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First Experiences of Pilot Clinical Studies on Boron Neutron Capture Therapy for Recurrent Gastrointestinal Cancers Using an Intravenous Injection of ^{10}BPA

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Abstract

Background/Aim: Boron neutron capture therapy (BNCT) is a novel treatment that induces targeted tumor cell damage through the selective accumulation of ^{10}B compounds in cancer cells followed by the production of alpha and lithium particles using thermal neutron irradiation. Despite its potential, clinical applications of BNCT for recurrent gastrointestinal cancers remain limited. This study presents the first pilot clinical evaluation of BNCT using intravenous boronophenylalanine (^{10}BPA) for such cancers.

Case Reports: Four patients with recurrent gastrointestinal cancers were enrolled in this phase I-II clinical study. All had tumors refractory to standard treatments, including surgery, chemotherapy, and radiotherapy. BNCT was performed using thermal neutron irradiation at Kyoto University Research Reactor. ^{10}BPA was administered

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intravenously at 400 mg/kg, and no severe adverse effects were observed. Tumor responses varied, with one patient achieving partial response and three demonstrating stable disease at three months post-treatment. Notably, BNCT alleviated cancer-related symptoms, such as pain and nerve compression, improving patients' quality of life. Dosimetric evaluations confirmed effective tumor doses with acceptable exposure to surrounding normal tissues.
Conclusion: BNCT is a promising modality for recurrent gastrointestinal cancers, offering symptom relief and potential antitumor effects. Its safety and feasibility were demonstrated in this study. Future research should explore fractionated BNCT and combination therapies with immunotherapy or targeted agents to enhance efficacy further.

Keywords: Boron neutron capture therapy (BNCT), Alpha particle, Boronophenylalanine (^{10}BPA), thermal neutron, recurrent gastrointestinal cancers, atomic reactor.

Introduction

Clinical applications of boron neutron capture therapy (BNCT) for the treatment of cancer have been increasing (1-3). BNCT has been used to treat various cancers, including malignant brain tumors, malignant melanoma, head and neck cancer, and angiosarcoma, and has increased survival times (4-31). Clinical trials have mainly examined the effects of two ^{10}Boron compounds, sodium mercaptoundecahydro-dodecaborate (^{10}BSH) and ^{10}B-*p*-borono-phenylalanine (^{10}BPA), and fructose complex (^{10}BPA-F) (32-35). The nuclear reaction between ^{10}B and thermal neutrons in BNCT induces tumor cell damage. The efficacy of BNCT therapy depends on the high accumulation of ^{10}B atoms in tumor cells, with only minimal uptake by adjacent healthy cells. ^{10}BPA is taken up by cells through the amino acid transporter LAT1, which is highly expressed on cancer cells, allowing it to selectively accumulate in cancer.

Positron emission tomography (PET) is an imaging modality that is commonly employed to detect cancers and metastasis. It has been applied to the field of BNCT, with the uptake of boron atoms by tumor cells and cancer cell activity being assessed using ^{18}F-labeled ^{10}BPA-PET (^{18}F-^{10}BPA-PET) (36-39). Kato *et al.* developed PET-CT using ^{18}F-^{10}BPA, performed neutron capture therapy on recurrent parotid gland cancer after confirming the selective accumulation of ^{10}BPA in tumors, and noted tumor regression (18, 19). Further expansion of indications for neutron capture therapy is expected in the future.

We started performing pilot clinical studies on BNCT for recurrent hepatic cancer and gastrointestinal cancers, with future plans for its application to recurrent breast cancer. Previous clinical studies used intravenous drip infusions of 250 and 900 mg/kg of ^{10}BPA; therefore, we selected a boron dose of 400 mg/kg of ^{10}BPA.

We herein present the first pilot clinical studies on the use of BNCT to treat recurrent gastrointestinal cancers.

Case Report

Protection of human subjects. The Institutional Review Board of Shin-Yamate Hospital, Japan Anti-Tuberculosis Association, Japan reviewed and provided their approval for this pilot study (Approval Number: 11001, 8th June, 2011). The eligibility of each patient and whether this pilot study was in accordance with the tenets of the Declaration of Helsinki were confirmed by the Institutional Review Board of Kyoto University Research Reactor Institute, Japan. All participants provided their informed written consent prior to study enrollment.

Clinical study design. Objective: Pilot clinical studies were conducted to evaluate the efficiency and safety of the application of BNCT using an intravenous injection of ^{10}BPA to cancers that did not respond to or were not indicated for standard therapies.

Inclusion criteria for patient registration. 1) Older than 20 years. 2) No response to standard therapy (chemotherapy, immunotherapy, or hormonal therapy). 3) Patients with advanced or recurrent cancer where surgery is not a viable option, those who had refused surgery, and those whose quality of life (QOL) will be negatively impacted by surgery. 4) Patients not cured by radiation therapy. 5) Patients whose tumor size can be measured in images [computed tomography (CT): ≥10 mm, Chest X-P: ≥20 mm, lymph nodes (LN): ≥15 mm]. 6) Patients more than 4 weeks after chemotherapy and surgery and more than two weeks after percutaneous ethanol injection therapy, microwave ablation, immunotherapy, or hormonal therapy. 7) Patients with sufficient bone marrow, hepatic, and renal functions. i) White Bllod Cell (WBC) ≥3,000/mm^3, Platelets ≥100,000/mm^3; ii) Aspartate aminotoransferase (AST)/Alanine aminotransferase (ALT): ≤120 IU/l, total bilirubin: ≤2.0 mg/dl; iii) Creatinine: ≤2 mg/dl. 8) Patients who provided their written informed consent.

Exclusion criteria. Patients with any one of the items below were not indicated for registration to this study. 1) A poor general condition (Performance status: ≥3). 2) Severe diseases or multiple active cancers other than the primary cancer. 3) Advanced metastasis in more than 3 organs. 4) Phenylketonuria or severe renal dysfunction. 5) Medical or social contraindications.

Procedure used in pilot studies. 1) Patients were referred to the registered hospital from another hospital. 2) Initial diagnosis and discussions were performed with KUR staff based on CT images of recurrent tumors. 3) Assessment of the uptake of Boron atoms in tumor was performed by ^{18}F-^{10}BPA-PET. 4) Provision of informed consent for the pilot study on BNCT was performed. 5) Scheduling of BNCT at KUR (neutron dosimetry by the BNCT irradiation dose planning system, SERA) was performed. 6) CT simulation in the same body position as in BNCT with the marking of tumor sites one week before treatment was performed. 7) BNCT procedure at KUR; Intravenous injection of ^{10}BPA-F 2 hours before BNCT (400 mg/kg) and measurement of the blood concentration of boron using prompt γ-spectroscopy (KUR) were performed, then treated the patient with BNCT. After BNCT, the patients were followed up by one week hospital stay. 8) After care; Assessments of tumor suppression based on decreases in the size of the tumor on CT and magnetic resonance imaging (MRI), and data on tumor markers were performed. Evaluations were also performed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria of the Japan Clinical Oncology Group.

The distribution of thermal neutron flux during medical irradiation as well as the absorbed dose rate distributions of thermal neutrons, fast neutrons, and γ-rays were estimated and evaluated using SERA (40-47).

Ten min after the start of irradiation, radiating wires for confirmation of thermal neutron fluence were extracted. On the collimator Bi-side (20 cm from the center), thermal neutron flux was evaluated using gold wires with a Cd cover. In the center of the surface irradiation field on the affected area, thermal and epithermal neutron fluxes were evaluated using gold and manganese wires.

Regarding the total irradiation dose near the surface of the affected area, neutron fluence was measured using gold and manganese wires, while the γ-ray absorbed dose was assessed using a thermoluminescent dosimeter [TLD (BeO)]. Radiating wires and TLD were placed near the surface center.

To evaluate whole-body exposure, thermal neutron fluence and the γ-ray dose were measured at six locations: the neck, chest, navel, localized area, knee, and ankle. Thermal neutron fluence was measured using a gold wire of approximately 0.25 mm in diameter and 10 cm in length that was inserted into a disc of approximately 1 cm in diameter. The γ-ray dose was measured using TLD (BeO), specifically National 170L, placed in a 6LiF thermal neutron shielding case. The measurement error of TLD is approximately 10%.

Blood concentrations of ^{10}B were evaluated using the prompt γ-ray method in an E-3 tube (40, 41). To calculate

Table I. *Relative biological effectiveness (RBE) and compound biological effectiveness (CBE) factors used to convert physical radiation doses (Gy) into photon-equivalent doses (Gy-Eq).*

Boron compound, Irradiation ray	Tumor	Skin	Normal nerve	Oral mucosa
BSH	2.5	0.8	0.37	0.3
BPA	3.8	2.5	1.35	4.9
Neutron	3.0	3.0	3.0	3.0
γ-ray	1.0	1.0	1.0	1.0

the absorbed dose rate, relative biological effectiveness (RBE) and compound biological effectiveness (CBE) shown in Table I and the following formula were used.

$$E_{Total}=E_{B10}+E_{Thermal}+E_{Fast}+E_{\gamma}$$

$$E_{B10}=(C_{BSH}\times CBE_{BSH}+C_{BPA}\times CBE_{BPA})\times 7.43\times 10^{-14}\times \Phi_{Thermal}$$

$$E_{Thermal}=N\times RBE_{Thermal}\times 6.78\times 10^{-14}\times \Phi_{Thermal}$$

$$E_{Fast}=RBE_{Fast}\times D_{Fast}$$

$$E_{\gamma}=RBE_{\gamma}\times D_{\gamma}$$

D: Physically absorbed dose (Gy), $\Phi_{Thermal}$: Thermal neutron fluence (cm^{-2}), N: Concentration of ^{14}Nitrogen (%, estimated to N=2%), C: Concentration of ^{10}Boron (ppm)

Case 1: 72-year-old male, gastric cancer. Clinical course. The first patient in the pilot study on BNCT using ^{10}BPA to treat recurrent gastric cancer was a 72-year-old male. Total gastrectomy with LN dissection and cholecystectomy and partial hepatic resection were performed in April 2007. Poorly differentiated adenocarcinoma was diagnosed based on pathological findings. Left cervical LN metastasis was detected two years later. Therefore, the patient was treated with Tegafur Gimeracil Oteracil potassium (TS-1), cis-diamminedichloro-platinum(II) (Cisplatin; CDDP), and Irinotecan hydrochloride (CPT-11) between September 2009 and May 2010. Radiation therapy for left cervical LN metastasis (total, 70 Gy) in March 2011 reduced the size of the tumor; however, regrowth was detected in September 2011. Following his referral to Shin-Yamate Hospital, Japan Anti-Tuberculosis Association for treatment with BNCT, the patient was informed of this pilot study and given information on the study procedure, the expected effects and potential risks, alternative treatment options,

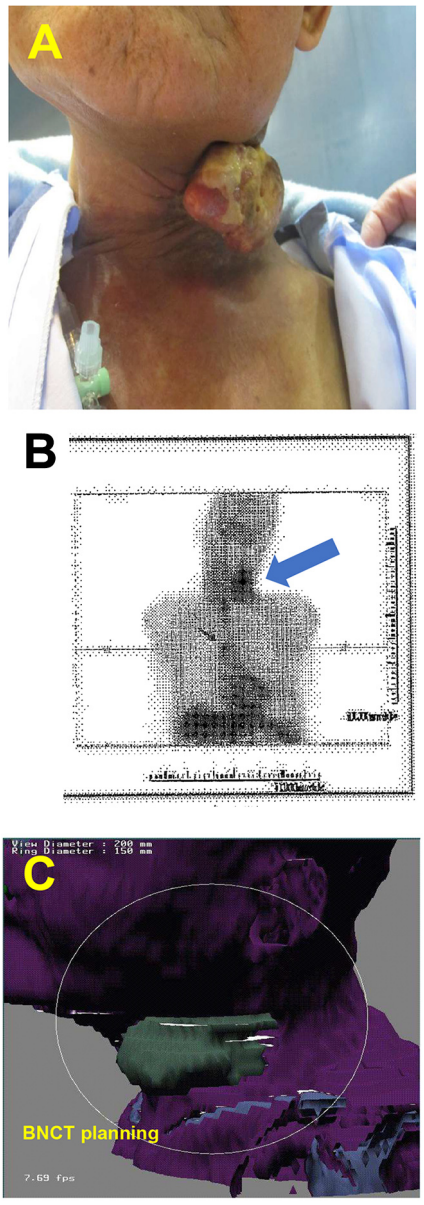


Figure 1. *Continued*

voluntary participation, and data management. The patient provided his informed consent for all activities at Shin-Yamate Hospital and Kyoto University Research Reactor Institute, and volunteered as a subject for this trial.

BNCT procedure and dose analysis. ^{18}F-^{10}BPA-PET showed high accumulation in left cervical LN metastasis. The

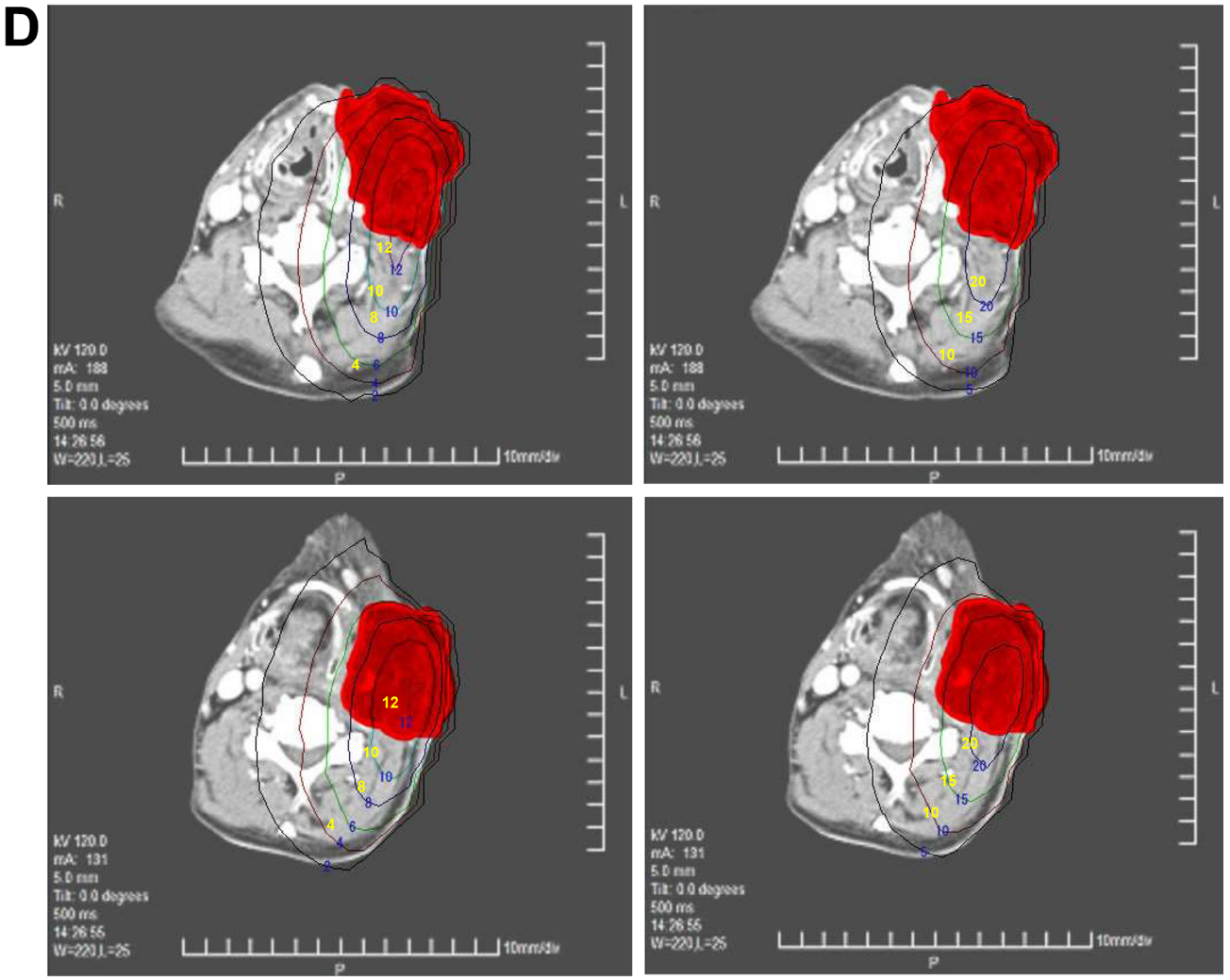


Figure 1. *Imaging and treatment planning for boron neutron capture therapy (BNCT) in Case 1. (A) Photograph of the metastatic cervical gastric tumor before BNCT. (B) ^{18}F-^{10}BPA-PET image showing boron accumulation in the tumor. (C) Three-dimensional BNCT treatment plan visualized from the neutron beam port. (D) Two-dimensional distribution of thermal neutron flux (Gy-Eq/h) in the left cervical tumor following frontal epithermal neutron beam irradiation. The upper panel shows the -1.5 cm cross-section from the tumor center (left: dose to normal skin; right: dose to tumor; red: tumor tissue). The lower panel shows the 0.0 cm cross-section from the tumor center (left: dose to normal skin; right: dose to tumor; red: tumor tissue).*

tumor/blood ratio on ^{18}F-^{10}BPA-PET was 2.7, indicating the selective accumulation of boron in the tumor. Hyperaccumulation was noted in the left cervical region with the maximum count in tumor (Tmax)=11,622 Bq/cc, the maximum count in normal tissue (Nmax)=7,041 Bq/cc, and the maximum count in blood (Bmax)=4,264 Bq/cc. Accumulation was also observed in the myocardium; however, difficulties were associated with setting an ROI in the cardiac cavity. Therefore, the ROI was set in the ascending aorta (Figure 1A-C).

RBE and CBE are shown in Table I. Based on corrected SERA pre-assessment results, thermal neutron flux, the fast neutron absorbed dose rate, and γ-ray absorbed dose rate at the affected surface were

estimated to be 1.24×10^8 cm^{-2} s^{-1}, 0.94 Gy-Eq/h, and 0.55 Gy-Eq/h, respectively. At a depth of 2.0 cm corresponding to the peak distribution of thermal neutron flux, thermal neutron flux, the fast neutron absorbed dose rate, and γ-ray absorbed dose rate were estimated to be 3.08×10^8 cm^{-2} s^{-1}, 0.58 Gy-Eq/h, and 0.87 Gy-Eq/h, respectively. Only BPA (400 mg/kg before3 h) was used to treat this patient. The estimated concentration of ^{10}B during irradiation was 24.4 ppm×0.8= 19.5 ppm for blood, skin, mucous membranes, and nerves and 52.7 ppm for tumors (T/B ratio=2.7) (Figure 1B), assuming that the concentration decayed to 80% during irradiation based on the measurement data of blood samples collected immediately before irradiation.

Dose estimations before BNCT: To irradiate the tumor with a dose of 16 Gy at a depth of 5 cm, a BNCT time of 90 min was selected. More than 41% of tumor fluence was 20 Gy-Eq and more than 70% of tumor fluence was 16 Gy-Eq (depth of 5.0 cm) with 90 min of BNCT (maximum 27 Gy-Eq on the tumor: depth of 2.0 cm). Maximum fluence of the normal mucosa, nerves, and skin were 14, 6, and 5 Gy-Eq, respectively (Figure 1D).

Since the general condition of the patient was good, he was transported to KURRI on 5th November 2011 to receive radiation therapy with an intravenous injection of ^{10}BPA.

In the post-evaluation, the average blood concentration of ^{10}B during the irradiation time was corrected to 23.5 ppm. On the beam axis, the surface skin dose was estimated to be 4.6 Gy-Eq, the normal mucosa dose was 11 Gy-Eq at the peak (depth of 3.8 cm), the normal nerve dose was 4.5 Gy-Eq at the peak (depth of 3.8 cm), and the tumor dose was 22 Gy-Eq at the peak (depth of 3.8 cm) and approximately 20 Gy-Eq at a depth of 5 cm (Figure 1D, Figure 2A-E).

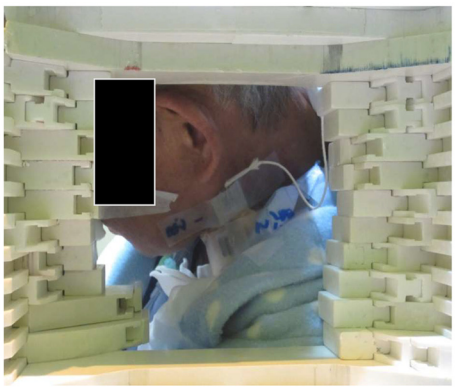
Figure 2F shows a dose-volume histogram (DVH) for the tumor and mucosa focused areas. Doses ≥20 Gy-Eq were delivered to 41% of the tumor area and ≥16 Gy-Eq to 70% of the tumor area, with a peak dose of 25 Gy-Eq. The maximum dose for normal nerves was 6.1 Gy-Eq according to DVH. Irradiation was performed in the sitting position.

Post-treatment course and clinical outcome. The patient was discharged 8 days after BNCT. The international criteria proposed by the RECIST committee were employed in this pilot study to assess the response to treatment and tumor progression. The inhibition of tumor growth was noted two months after BNCT. The left internal jugular vein was recanalized after BNCT. The patient developed left cervical skin edema, oral erosion, and throat pain or discomfort in the follow-up period after BNCT (Figure 3).

Since the significant tumor growth inhibitory effect was also observed three months after BNCT, the patient was considered to be in partial remission (PR). The patient died due to aspiration pneumonia six months after BNCT.

Case 2: 51-year-old female, rectal cancer. Clinical course. A 51-year-old female patient underwent low anterior resection with LN dissection in October 2006. Pathological findings revealed adenocarcinoma of the rectum, tub2, type 2, 6×7cm, AW(–), OW(–), n(+)(1/13)(#251), postoperative staging: (Ra) pSE pN1 sH0 sP0 sM0 fStage IIIa. Two years later, local recurrence in the pelvic cavity & invasion to sacral bone were detected. Therefore, irradiation at a dose of 45 Gy was delivered to the pelvic cavity, with a booster of 14.4 Gy to the recurrent tumor. She then received chemotherapy (mFOLFOX6+Bevacizumab). She underwent Hartmann's procedure+sacral bone resection (below S3) in March 2010, and received chemotherapy (XELOX) in May 2010. Since recurrence was detected in S2 in February 2011, she was administered chemotherapy [Irinotecan plus a combination of tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate (S-1); IRIS therapy+Panitumumab (Pmab), and S-1 plus Oxaliplatin (SOX)+Pmab]. A subcutaneous abscess developed at the residual tumor on the sacral bone in August 2011, and subsequently, tumor regrowth, gait disturbance with pain at the sacral nerve was noted in December 2011. The patient provided her written informed consent for all activities at Shin-Yamate Hospital and Kyoto University Research Reactor Institute, and volunteered as a subject for this trial. BNCT was performed in February 2012.

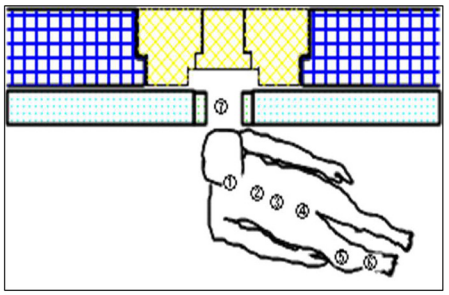
A



D

Position	Thermal neutron fluence (cm^{-2})	Γray dose* (cSv)
Cervix ①	6.2E+10	66.1
Chest ②	1.1E+10	28.2
Umbilicus ③	3.5E+09	15.9
Inguinal region ④	2.7E+10	21.3
Knee ⑤	8.6E+09	10.5
Instep ⑥	2.0E+09	4.8
Tumor site ⑦	1.16E+12	238.4

B BNCT Direction (from beam port)



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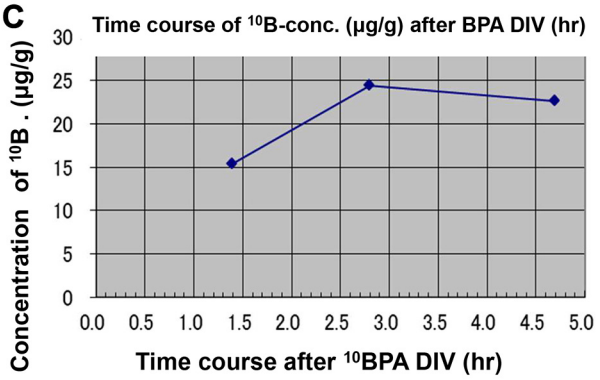

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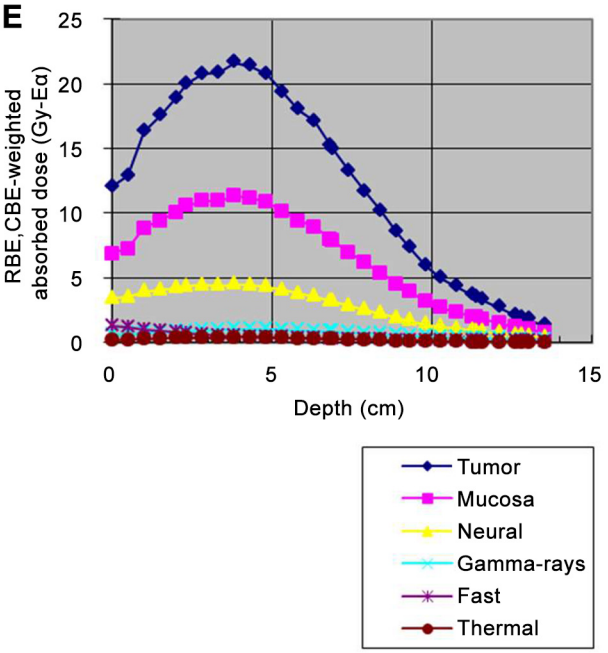

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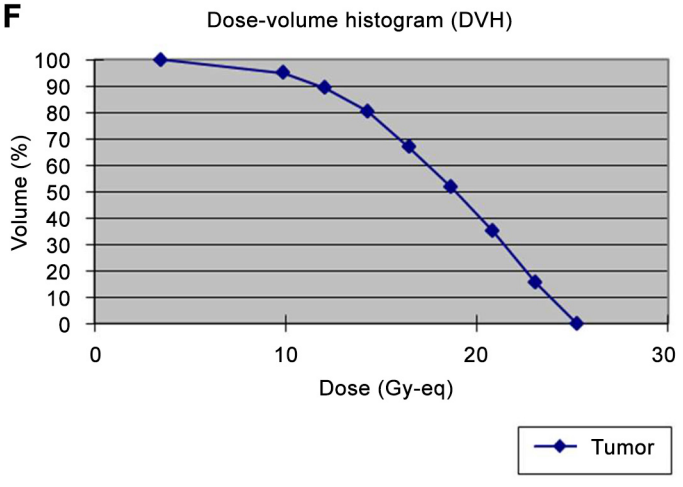


Figure 2. *Patient positioning, neutron dosimetry, and dose distribution for boron neutron capture therapy (BNCT) in Case 1. (A) Photograph showing the body position of Case 1 for BNCT from the beam port. (B) Schematic representation of the body position for BNCT from the beam port. (C) Time course of changes in ^{10}B concentration (μg/g) following intravenous infusion of ^{10}BPA (absolute values in Case 1). (D) Measured thermal neutron fluence and gamma-ray dose delivered to the body. The measurable lower limits were approximately 5×10^{7} cm^{-2} for thermal neutron fluence and ~0.01 cSv for gamma-ray dose (absolute values in Case 1). (E) Dose distribution along the beam axis in thermal neutron irradiation mode (CO-0000-F+ collimator, irradiation field: 15 cm×15 cm). Tumor: Tumor dose; Mucosa: oral mucosal dose; Neural: normal nerve dose; Gamma-rays: Gamma ray dose; Fast: fast neutron dose; Thermal: thermal neutron dose. (F) Calculated dose-volume histogram (DVH) of the tumor (tumor volume: 151.76 cm^3). To achieve a tumor dose of 16 Gy at a depth of 5 cm, the BNCT irradiation time was set to 90 minutes.*

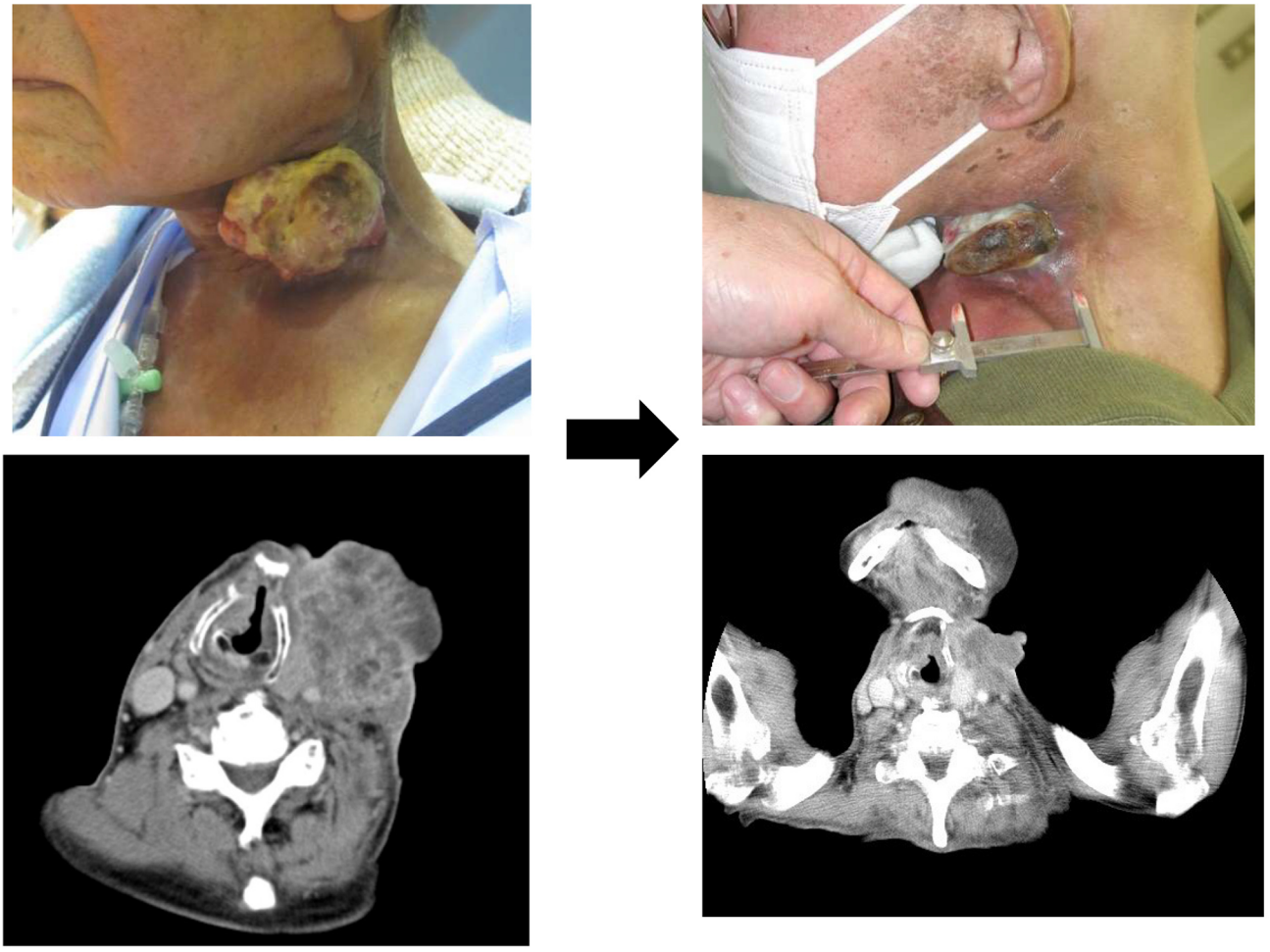


Figure 3. *Tumor response before and after boron neutron capture therapy (BNCT) in Case 1. Photographs and computed tomography (CT) images taken before (Left) and two months after BNCT (Right). Tumor growth was suppressed, and recanalization of the left internal jugular vein was observed following BNCT.*

BNCT procedure and dose distribution analysis. Irradiation was performed in the lateral position. RBE and CBE shown in Table I were used to calculate the absorbed dose rate. Based on corrected SERA pre-evaluation results, thermal neutron flux, the fast neutron absorbed dose rate, and γ-ray absorbed dose rate at the surface of the affected area were estimated to be 3.06×10^{8} cm^{-2} s^{-1}, 2.04 Gy-Eq/h, and 1.48 Gy-Eq/h, respectively. At a depth of 1.8 cm, corresponding to the peak distribution of thermal neutron flux, these values were estimated to be 7.96×10^{8} cm^{-2} s^{-1}, 1.33 Gy-Eq/h, and 2.48 Gy-Eq/h, respectively (Figure 4).

Only BPA (400 mg/kg) was used three hours before medical irradiation. The concentration of ^{10}B during medical irradiation was estimated to be 27 ppm in blood, skin, mucosa, and nerve tissue and 56.7 ppm in tumors (with a T/B ratio of 2.6), assuming decay during irradiation based on measurement data from blood samples taken just before irradiation (Figure 5A-D). To achieve a tumor dose of approximately 15 Gy-Eq at a depth of 8 cm, the irradiation time was set at 69 min. At this time, the tumor dose was estimated to be 57 Gy-Eq at the peak (a depth of 1.8cm), 37 Gy-Eq at a depth of 5 cm, and the

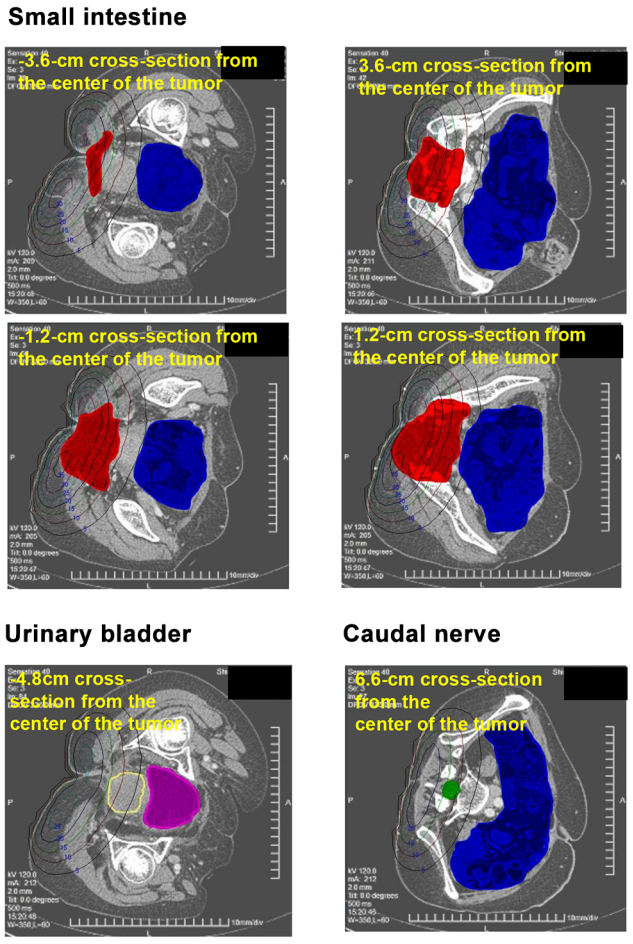


Figure 4. *Two-dimensional distribution of neutron flux in the pelvic cavity in Case 2. Two-dimensional distribution of neutron flux (Gy-Eq/h) in the pelvic cavity. The upper and middle panels show the distribution at -3.6 cm, 3.6 cm, -1.2 cm, and 1.2 cm cross-sections from the tumor center (Gy-Eq), with red indicating the tumor and blue indicating the small intestine. The lower left panel shows the distribution at a -4.8 cm cross-section, with purple indicating the urinary bladder. The lower right panel shows the distribution at a 6.6 cm cross-section, with green indicating the caudal nerve and blue indicating the small intestine.*

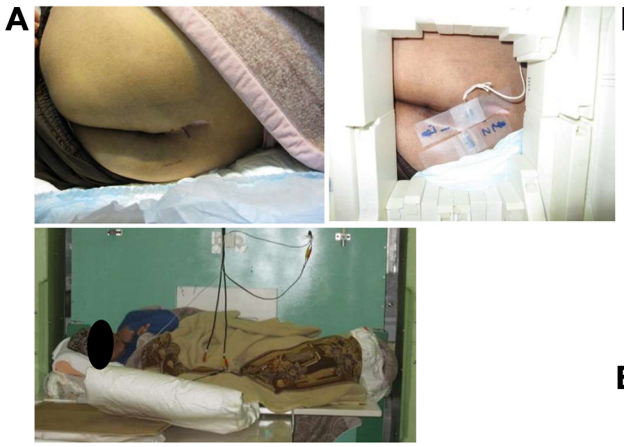
skin dose was expected to be 11 Gy-Eq (Figure 5E). Figure 5F shows a DVH for the tumor and target organs (the small intestine, cauda equina nerve, and bladder). Doses exceeding 20 Gy-Eq were delivered to 90% of the tumor region, with a maximum estimated dose of 59 Gy-Eq. The maximum estimated doses for the small intestine, cauda equina nerve, and bladder were 7.3, 8.9, and 4.3 Gy-Eq, respectively.

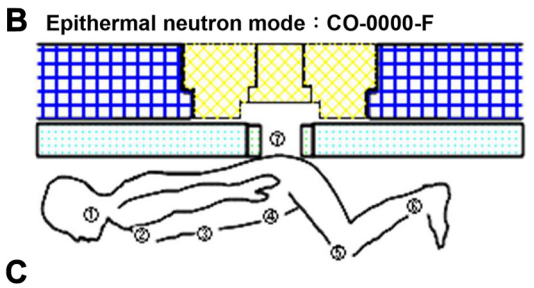
In the post-evaluation, the average blood concentration of ^{10}B during the irradiation period was corrected to 25.2 ppm. On the beam axis, the estimated skin dose was 10 Gy-Eq and the estimated tumor dose was approximately 54 Gy-Eq at the peak (a depth of 1.8 cm) and 35 Gy-Eq at a depth of 5 cm (Figure 5E, F). The dose delivered to 90% of the tumor volume was >20 Gy-Eq, and the maximum tumor dose was 59 Gy-eq.

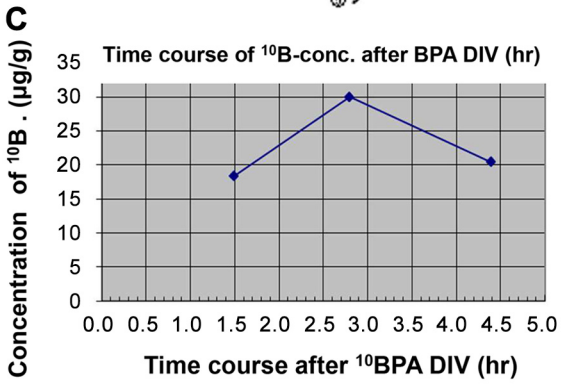
Post-treatment course and clinical outcome. There were no adverse events or side effects associated with BNCT. Approximately two weeks after BNCT, marked improvements were observed in lower limb pain in the sacral nerve area and walk disturbance. BNCT was able to suppress tumor growth, so there were no visible changes in the area around the buttocks or tumor regrowth (stable disease, SD) two months after BNCT. Tumor markers were within normal ranges: before and two months after BNCT, carcinoembryonic antigen (CEA) levels were 2.3 and 2.1 (ng/ml) and carbohydrate antigen 19-9 (CA19-9) levels were 10.7 and 9.9 (U/ml), respectively (Figure 6). After the follow-up period of BNCT ended, we administered chemotherapy [S-1 plus Oxaliplatin (SOX)+Bevacizumab (BV)]. The tumor size was smaller four months after BNCT with chemotherapy than before BNCT. The tumor size increased seven months after BNCT, and a subcutaneous abscess was detected.

The QOL and overall condition of the patient, such as pain relief, both improved in the follow-up period after BNCT. It was considered that BNCT might have the potential to relieve nerve compression caused by the tumor. So, additional fractionated BNCT was considered desirable.

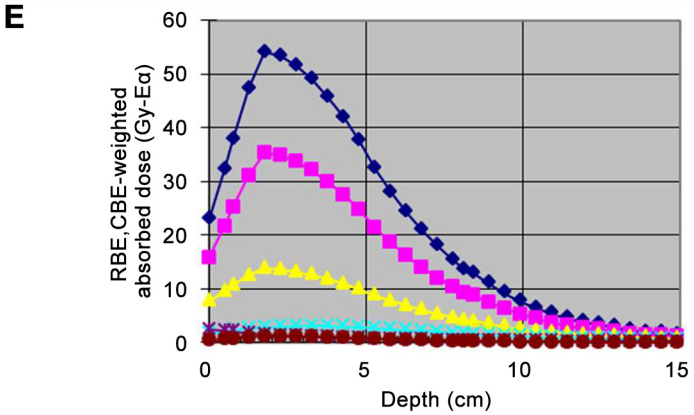
Case 3: 56-year-old female, rectal cancer. Clinical course. A 56-year-old female patient underwent low anterior resection with LN dissection in December 2006. Pathological findings revealed adenocarcinoma of the rectum (Type 2, tub2, se, ly2, v2, n1). One year later, local recurrence was observed in the pelvic cavity, and the patient underwent Hartmann's procedure in July 2007. Local recurrence in the presacral bone area of the pelvic







Position	Thermal neutron fluence (cm^{-2})	Γray dose* (cSv)
Cervix ①	1.4E+09	9.1
Chest ②	1.3E+09	12.8
Umbilicus ③	4.3E+09	18.8
Inguinal region ④	5.6E+09	28.2
Knee ⑤	1.2E+09	12.7
Instep ⑥	1.7E+09	3.7
Tumor site ⑦	1.02E+12	252.8



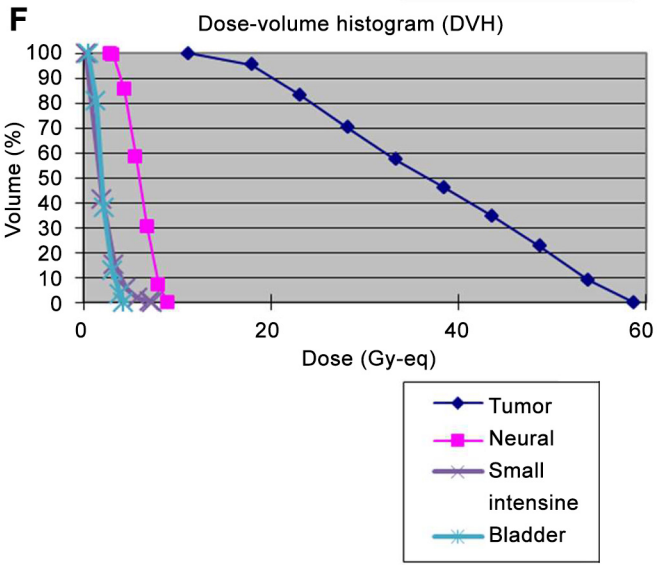
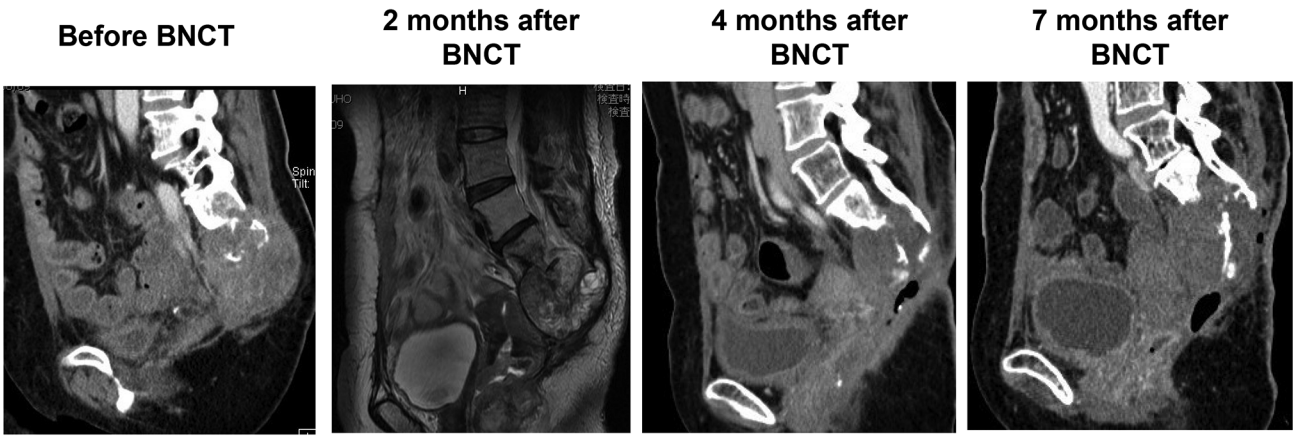


Figure 5. *Patient positioning, neutron dosimetry, and dose distribution for boron neutron capture therapy (BNCT) in Case 2. (A) Photograph showing the body position of Case 2 for BNCT. (B) Schematic representation of the body position for BNCT from the beam port. (C) Time course of changes in ^{10}B concentration (μg/g) following intravenous infusion of ^{10}BPA (absolute values in Case 2). (D) Measured thermal neutron fluence and gamma-ray dose delivered to the body. The measurable lower limits were approximately $5×10^7$ cm^{-2} for thermal neutron fluence and ~0.01 cSv for gamma-ray dose (absolute values in Case 2). (E) Dose distribution along the beam axis in thermal neutron irradiation mode (CO-0000-F+ collimator, irradiation field: 14 cm×16 cm). Tumor: Tumor dose; Bladder: urinary bladder dose; Neural: normal nerve dose; Gamma-rays: Gamma ray dose; Fast: fast neutron dose; Thermal: thermal neutron dose. (F) Calculated dose-volume histogram (DVH) for BNCT in Case 2 (tumor volume: 342.33 cm^3; caudal nerve: 11.26 cm^3; small intestine: 1,377.59 cm^3; urinary bladder: 60.59 cm^3). To achieve a tumor dose of 15 Gy at a depth of 8 cm, the BNCT irradiation time was set to 69 minutes.*



	Pre BNCT	Post 1 M	Post 2M
Marker			
CEA	2.3	1.6	2.1
CA19-9	10.7	11.0	9.9

Figure 6. *Tumor response following boron neutron capture therapy (BNCT) in Case2. Tumor growth was suppressed after BNCT. Four months post-treatment, the tumor volume showed a slight decrease, and the patient was classified as having stable disease according to the RECIST criteria.*

cavity was noted in February 2008. Irradiation was delivered at a dose of 57.8 Gy to the pelvic cavity in April 2008. Local recurrence in the pelvic cavity & invasion to the sacral bone were detected in January 2009. Therefore, the patient was administered chemotherapy (FOLFORI, CPT-11+Arbitax) in 2009-2010. Tumor regrowth was noted in April 2012.

To treat recurrent rectal cancer in the pelvic cavity by BNCT, the patient provided her written informed consent for all activities at Shin-Yamate Hospital and Kyoto University Research Reactor Institute, and volunteered as a subject for this trial. BNCT was performed in June 2012.

BNCT procedure and dose distribution analysis. ^{18}F-^{10}BPA-PET showed high accumulation in the tumor in the pelvic cavity. The tumor/blood ratio on ^{18}F-^{10}BPA-PET was 2.9, indicating the selective accumulation of boron in tumor cells (Figure 7A-C).

RBE and CBE shown in Table I were used to calculate absorbed dose rates. Based on corrected SERA pre-evaluation results, thermal neutron flux, the fast neutron absorbed dose rate, and γ-ray absorbed dose rate at the surface of the affected area were estimated to be 3.53×10^{8} cm^{-2} s^{-1}, 2.29 Gy-Eq/h, and 1.78 Gy-Eq/h, respectively. At a depth of 2.0 cm, corresponding to the peak distribution of thermal neutron flux, these values were estimated to be 8.07×10^{8} cm^{-2} s^{-1}, 1.34 Gy-Eq/h, and 2.78 Gy-Eq/h, respectively (Figure 7D). To position the patient correctly in the irradiation room, we referred to four lines and one central point on the skin that marked the upper, lower, right, and left margins and center of the tumor on CT before BNCT at KUR. The patient was treated with forward-directed thermal neutron beams delivered through a collimator encompassing the pelvic region. A 20-cm square collimator encompassing the pelvic portion was used to deliver the beams. The dose delivered and irradiation time employed in this pilot study were restricted to the doses delivered to the small intestine and skin. In the present case, the irradiation time selected delivered a maximum dose of 7 Gy-Eq to the normal small intestine and 8 Gy-Eq to normal skin.

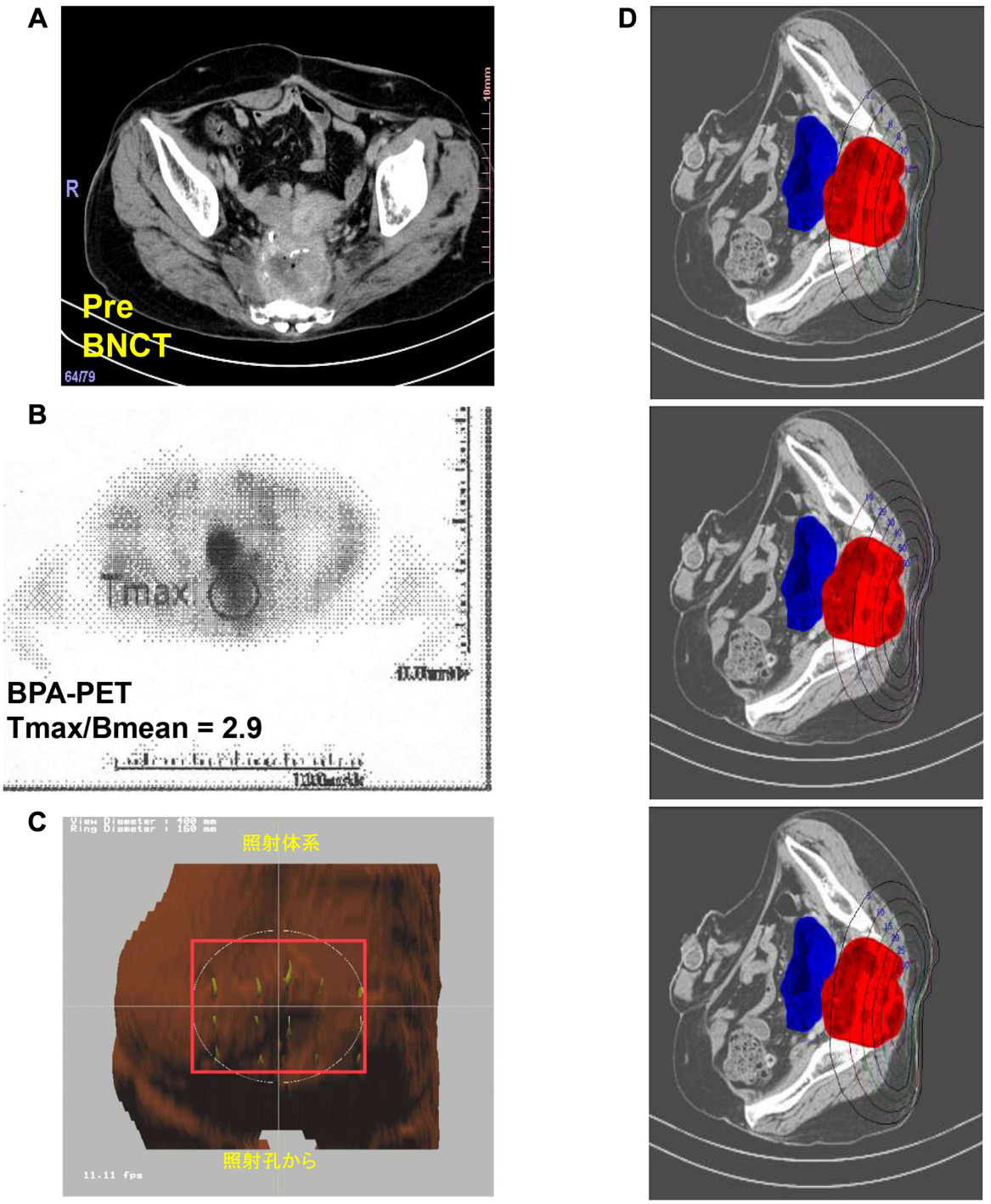


Figure 7. *Imaging and treatment planning for boron neutron capture therapy (BNCT) in Case 3. (A) Photograph of the recurrent rectal tumor in the pelvic cavity before BNCT. (B)* ^{18}*F-*^{10}*BPA-PET image showing boron accumulation in the tumor. (C) Three-dimensional BNCT treatment plan visualized from the neutron beam port. (D) Two-dimensional total dose distribution at a 0-cm cross-section from the tumor center (Gy-Eq). The left panel shows the normal nerve dose, the center panel shows the dose to the mucosa of the small intestine, and the right panel shows the tumor dose. Red indicates the tumor, and blue indicates the small intestine.*

The patient received an intravenous injection of ^{10}BPA-F (400 mg/Kg). The blood concentration of ^{10}B during medical irradiation was estimated based on the measurement data of blood samples taken just before irradiation, considering decay during irradiation as follows: blood, skin, mucosa, and nerves 25.3 ppm; kidney 50.6 ppm (estimated kidney/blood ratio=2); tumor 73.3 ppm (estimated T/B ratio=2.9) (Figure 8A-D). With the aim of delivering a tumor dose of approximately 15 Gy-Eq at a depth of 8 cm, the irradiation time selected was 70 min.

In the post-evaluation, the average blood concentration of ^{10}B during irradiation was corrected to 23 ppm. On the beam axis, estimated doses were approximately 10 Gy-Eq for the surface of the skin, 67 Gy-Eq at the peak of the tumor (depth of 1.5 cm), 36 Gy-Eq at a depth of 5 cm, and 13 Gy-Eq at a depth of 8 cm (Figure 8E).

Figure 8F shows DVH for the tumor and target organs (the small intestine, left kidney, and right kidney). Doses >15 Gy-Eq were delivered to 82% of the tumor region, with 20 Gy-Eq to 68% and >30 Gy-Eq to 45%, and the maximum estimated dose was 69 Gy-Eq. Maximum estimated doses for the small intestine, left kidney, and right kidney were 4.9, 1.2, and 0.2 Gy-Eq, respectively. Since neutron beams were emitted from a fixed port in the irradiation room of KUR, the patient was treated with forward-directed thermal neutron beams delivered to target organs with the patient placed in the right-decubitus position (Figure 8A, B). The patient did not develop any adverse events during or after irradiation; however, cloudy urine, which was suspected to be due to ^{10}BPA crystallization, was observed after BNCT. To prevent renal dysfunction, an additional fluid infusion was administered, which improved the condition of urine (Figure 8A).

Post-treatment course and clinical outcome. The patient was discharged 14 days after BNCT. Follow-up pelvic CT 1, 2, and 3 months after BNCT showed that the size of the tumor in the pelvic cavity had slightly decreased, with tumor necrosis being observed one month after BNCT. Therefore, the patient was considered to have SD according to criteria proposed by the RECIST committee (Figure 9A and B). No significant changes were observed in biochemical blood data in the three months following BNCT.

With a single BNCT irradiation, the tumor did not grow and instead shrank during the 3-month follow-up period. Additionally, improvements such as relief from a sense of pressure in the buttocks were observed, and BNCT did not reduce the patient's QOL at all.

The recurrent tumor was additionally treated with molecular targeting therapies from three months after BNCT. The patient died due to infection as a result of the local regrowth of the tumor seven months after BNCT.

Case 4: 38-year-old male, liver metastasis of sigmoidal colon cancer. *Clinical course.* A 38-year-old male patient with sigmoidal colon cancer & multiple hepatic metastases underwent sigmoidectomy and received intra-arterial (IA) chemotherapy (CDDP) and molecular targeted therapy (XELOX+Cmab, XELOX+Pmab, and IRIS+Pmab). However, the volume of hepatic metastases continued to increase and caused local pain.

Metastatic lesions were considered to be refractory to further chemotherapy and molecular targeting therapies. Following his referral to Shin-Yamate Hospital for treatment with BNCT, the patient was informed of this pilot study and given information on the study procedure, expected effects and potential risks, alternative treatment options, voluntary participation, and data management. The patient provided his written informed consent for all activities at Shin-Yamate Hospital and Kyoto University Research Reactor Institute, and volunteered as a subject for this trial.

To reduce the volume of metastatic lesions, BNCT was performed in January 2012 as follows: 1) target lesion: S4 hepatic metastatic lesions, 2) drip infusion of ^{10}BPA at 400 mg/kg, 3) tumor dose: >30 Gy-Eq/5 cm, normal liver dose: <4.9 Gy-Eq, 4) tumor/blood ratio on ^{18}F-^{10}BPA PET of 2.6. Since the general condition of the patient was good, he was transported to KURRI in January 2012 for irradiation and received BNCT.

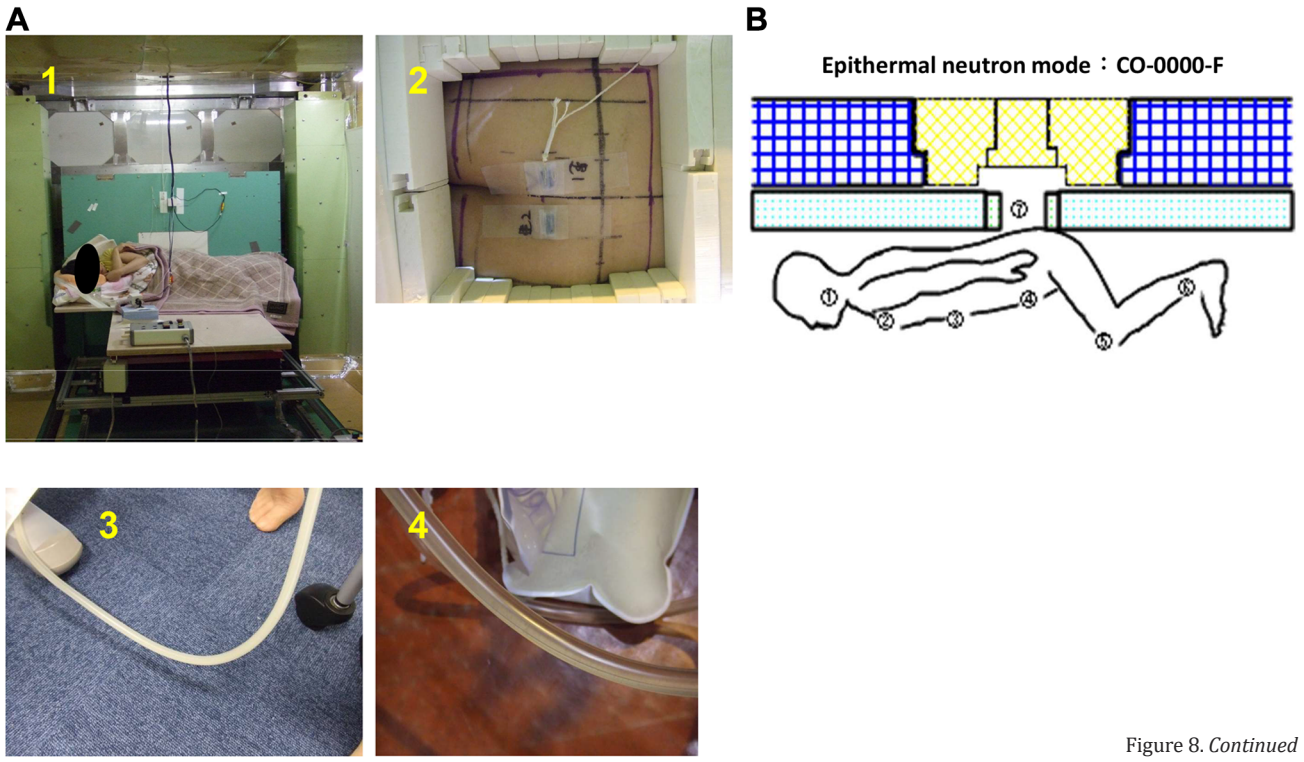
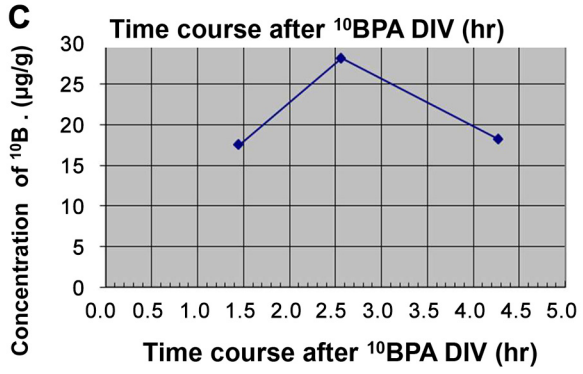


Figure 8. *Continued*

BNCT procedure and dose distribution analysis. To position the patient correctly in the irradiation room, we referred to four lines and one central point on the skin that marked the upper, lower, right, and left margins and center of the tumor on CT before BNCT at KUR. The patient was treated with forward-directed thermal neutron beams delivered through a collimator encompassing the right lobe. A 20-cm square collimator encompassing the right lobe was used to deliver the beams. The dose delivered and irradiation time employed in this pilot study were restricted to the dose delivered to a normal liver in a previous study (30). In the present case, the irradiation time selected to deliver a maximum radiation dose was 5.0 Gy-Eq to normal liver tissue. RBE and CBE used in the pilot study are shown in Table I. The patient was treated with forward-directed thermal neutron beams delivered to target organs with the patient placed in the right-decubitus position. The distribution of the dose delivered with irradiation using frontal neutron beams is shown in Figure 10. Only BPA (400 mg/kg, three hours before) was used to treat this patient. The blood concentration of ^{10}B during medical irradiation was estimated based on the measurement data of blood samples taken just before irradiation, considering decay during irradiation, as follows: blood, skin, mucosa, and nerves 19 ppm; tumor 51.3 ppm (estimated T/B ratio=2.7) (Figure 11A-D). The highest dose delivered to the left lobe of the normal liver was 3.2 Gy-Eq. Peak and mean doses of 19 and 12 Gy-Eq, respectively, were delivered to the tumor. Based on corrected SERA pre-evaluation results, thermal neutron flux, the fast neutron absorbed dose rate, and γ-ray absorbed dose rate at the surface of the affected area were estimated to be 2.50×10^8 cm^{-2} s^{-1}, 1.84 Gy-Eq/h, and 1.48 Gy-Eq/h, respectively. At a depth of 2.1 cm, corresponding to the peak distribution of thermal neutron flux, these values were estimated to be 7.82×10^8 cm^{-2} s^{-1}, 1.06 Gy-Eq/h, and 2.58 Gy-Eq/h, respectively (Figure 11E).

Based on DVH to ensure that at least 50% of the tumor volume received a dose ≥20 Gy-Eq, the irradiation time

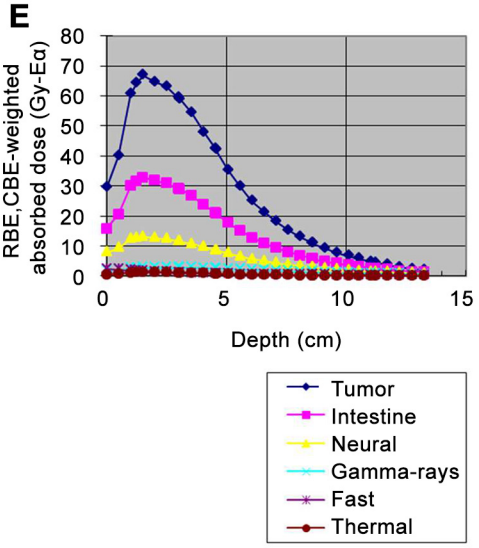
C



D

Position	Thermal neutron fluence (cm^{-2})	Γray dose* (cSv)
Cervix ①	1.8E+09	5.9
Chest ②	9.4E+08	11.8
Umbilicus ③	1.4E+09	19.6
Inguinal region ④	1.3E+09	23.5
Knee ⑤	8.2E+08	12.5
Instep ⑥	3.5E+09	10.4
Tumor site ⑦	1.38E+12	268.8

E



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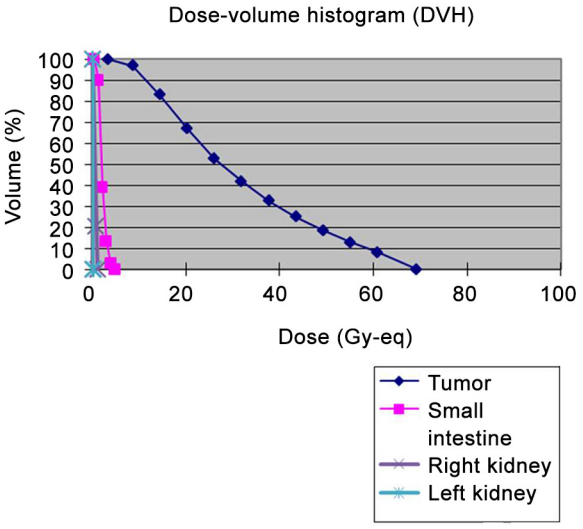


Figure 8. *Patient positioning, neutron dosimetry, and dose distribution for boron neutron capture therapy (BNCT) in Case 3. (A) Photograph showing the body position of Case 3 for BNCT (A-1, 2). After BNCT, cloudy urine, suspected to be due to BPA crystallization (A-3), was observed. To prevent renal dysfunction, additional fluid infusion was administered, leading to an improvement in urine condition (A-4). (B) Schematic representation of the body position for BNCT from the beam port. (C) Time course of changes in ^{10}B concentration (μg/g) following intravenous infusion of ^{10}BPA (absolute values in Case 3). (D) Measured thermal neutron fluence and gamma-ray dose delivered to the body. The measurable lower limits were approximately 5×10^{7} cm^{-2} for thermal neutron fluence and ~0.01 cSv for gamma-ray dose (absolute values in Case 3). (E) Dose distribution along the beam axis in thermal neutron irradiation mode (CO-0000-F+ collimator, irradiation field: 14 cm×16 cm). Tumor: Tumor dose; Intestine: small intestine dose; Neural: normal nerve dose; Gamma-rays: Gamma ray dose; Fast: fast neutron dose; Thermal: thermal neutron dose. (F) Calculated dose-volume histogram (DVH) for BNCT in Case 3 (tumor volume: 352.21 cm^3; small intestine: 293.64 cm^3). BPA intravenous infusion (400 mg/kg) was performed three hours before thermal neutron irradiation. Based on an ^{18}F-^{10}BPA PET analysis, the estimated ^{10}B concentrations were: blood, skin, mucosa, and nerves (25.3 ppm); kidney (50.6 ppm); and tumor (73.3 ppm). To achieve a tumor dose of 15 Gy at a depth of 8 cm, the BNCT irradiation time was set to 70 min.*

selected was 58 min. At this time, the maximum estimated tumor dose was 40 Gy-Eq, while the maximum estimated dose to the normal liver was 3.0 Gy-Eq (Figure 11F).

In the post-evaluation, the average blood concentration of ^{10}B during irradiation was corrected to 16.4 ppm. On the beam axis, estimated doses were approximately 5.5 Gy-Eq for the surface of the skin, 37 Gy-Eq at the peak of the tumor (depth of 2.1 cm), and 18 Gy-Eq at a depth of 6 cm (Figure 11E). Figure 11F shows DVH for the tumor and normal liver. Doses >20 Gy-Eq were delivered to 38% of the

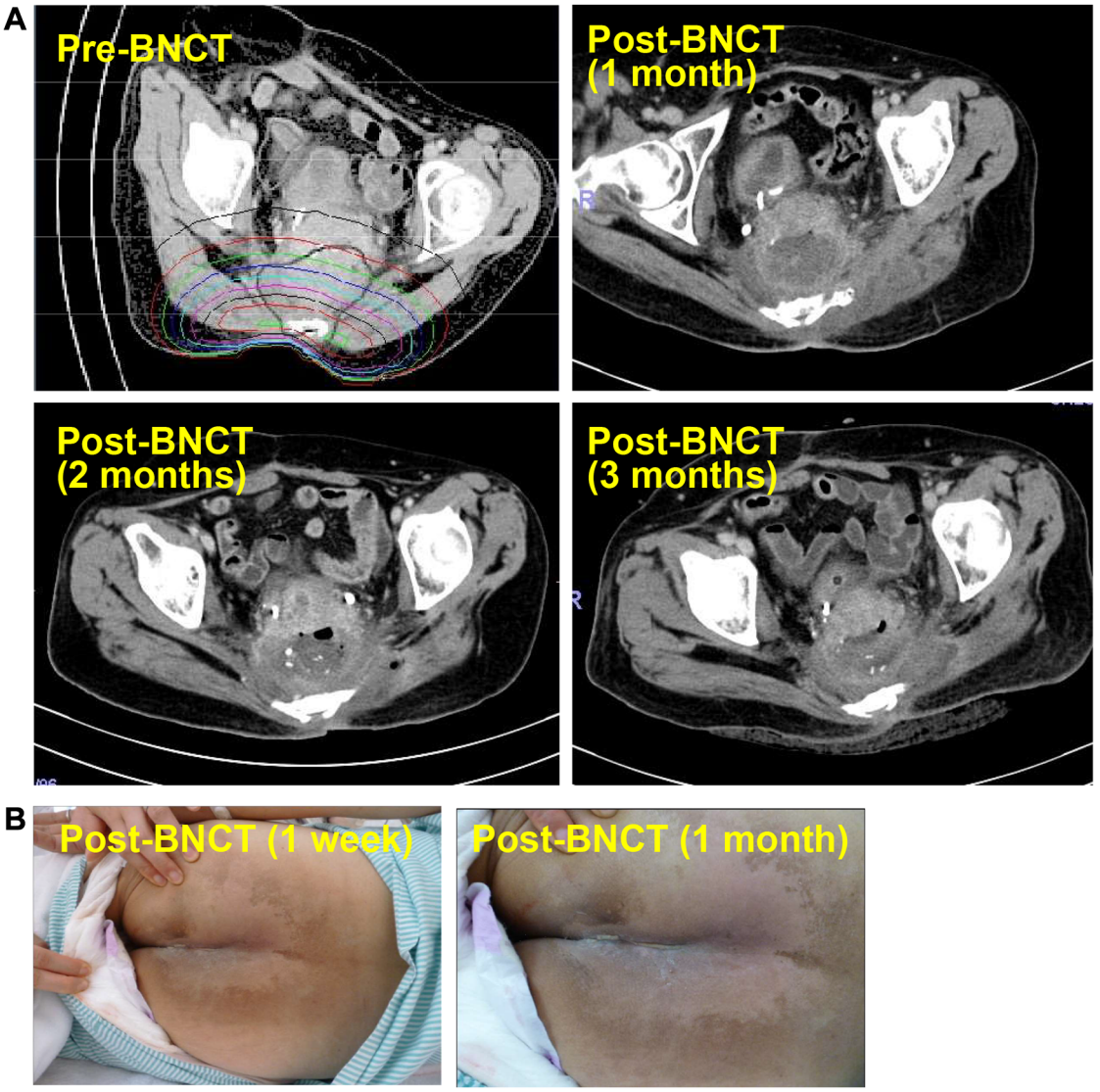


Figure 9. *Tumor response and skin condition following boron neutron capture therapy (BNCT). (A) Post-BNCT imaging at one, two, and three months after treatment. The tumor size remained stable, and a low-density area was observed in the tumor center at each time point. Tumor invasion into the surrounding tissue was detected at two and three months post-BNCT. (B) No skin necrosis was observed following BNCT.*

tumor region, with a maximum estimated dose of 42 Gy-Eq. The average estimated dose delivered to the normal liver was 2.0 Gy-Eq, with a maximum dose of 17 Gy-Eq.

Post-treatment course and clinical outcome. The patient was discharged 8 days after BNCT. The response to treatment and tumor progression were assessed in this pilot study using the international criteria proposed by the RECIST committee. Follow-up abdominal CT three months after BNCT showed that the size of the tumor in the left lobe remained unchanged and, thus, was judged to be SD (Figure 12). The volume of the tumor decreased and the oppressive feeling as the chief complaint of the patient subsided following BNCT. The local growth of metastatic

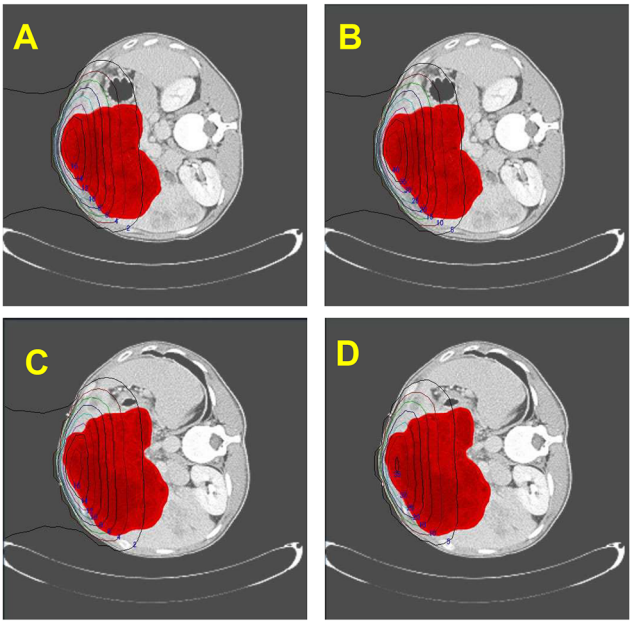


Figure 10. *Two-dimensional total dose distribution in the liver and tumor in Case 4. Two-dimensional total dose distribution in a -2.0-cm plane. (A) Normal liver dose; (B) Tumor dose (unit: Gy-Eq). Red indicates the tumor. Two-dimensional total dose distribution in a +1.0-cm plane. (C) Normal liver dose; (D) Tumor dose (unit: Gy-Eq). Red indicates the tumor.*

lesions was inhibited after three months by only single irradiation of BNCT. Recurrent nodules of metastatic colon cancer in the liver were treated with chemotherapy and molecular targeting agents from three months after BNCT. The patient died due to liver failure as a result of metastatic lesions in the liver and respiratory failure caused by metastasis to the lungs seven months after BNCT.

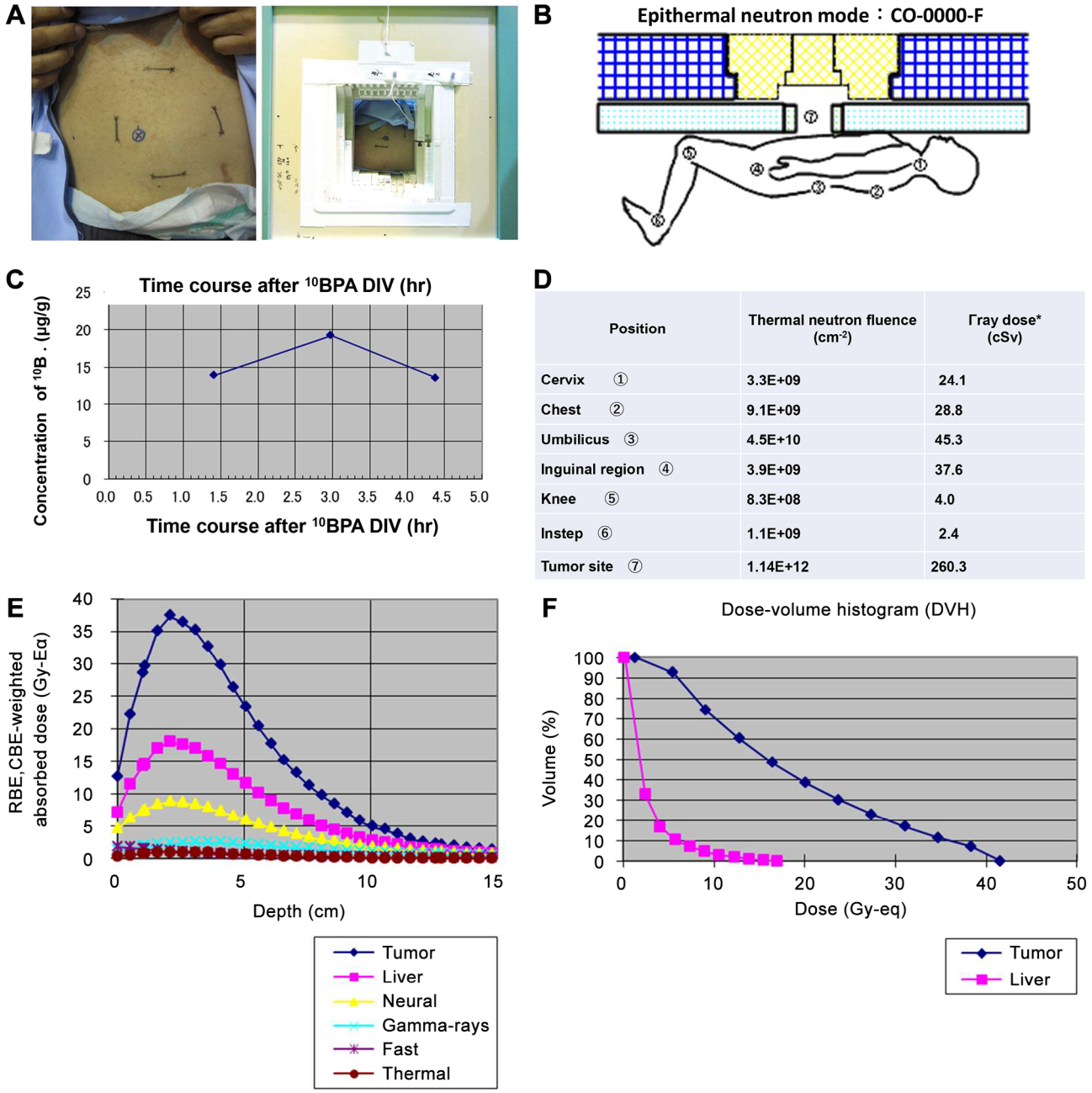
Discussion

We aimed to apply BNCT as an intensive combined cancer therapy for local recurrent & metastatic cancer in gastrointestinal regions. We herein demonstrated the potential of BNCT as an effective treatment for recurrent gastrointestinal cancers.

In Case 1 of recurrent gastric cancer, we performed BNCT while referencing the techniques used in BNCT for head and neck cancer to prevent the occurrence of carotid blowout syndrome. Initially, we had planned fractionated irradiation for BNCT in this case; however, we were able to achieve tumor growth suppression with a single irradiation.

We previously conducted pilot clinical studies on BNCT for locally recurrent rectal cancer. We safely performed BNCT with no adverse events or side effects and showed that it inhibited tumor growth. We noted that the effects of targeted molecular therapy were enhanced after BNCT, which appeared to be attributed to cancer cells being damaged by BNCT and, thus, being more susceptible to the cytotoxic effects of targeted molecular therapy. Furthermore, QOL recovered after BNCT. The volume of the tumor in Case 2 slightly decreased with chemotherapy, and walk disturbance and pain in the sacral nerve area both improved one month after BNCT.

The main tumor volume decreased in Case 3 (SD); however, invasion by the surrounding tumor was detected three months after BNCT. Pain in the nerve area improved. F-^{10}BPA-PET was performed on Case 2 and Case 3. The tumor/blood ratio on ^{18}F-^{10}BPA PET was used for calculations of neutron dosimetry (Case 2: T/B ratio=2.6, Case 3: T/B ratio=2.9). We used CBE of the oral mucosa (4.9) to estimate CBE of the small intestine. In the CT images, the small intestine is located anterior to the pelvic tumor within the abdominal cavity; therefore, we performed BNCT with careful consideration of the maximum neutron dose to the small intestine. Since the urine/blood ratio in the urinary bladder on F-^{10}BPA-PET was 10, we carefully considered the dose delivered to the mucosa of the urinary bladder in BNCT to the pelvic cavity. In Case 2 and Case 3, there was no hematuria or inflammation after irradiation. We wanted to perform a second course of BNCT, but lacked the relevant funding; therefore, BNCT was only conducted once to assess its safety, and the neutron capture effect. Our pilot clinical studies showed the safety of BNCT for gastrointestinal cancers. Kato *et al.* previously reported the potential of fractional BNCT for further tumor growth suppression (18, 19). Therefore, future studies are needed to increase the suppressive effects of BNCT by 1) preventing any change in body position during irradiation, and 2) administering boron compounds (DIV methods and the combination of BPA and BSH). Accelerated BNCT may be applied to patients



Position	Thermal neutron fluence (cm^{-2})	Γray dose* (cSv)
Cervix ①	3.3E+09	24.1
Chest ②	9.1E+09	28.8
Umbilicus ③	4.5E+10	45.3
Inguinal region ④	3.9E+09	37.6
Knee ⑤	8.3E+08	4.0
Instep ⑥	1.1E+09	2.4
Tumor site ⑦	1.14E+12	260.3

Figure 11. *Patient positioning, neutron dosimetry, and dose distribution for boron neutron capture therapy (BNCT) in Case 4. (A) Photograph showing the body position of Case 4 for BNCT. (B) Schematic representation of the body position for BNCT from the beam port in epithermal neutron irradiation mode (CO-0000-F). (C) Time course of changes in ^{10}B concentration (μg/g) following intravenous infusion of ^{10}BPA in Case 4 (absolute values in Case 4). (D) Measured thermal neutron fluence and gamma-ray dose delivered to the body of Case 4. The measurable lower limits were approximately 5×10^{7} cm^{-2} for thermal neutron fluence and ~0.01 cSv for gamma-ray dose (absolute values in Case 4). (E) Dose distribution along the beam axis in reference thermal neutron irradiation mode (CO-0000-F+ collimator, irradiation field: 15 cm×18 cm). Tumor: Tumor dose; Liver: liver dose; Neural: normal nerve dose; Gamma-rays: Gamma ray dose; Fast: fast neutron dose; Thermal: thermal neutron dose. (F) Calculated dose-volume histogram (DVH) for the tumor and normal liver (tumor volume: 1,698.73 cm^3; normal liver volume: 1,727.36 cm^3). The BNCT irradiation time was 58 minutes to deliver more than 20 Gy to 50% of the tumor volume.*

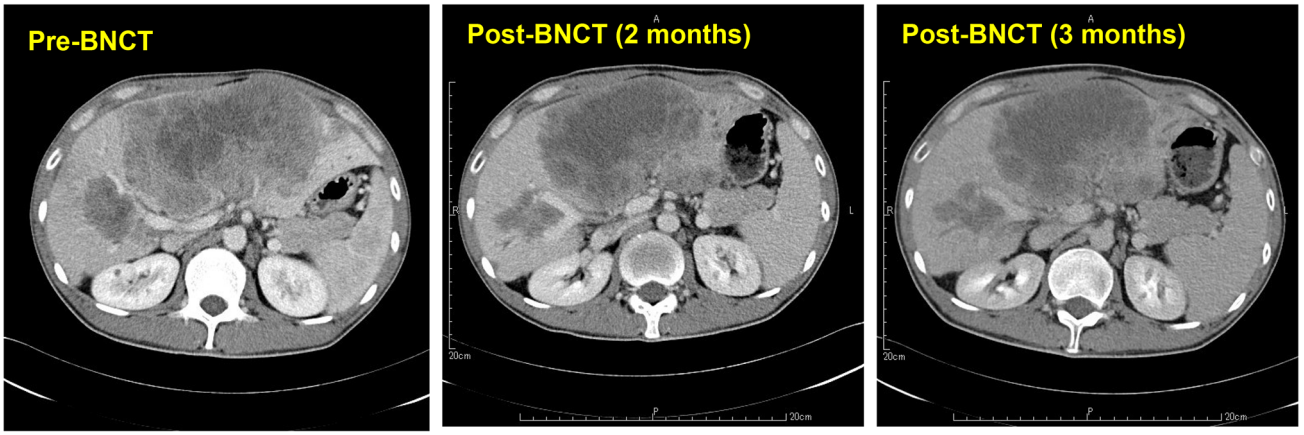


Figure 12. *Tumor response and pain relief following boron neutron capture therapy (BNCT). Tumor growth was suppressed after BNCT, and local pain caused by tumor swelling significantly decreased.*

with gastrointestinal cancers (including hepatocellular carcinoma) and breast cancer in the near future.

We applied BNCT to the treatment of hepatic metastatic sigmoidal colon cancer in case 4. We encountered one case in which an IA injection of the immunostimulating substance OK-432 (Picibanil) was used to treat multiple large metastases in a patient with colon cancer after surgery and systemic & IA chemotherapies (48). The findings obtained showed a decrease in the volume of the tumor and the recovery of QOL.

We intend to apply combination therapies with BNCT and IA immunotherapy in the future. Immunotherapies have become an attractive combination therapy for cancer. Cytotoxic T lymphocyte/Natural killer cell therapy (49), dendritic cell therapy (50), OK-432-IA, and immune checkpoint blockade (51, 52) will be considered for the treatment of liver cancer in the near future. Treatment efficacy may be increased by the combined use of dendritic cell hepatic arterial infusions and immune checkpoint inhibitors. We aim to advance future research on combination therapies with BNCT.

Conclusion

We first performed pilot clinical studies on the use of BNCT as an intensive combined cancer therapy for local recurrent & metastatic cancer in gastrointestinal regions. BNCT not only promotes symptom relief, but also has the potential to enhance antitumor effects when combined with multidisciplinary treatment. We intend to accumulate more cases treated with BNCT in order to evaluate its effects in these regions.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

H.Y., S.M., K.O., Y.O., S.K., Y.N., R.H., M.S., S.M., Y.S., N.K., H.T., A.M., and K.O. treated the patients and collected the clinical data. H.Y. wrote the original manuscript. H.Y., Y.F., T.S., and H.T. edited the manuscript. All Authors reviewed and approved the manuscript.

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University of Tokyo, began basic research on this topic. Dr. Isao Osada, the former chairman of the Japan Anti-Tuberculosis Association, also participated, and research has been ongoing under their guidance, for which the Authors are grateful. The Authors would like to thank Professor Masayuki Nashimoto for the useful discussions. This clinical study was supported in part by a grant from Uneuto Science Co., Ltd. Although there were delays due to the Great East Japan Earthquake and the COVID-19 pandemic, the Authors are now able to report the cases and extend their gratitude to everyone who cooperated.

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