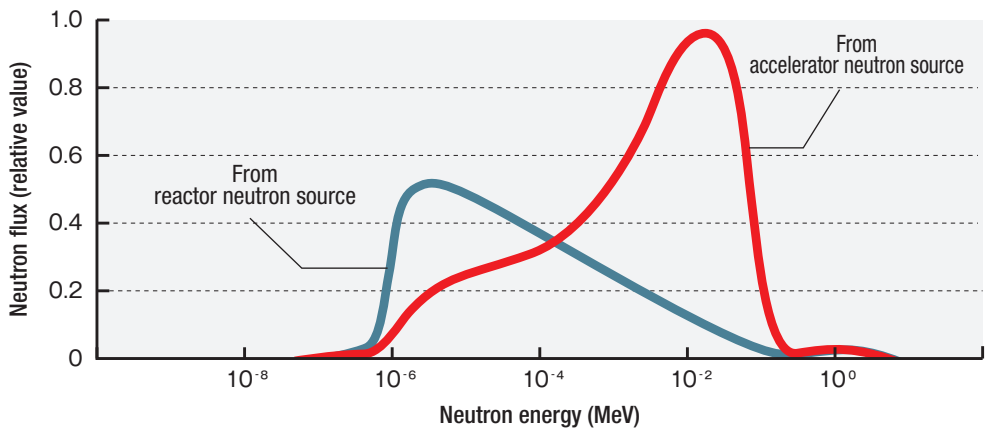


Figure 3. Epithermal Neutron Energy Distribution
The mode energy values for epithermal neutrons produced in the reactor and accelerator are approximately 1 eV and 10 keV, respectively.

Irradiation field and internal dose distribution

Radiation at the BNCT epithermal neutron irradiation field consists of the following components: fast neutrons, epithermal neutrons, and thermal neutrons deriving from the produced neutron as well as gamma radiation given off by nuclear reactions in the deceleration system. Additionally, the primary types of radiation in the water phantom include incident radiation as well as recoiled protons and recoiled oxygen generated in the phantom and gamma radiation resulting primarily from ^{1}H (n, γ) ^{2}H reactions. Following administration of an intravenous boron agent, the internal dose includes not only the above radiation, but also alpha particles and ^{7}Li derived from ^{10}B as well as gamma radiation resulting from reactions between the elements that make up the body (for example nitrogen and sodium chloride in bodily fluids) and neutrons.

Figure 4 illustrates the distribution as epithermal neutrons are decelerated in the water phantom and thermalized. This data was observed during epithermal neutron mode irradiation at the KUR heavy-water irradiation facility. The peak depth of the thermal neutron flux is approximately 2.5 cm. This peak domain is about 5.5 cm in diameter, or approximately half the diameter of the collimator. Please note how broadening of the epithermal neutron direction of incidence and broadening due to scattering during the deceleration process in the phantom exceed similar increases seen in other radiation treatments. This characteristic determines the margin for BNCT planning target volume (PTV: the tumor volume for irradiation planning purposes, calculated based on three-dimensional image data of the tumor along with the extent of projected development, body movement, and irradiation field ambiguity).

Figure 5 illustrates the depth dose distribution of the ^{10}B radiation dose, nitrogen radiation dose, hydrogen radiation dose, and gamma radiation dose inside a tumor with a ^{10}B concentration of 30 ppm as well as the total distribution (total for all types of radiation) as calculated using the radiation dose and dose distribution plan. Under these conditions, ^{10}B radiation accounts for approximately 85% of the total exposure. It is necessary to note that this proportion does not obtain uniformly throughout the irradiation field.

In order to assure the quality of BNCT, it is necessary to assess an extremely complex radiation composition as described above, to accurately evaluate the dose of each type, and to measure the benefit-versus-dose curve. Although it has not been implemented yet, real-time measurement of the ^{10}B (n, α) ^{7}Li and ^{14}N (n, p) ^{14}C reaction distributions in the body is the most important measurement issue that needs to be addressed.

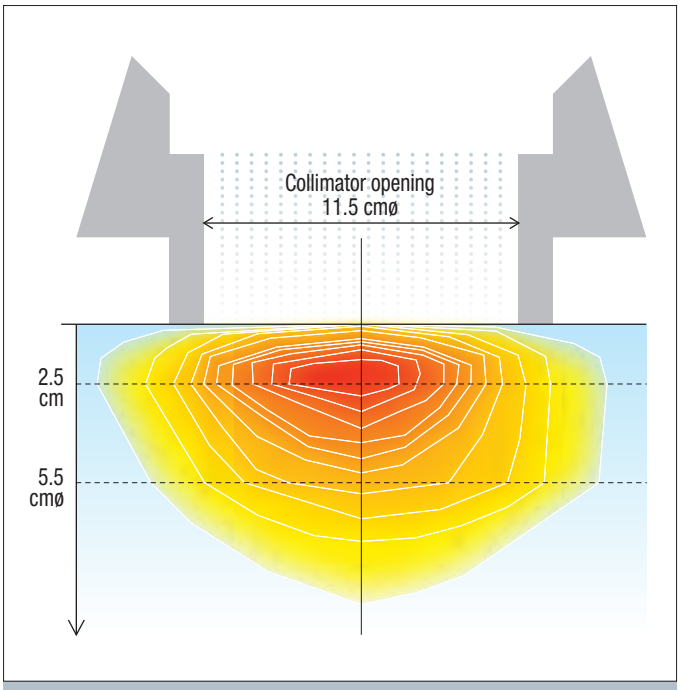


Figure 4. Two-dimensional Thermal Neutron Distribution

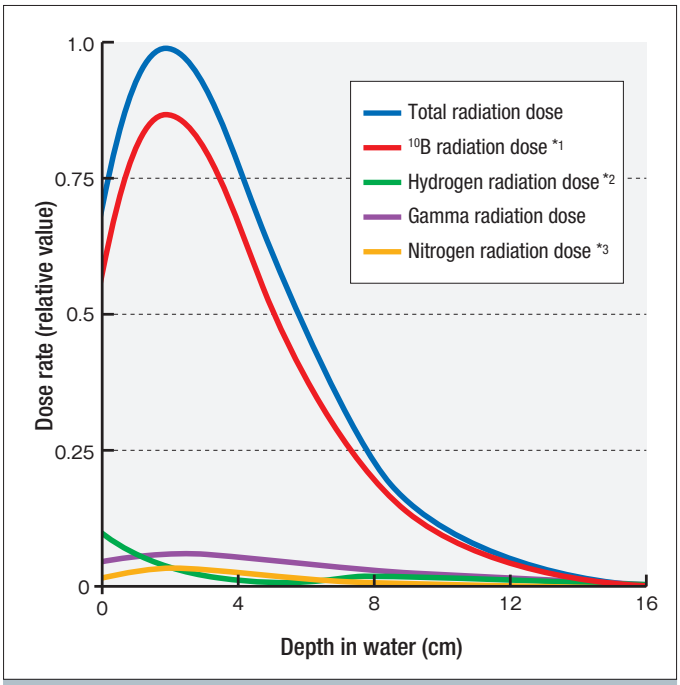


Figure 5. Depth Dose Distribution by Radiation Type

- Dose of each radiation concerned in BNCT is estimated as a dose-equivalent (unit; Gy-eq)
- Maximum value of the total dose is normalized to 1.

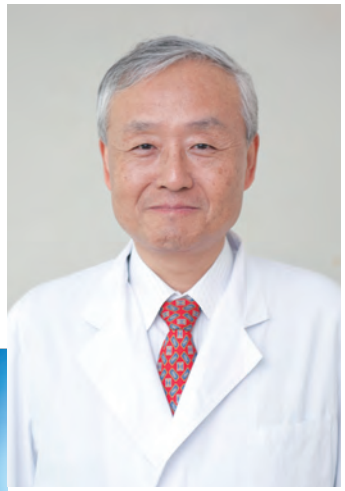
*1: The dosage released in the nuclear reaction between neutrons and ^{10}B (which is part of a Boron compound).
*2: The dosage released from the elastic scattering between neutrons and hydrogen atoms in the body.
*3: The dosage released in the nuclear reaction between neutrons and nitrogen atoms in the body.

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***

For more information about issues involving human resources development, see the separate sheet included with this pamphlet.



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BNCT Promotion and Research Society

The BNCT Promotion and Research Society is studying ways to resolve various challenges in the effort to form a leading cancer treatment facility and to commercialize BNCT as created in Osaka through partnerships linking industry, universities, and government.

Secretariat

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Accelerating the commercialization of BNCT has been identified as a core part of the Kansai Innovation Comprehensive Global Strategic Special Zone program. It is a medical technology that promises to receive even more attention in the future as part of Japan's Healthcare and medical strategy. http://kansai-tokku.jp/