had higher tissue boron concentration (data not shown). Therefore, the observed large SD values within a group of animals could be due to the difference in the blood clearance of the administered BSH among the animals contributed by the differences in their sensitivity to BSO and thus the level of GSH depletion.

Although the mechanism behind the aforementioned phenomenon is not known, all these findings indicate a close association between GSH and BSH metabolism. Metabolic transformation of BSH in vivo produces BSH metabolites, such as BSH sulfenic acid (BSOH), BSH sulfinic acid (BSO(2)H), BSH disulfide (BSSB), BSH thiosulfinate (BSOSB), and BSH–*S*-cysteine conjugate (BSH–CYS) [22]; it is therefore of our interest to examine if one or more of these metabolites are involved in GSH depletion process.

4.2. Delayed tumor growth by BSH–BSO-mediated BNCT

Although there were apparent differences in tumor growth between the BSO+ and the BSO− groups or the BSO− and the control groups, the significant difference was observed only between the BSO+ and the control groups. This unexpected finding, despite significantly enhanced boron concentration in all tissues examined, could be partially explained by insufficient radiation dose.

The respective tissue boron concentration for the BSO+ and the BSO− groups was 11.9 ± 7.8 ppm and 1.3 ± 0.6 ppm. With thermal neutron fluence of 1.33×10^{12} n/cm^2, D_b for the BSO+ and the BSO− groups was calculated to be 1.19 Gy and 0.13 Gy, respectively. Since $D_n = 0.20$, $D_f = 0.017$, and $D_\gamma = 570.8 \pm 31.0$ mGy, the calculated gamma ray equivalent dosage was 3.72 Gy-eq in the BSO+ group and 1.28 Gy-eq in the BSO− group. In comparison with 20–100 Gy-eq used in the clinical practice, the therapeutic radiological dosage in our animal experiments was significantly lower. It may therefore be necessary to raise the dosage by increasing the BSH administered or irradiation time in forthcoming experiments.

In conclusion, this study denotes that the combined use of BSH and BSO in BNCT can induce sustained and high level of boron in different tissues. With further improvement, BSH–BSO-mediated BNCT should allow shorter radiation exposure time and consequently reduction in irradiation damage to normal tissues. Since this study was the first partial body irradiation experiment of rats at the JRR-4 reactor, all-around improvement in the experimental conditions is in progress for our on-going research.

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CLINICAL STUDY - PATIENT STUDY

Survival benefit of Boron neutron capture therapy for recurrent malignant gliomas

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Abstract We have applied boron neutron capture therapy (BNCT) to malignant brain tumors. Here we evaluated the survival benefit of BNCT for recurrent malignant glioma (MG). Since 2002, we have treated 22 cases of recurrent MG with BNCT. Survival time was analyzed with special reference to recursive partitioning analysis (RPA) classification, by Carson et al. (J Clin Oncol 25:2601–2606, 2007). Median survival times (MSTs) after BNCT for all patients and for glioblastoma as on-study histology at recurrence was 10.8 months ($n = 22$; 95% CI, 7.3–12.8 months) and 9.6 months ($n = 19$; 95% CI, 6.9–11.4 months), respectively. In our study, MST for the high-risk RPA classes was 9.1 months ($n = 11$; 95% CI, 4.4–11.0 months). By contrast, the original journal data showed that the MST of the same RPA classes was 4.4 months ($n = 129$; 95% CI, 3.6–5.4 months). BNCT showed a survival benefit for recurrent MG, especially in the high-risk group.

Keywords BNCT · BPA–PET · GBM · MG · RPA

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Introduction

We have applied a form of tumor-selective particle radiation, boron neutron capture therapy (BNCT), for malignant gliomas (MGs) [1, 2] and malignant meningiomas [3, 4]. BNCT comprises a binary approach [5]: a boron-10 (^{10}B)-labeled compound is administered that delivers high concentrations of ^{10}B to the target tumor relative to the surrounding normal tissues. This is followed by irradiation with thermal neutrons. When neutrons collide into ^{10}B atoms, high linear-energy-transfer (LET) alpha and ^{7}Li particles are released from the ^{10}B (n, alpha) ^{7}Li neutron capture reaction. The short range (5–9 micrometers) of these particles allows for relatively selective tumor killing without significant damage to the adjacent normal brain tissue.

The prognosis of recurrent MGs, especially glioblastoma multiforme (GBM) is poor [6]. We reported the effectiveness of BNCT on neuroimages for MGs [1, 2], and recently reported the survival benefit of BNCT for newly diagnosed MGs [7]. Unfortunately, the standard treatment for recurrent MG has not yet been established. Therefore, evaluation of the survival benefit of BNCT for recurrent MGs is difficult. Also with limited case numbers like this study, it is difficult to elucidate some objective assessments

of the survival benefit of BNCT. To evaluate this in low and high-risk group of recurrent MGs, we adopted the recursive partitioning analysis (RPA) classification for recurrent MG advocated by Carson et al. in a 2007 article in the *Journal of Clinical Oncology*, in which the results of 10 recent protocols of phase-1 and -2 trials applied by the new approaches to brain tumor therapy CNS consortium (NABTT) for recurrent MG were summarized [8]. They included six systemic treatment and four local treatment trials. Originally this RPA classification was not aimed at the evaluation of the effectiveness of each trial for recurrent MG; however, this RPA classification gave us a uniform background and median survival time (MST) for each recurrent MG-type patient at the time of recurrence. So we classified our recurrent MG patients treated by BNCT and compared their survival to the MSTs presented in the above journal.

Patients and methods

Patient enrollment

From 2002 to 2007 we treated a total of 22 cases of recurrent MG using BNCT. Our eligibility criteria for this trial were as follows: (1) age 15 years or older; (2) histologically proven supratentorial MG (GBM, AA, AO, or anaplastic oligodendroglioma, as on-study histology) that had proved to be progressive or recurrent after radiation therapy; (3) depth of the tumor from scalp less than 6 cm (if the lesion is deeper than 6 cm from the scalp, partial removal or cyst evacuation was applied to fit this criteria, see below); (4) no cerebrospinal fluid (CSF) dissemination at recurrence; (5) estimated life expectancy longer than 3 months, not pregnant or breast feeding, and having a KPS score of 60 or greater.

Clinical regimen of BNCT

After the confirmation of the tumor progression or recurrence of the original lesions on MRI, the patients received a BPA–PET to assess the distribution of boronophenylalanine (BPA) [9, 10]. The lesion/normal brain (L/N) ratio of BPA uptake can be estimated from this type of study, and dose planning was performed according to the L/N ratio, as described previously [1, 2]. If the lesions were deeper than 6 cm from the scalp, partial removal of the mass or cyst evacuation was applied. At this procedure, air instillation via an Ommaya reservoir was performed so that the neutron flux would penetrate to the deepest part of the tumor [11]. Within a month after the surgery, BNCT was performed.

In protocol 1, the patients were administered 100 mg/kg of sodium borocaptate (BSH) and 250 mg/kg of BPA for one hour intravenously 12 h prior and just prior to neutron irradiation, respectively. In protocol 2, the patients were administered 100 mg/kg of BSH intravenously for one hour, 12 h prior to neutron irradiation and 700 mg/kg of BPA continuously for 6 h before the irradiation. In both protocols, the neutron irradiation time was determined not to exceed 13 Gy-Eq to the normal brain by simulation. Here, Gy-Eq (Gy: Gray) corresponds to the biologically equivalent X-ray dose that would have equivalent effects on tumors and on the normal brain. For some deep tumors, air instillation was performed as stated above just prior to neutron irradiation.

Patient follow-up

Patients were followed up by bimonthly Gd-enhanced MRI. When the lesions became enlarged or new lesions appeared on the follow-up MRI, we applied BPA–PET to evaluate the tumor activity [12]. If the positron emission tomography (PET) results suggested tumor progression (TP), additional treatments were applied. If PET suggested the high possibility of radiation necrosis (RN), medical treatments for this pathology or surgical resections were applied [12, 13].

Patient characteristics

The patients' age, gross tumor volume (GTV) (Gd-enhanced lesions on MRI at relapse, use of temozolomide (TMZ) and absorbed dose by BNCT (minimum tumor dose and maximum brain dose) are summarized in Table 1. In 12 cases surgery was applied before BNCT, as a form of cyst evacuation or partial tumor removal to make a cavity to establish an Ommaya reservoir as described above. Ten cases were administered TMZ, three before the relapse and seven after BNCT. Individual information of TMZ usage is

Table 1 Patient characteristics

Description		
Age (median (range))	51	(15–67)
[a]GTV at the relapse (median (range))	42.0	(4.1–64.5) ml
[b]Reoperated cases at relapse	12	
TMZ	10	
Before BNCT	3	
After BNCT	7	

[a] GTV was measured on contrast-enhanced MRI at the relapse

[b] Cyst puncture or partial removal to make cavity for air instillation

Table 2

Case No	Age	Sex	Histology		RPA by Carson et al.	TMZ		BNCT protocol	Absorbed dose (Gy-Eq)		Survival (months)after BNCT	Cause of death
			Initial	On-study		Before	After		Min tumor	Max brain		
1	42	M	AA	GB	1	−	+	1	15.5	12.4	43.1	TP
2	57	F	AA	GB	1	−	+	2	37.3	8.3	22.0	D
3	15	F	AA	AA	2	−	+	2	56.3	10.7	33.4	A
4	53	M	Oligo	GB	2	−	−	2	73.9	13.2	6.9	D
5	51	M	AOA	AOA	2	−	−	2	27.4	8.1	32.4	D
6	33	F	G2	AA	2	−	−	1	12.7	7.1	15.0	OC
7	61	M	AA	GB	3	−	−	1	34.4	3.7	10.8	RN
8	29	F	AA	GB	3	−	−	1	25.7	5.9	9.6	B
9	62	M	AA	GB	3	−	−	1	23.4	9.9	2.5	OC
10	31	M	G2	GB	3	−	−	1	29.3	14.2	4.4	D
11	51	M	AA	GB	3	+	−	2	44.9	13.6	9.1	TP
12	48	M	GB	GB	4	−	−	1	27.2	11.1	7.8	D
13	46	F	GB	GB	4	−	+	2	49.2	12.1	12.8	D
14	41	M	GB	GB	4	+	−	2	54.3	12.7	10.3	D
15	35	M	GB	GB	5	−	−	2	37.7	13.4	6.0	D
16	45	M	GB	GB	5	+	−	2	59.0	13.8	11.4	RN
17	59	M	GB	GB	7	−	−	1	32.8	11.2	8.6	TP
18	50	M	GB	GB	7	−	−	1	32.6	13.6	15.3	RN
19	63	M	GB	GB	7	−	−	2	34.7	9.4	11.0	D
20	67	F	GB	GB	7	−	+	2	58.0	11.7	12.3	D
21	60	F	GB	GB	7	+	+	2	34.9	7.5	5.8	TP
22	54	M	GB	GB	7	−	+	2	19.7	10.7	7.4	TP

M, male; F, female; AA, anaplastic astrocytoma; Oligo, oligodendroglioma; AOA, anaplastic oligoastrocytoma; G2, grade 2 astrocytoma; GB, glioblastoma; RPA, Recursive partitioning analysis; TMZ, temozolomode; Gy-Eq, Gray equivalent; Min, minimum; Max, maximum; BNCT, boron neutron capture therapy; TP, local tumor progression; A, alive; D, CSF dissemination; RN, radiation necrosis; OC, other cause; B, both dissemination and local tumor progression

listed in Table 2. In Table 2, two histological diagnoses were prepared. One is initial histology and the other is on-study histology. Here, on-study histology means the histology that was confirmed at the last surgery for each patient, prior to BNCT.

Statistical methods

Continuous data are summarized with medians, ranges and *P*-values. Univariate analysis was performed using chi-square log-rank testing. Survival distributions (MSTs and 95% CIs) were estimated using the product limit method. The analysis was intention-to-treat and included all eligible patients. Data were entered into Microsoft Excel (Microsoft Corporation) and analyzed using JMP software version 7 (SAS Institute, Cary, NC, USA).

RPA classification

To objectively evaluate the survival benefit of BNCT for recurrent MG, we classified our BNCT cases according to the RPA classification advocated in some journals [8]. These classifications can be summarized as follows: class 1, not GBM (initial histology), KPS $\geq$ 80, frontal (tumor location); RPA class 2, not GBM, KPS $\geq$ 80, not frontal; RPA class 3, not GBM, KPS $\leq$ 70; RPA class 4, GBM, Age $\leq$ 50, KPS $\geq$ 90; RPA class 5, GBM, Age $\leq$ 50, 60 $\leq$ KPS $\leq$ 80; RPA class 6, GBM, Age $\geq$ 50, no steroid use; RPA class 7, GBM, Age $\geq$ 50, steroid use. Individual class of RPA of our cases treated by BNCT is listed in Table 2.

Analysis of the cause of death after BNCT

Unfortunately, 21 out of the 22 patients died during the observation period, as listed in Table 2. The cause of death was analyzed with the following categories: local TP, CSF dissemination, RN, and other cause of death. These classifications were based on Gd-enhanced MRI, BPA–PET, histology of the surgical specimen and autopsy. In one case, both CSF dissemination and local TP occurred simultaneously and it was impossible to determine a single pathology as the major cause of death.

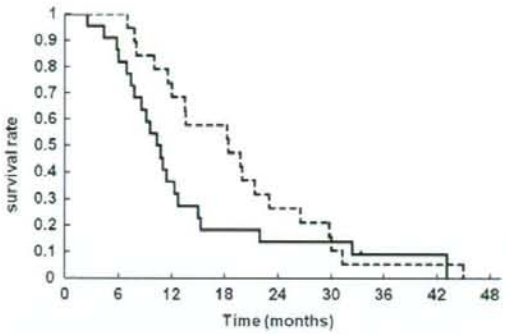

Fig. 1 Kaplan–Meier survival curves for recurrent MG cases treated by BNCT. The continuous line shows the survival of all patients after BNCT ($n = 22$). The broken line shows the survival of GBM (on-study histology) after diagnosis of GBM ($n = 19$)

Results

Survival after BNCT and after diagnosis

Individual histology (initial and on-study at relapse), RPA class, TMZ use, BNCT protocol (1 or 2), absorbed dose by BNCT, survival period after BNCT, and cause of death are summarized in Table 2. Survival after BNCT ($n = 22$) and that from initial GBM diagnosis ($n = 19$, on-study histology as GBM) are shown in Fig. 1. MST after BNCT for all patients ($n = 22$) was 10.8 months (95% CI, 7.3–12.8 months). MST after BNCT for GBM cases as on-study histology at recurrence ($n = 19$) was 9.6 months (95% CI, 6.9–11.4 months). MST after initial GBM diagnosis ($n = 19$) was 19.1 months (95% CI, 11.6–23.0 months).

Survival with special reference to RPA classes

The MSTs (months) of our BNCT cases classified according to RPA classes are shown in Table 3 and compared in each case with the values from Carson et al.: Class 1 ($n = 2$): 32.6 vs. 25.7 (Carson et al.), Class 2 ($n = 4$): 23.7 vs. 17.2, Class 3 ($n = 5$): 9.1 vs. 3.8, Class 4 ($n = 3$): 10.2 vs. 10.4, Class 5 ($n = 2$): 8.5 vs. 6.4, Class 7 ($n = 6$): 9.8 vs. 4.9. The tendencies in patient survival of our cases after BNCT were very similar to those of the original report in terms of RPA classification. Since our cases were so limited in number, we joined the worst prognosis classes (Class 3 and 7) together into one class. The MST of our cases in this combined class was 9.1 months ($n = 11$; 95% CI, 4.4–11.0 months), while that in Carson et al. was 4.4 months ($n = 129$; 95% CI, 3.6–5.4 months).

Cause of death after BNCT

We lost 21 cases out of 22. The causes of deaths were CSF dissemination (10 cases), local TP (5), both (1), RN (3), and other (2), as shown in Table 2. With regard to RN, we discuss more extensively in "Discussion".

Adverse effects of BNCT

No serious adverse effects were observed both in protocols 1 and 2 in this study of BNCT for recurrent MGs, even though all patients were applied with radiotherapy previously. Hematuria was reported in the literature using large amounts of BPA in BNCT [14]. Fortunately, we did not experience this adverse effect at all, however, three cases in protocol 2 showed transient decrease volume and turbidity of urine and fever during the first 24 h after BNCT. We concluded these side effects were caused by recrystallization of BPA in urine. Thereafter, we over hydrated the remaining patients after BNCT, and no such side effects were observed again.

Univariate analysis for the survival after BNCT

In Table 4, we analyzed factors for survival after BNCT, such as sex, age, TMZ or steroid usage, KPS, minimum absorbed dose in tumors, initial histology, GTV at the relapse, BNCT protocol (1 or 2) and RPA classes. Among them, only RPA class (RPA class 3 and 7 or others) showed a statistical significant influence on survival after BNCT.

Table 3 Comparison of NABTT trials and our BNCT series

	All patients			RPA 3 + 7		
	MST	95% CI	Number in series	MST	95% CI	Number in series
NABTT	7.0	6.2–8.0	$n = 310$	4.4	3.6–5.4	$n = 129$
BNCT	10.8	7.3–12.8	$n = 22$	9.1	4.4–11.0	$n = 11$

[a] New Approaches to brain tumor therapy CNS Consortium; 10 phase-1 and -2 trials reported by Carson et al. (J Clin Oncol 25:2601–2606, 2007)

MST, Median survival time; CI, confidence interval

Table 4 Univariate analysis of factors for survival after BNCT

Factor	Group	Survival (months)				*P*-Value
		Median	95% CI			
Sex	Male ($n = 15$)	9.1	6.0	–	11.0	$P = 0.2456$
	Female ($n = 7$)	12.8	5.8	–	22.0	
Age	≦50 ($n = 11$)	11.4	6.0	–	15.3	$P = 0.2482$
	>50 ($n = 11$)	9.1	5.8	–	12.3	
	≦57 ($n = 16$)	11.4	7.4	–	15.3	$P = 0.0982$
	>57 ($n = 6$)	10.8	2.5	–		
KPS	≦80 ($n = 13$)	9.6	6.0	–	11.4	$P = 0.1271$
	>80($n = 9$)	12.8	5.8	–		
Initial Histology	GBM ($n = 11$)	10.3	6.0	–	12.3	$P = 0.1329$
	Not GBM ($n = 11$)	10.8	4.4	–	32.4	
TMZ	Used ($n = 10$)	12.3	5.8	–	22.0	$P = 0.1468$
	Not used ($n = 12$)	9.6	4.4	–	15.0	
Steroid	Used ($n = 13$)	9.6	6.9	–	11.4	$P = 0.1445$
	Not used ($n = 9$)	12.8	2.5	–		
GTV (ml)	≦37.2($n = 11$)	9.1	4.4	–	12.8	$P = 0.5273$
	>37.2 ($n = 11$)	10.8	7.4	–	15.3	
Minimum tumor	≦34.0($n = 12$)	9.6	2.5	–	15.3	$P = 0.9110$
Dose (Gy-Eq)	>34.0($n = 10$)	11.0	6.0	–	12.8	
	≦37.0($n = 13$)	9.6	5.8	–	15.0	$P = 0.6548$
	>37.0($n = 9$)	11.4	6.0	–	22.0	
BNCT protocol	1 ($n = 9$)	9.6	2.5	–	15.3	$P = 0.8184$
	2 ($n = 13$)	11.0	6.9	–	12.8	
RPA class	RPA 3&7 ($n = 11$)	9.1	4.4	–	11.0	$P = 0.0216$
	RPA not 3&7 ($n = 11$)	12.8	6.9	–	32.4	

Representative case

A 48-year-old man with a right temporal mass was operated emergently for consciousness disturbance in a hospital. The operation was partial tumor removal and histological diagnosis was GBM. He received fractionated X-ray radiation therapy (XRT) with a total dose of 80 Gy and chemotherapy consisting of nimustine and vincristine. Even during the radiotherapy, the tumor continued to enlarge, and the patient was referred to our institute for BNCT (Fig. 2 a, a′). He was classified as RPA class 4. The BNCT was performed with the minimum tumor absorbed dose of 27.2 Gy-Eq, and maximum brain absorbed dose of 11.1 Gy-Eq. One week after BNCT the mass shrunk rapidly (Fig. 2 b, b′). Three months after BNCT, the original mass became enlarged in Gd-MRI. He was operated on again. The histology was mainly necrosis with small pocket of residual tumor cells. He was well for another 4 months. We lost this case 7.8 months after BNCT and 13.5 months after initial surgery, due to CSF dissemination (Fig. 2 c, c′). This is a representative case of recurrent MG treated by BNCT, with regard to the rapid tumor shrinkage after BNCT and the occurrence of radiation necrosis and CSF dissemination as the cause of death.

Discussion

Here we reported the survival benefit of BNCT for recurrent MG cases, mainly GBM. The MST after BNCT for GBM cases as on-study histology at recurrence ($n = 19$) was 9.6 months (95% CI, 6.9–11.4 months). In the literature, we found a summary of a large series of eight phase-2 trials of chemotherapies for recurrent GBM cases [15]. In this report, the authors mentioned the MST of GBM after relapse as 25 weeks (5.8 months; 95% CI, 21–28 weeks, 4.9–6.5 months; $n = 225$). In comparison with this result, our data for the survival benefit of BNCT in recurrent GBM was not bad.

As to BNCT for recurrent GBM, two small series have been reported in the literature. A Swedish group and a Finnish group reported that MSTs for recurrent GBM after BNCT were 8.7 ($n = 12$) [16] and 7.5 months ($n = 7$) [17], respectively. Our data in the current report is almost equal to/somewhat better than the findings in these reports.

Kaplan–Meyer analysis in Fig. 1 showed that MST after BNCT for all patients ($n = 22$) was 10.8 months (95% CI, 7.3–12.8 months). We are not sure whether this result is reliable, as this is the result of a small series from a single institute. To evaluate the survival benefit of BNCT in low

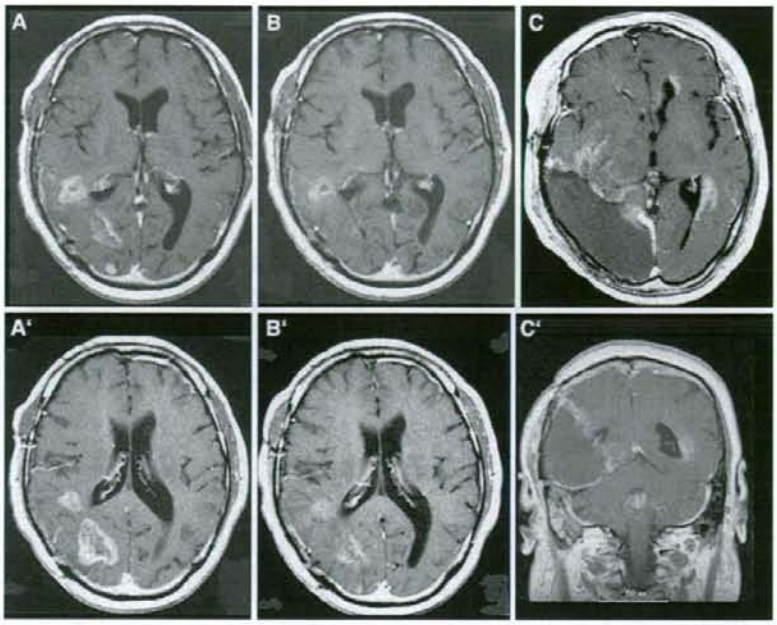

Fig. 2 A representative case of recurrent GBM treated by BNCT. (**a**, **a'**) MRI, prior to BNCT. Gd-enhanced lesions were at the right temporo-occipital lobe; (**b**, **b'**) MRI, 48 h after BNCT. Marked shrinkage of the lesions was recognized; (**c**, **c'**) MRI, 7 months after BNCT. CSF dissemination was prominent

and high-risk group of recurrent MGs, we applied RPA to our cases as advocated in the literature [8]. Inclusion criteria for our trial and the 10 NABTT phase-1 and -2 trials reported in Carson et al. were not very different. Our case numbers for each RPA class were so limited, however, that the MST of our cases in each RPA class were relatively better in comparison with original NABTT results, as listed above. In the original article, RPA class 3 (Not GBM, KPS $\leq$ 70) and class 7 (GBM, Age $\geq$ 50, steroid use) showed extremely poor prognosis (supplementary Table 1). The MST of our combined class 3 and class 7 cases was 9.1 months (n = 11; 95% CI, 4.4–11.0 months), while that in the original article was 4.4 months (n = 129; 95% CI, 3.6–5.4 months). We cannot know whether our current MST data is significantly better than that of each NABTT trial because their raw data were not available. But at least, BNCT showed a good survival benefit even for the highest-risk group, RPA class 3 and 7.

TMZ is the sole promising drug for GBM so far. A Swedish BNCT group reported potential TMZ effects with combination of BNCT at the relapse of GBM [16]. However, in our univariate analysis, TMZ did not contribute prominently to the prolongation of survival in our series (Table 4). In our 22 cases, we used TMZ in 10 cases, before BNCT in 3 cases (Cases 11, 14 and 16) and after BNCT in 7 (Cases 1, 2, 3, 13, 20, 21 and 22). For the former three cases, TMZ could not control the tumor growth and methylation-specific PCR showed an unmethylated O6-methylguanine DNA methyltransferase (MGMT) promoter [18] (data not shown). We stopped the administration of TMZ after BNCT as we judged TMZ was not efficacious for these three cases. Among the latter seven cases, only two (Cases 1 and 2, both classified as RPA class 1) showed methylated promoter status for MGMT, with good prognoses. For the other five cases, we were not sure of the MGMT expression status of the tumor. In the high-risk group in our series (RPA class 3 and 7), three cases were administered TMZ after BNCT (Cases 20, 21 and 22). Among them, Case 21 and 22 showed a relatively short survival after BNCT. We do not deny the meaning of TMZ use at relapse; however, in our series for this high-risk group, the survival benefit of TMZ was limited. In the literature, TMZ has actually shown modest survival benefit at relapse of recurrent GBM [19]. Brada et al. reported only 5.4 months prolongation as MST with TMZ at relapse in the report.

There are several reports with relatively good results for recurrent MG, with an MST of around 10 months after the stereotactic radiosurgery (SRS) [20] or stereotactic radiotherapy (SRT) [21] at relapse. However, there was big difference in GTV at the relapse between these SRS or SRT cases and ours. The median GTV of the former two was 10.1 and 12.7 ml, while the median GTV of our cases was 42.0 ml. There might also be a difference as to performance status or age between the SRS or SRT reports and our cases. The result of re-irradiation for recurrent

GBM was poor [22]. The MST of this report was 26 weeks after the treatment. In addition, BNCT can be applied in only one day. Taken together, BNCT could be one of the promising radiation treatment options for recurrent MG at relapse.

We lost many cases of recurrent MGs after BNCT by CSF dissemination, as we reported (in preparation) and as shown in Table 2 and Fig. 2. In other words, local control by BNCT for even recurrent MG was fairly good. There was a tendency for CSF dissemination to occur in relatively long-term survivors from diagnosis (data not shown). On the other hand, a major problem in BNCT for recurrent MG was the occurrence of RN. We experienced RN by BNCT especially for recurrent MG, because the patients had been treated by radiotherapy prior to BNCT. Although BNCT is cell-selective particle radiation, some particle dose is inevitably absorbed by the normal brain tissue as shown in Table 2. The diagnosis of this pathology is difficult; however, amino acid PET may give us good clue for it, as stated above [12]. Most of RN could be controlled with medical or surgical treatments as above; however, we lost three cases by RN in our series. Preventive medical treatments such as by anticoagulants or by vitamin E must be considered after BNCT, especially for recurrent cases. This is not mentioned in other BNCT reports for recurrent MG [16, 17]; however, it should be seriously considered. In Swedish reports of BNCT for recurrent GBM, the authors mentioned a median time to tumor progression of 6 months after BNCT, but there was no statement as to how TP was judged in their report. It is very difficult to differentiate RN and TP on MRI, especially with high-dose radiation treatment. So we did not apply the analysis of time to tumor progression in our series. In univariate analysis (Table 4), there was no correlation of minimum tumor dose by BNCT and survival after BNCT. Especially for recurrent cases, if we increase the minimum tumor dose by BNCT, the incidence of RN probably increases, as discussed here. Therefore, it is very difficult to elucidate the most suitable dose of BNCT at relapse. Regardless, RN is a serious problem to be overcome in the field of BNCT.

XRT plus concomitant TMZ (Stupp's regimen) has been the global standard so far for newly diagnosed GBM [23]. Pellettieri et al. reported that BNCT at relapse after Stupp's regimen might be the best treatment of GBM [16]. Also in our series BNCT at relapse showed a good MST after the initial GBM diagnosis of 19.1 months ($n = 19$; 95% CI, 11.6–23.0 months). But it cannot be concluded so easily that BNCT at relapse after Stupp's regimen is the best for the treatment of GBM because 19 cases in our series were referred to our institute at relapse with a significant interval after initial treatments. This interval might prolong the survival after initial GBM diagnosis at a glance.

In summary, the RPA classification advocated by Carson et al. predicted the patient survival trends of our BNCT series; however, BNCT showed the most prominent survival benefit in the high-risk group (RPA classes 3 and 7).

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BNCT in mesothelioma

A novel concept of treatment of diffuse or multiple pleural tumors by boron neutron capture therapy (BNCT)

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Abstract

Two patients, one with malignant pleural mesothelioma and one with a malignant short spindle cell tumor, received boron neutron capture therapy (BNCT). In each case, the tumors regressed or remained stable in size for 3–6 months following BNCT. No acute or late adverse events higher than grade 2 were observed.
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Keywords: Boron neutron capture therapy; Thoracic tumor; Malignant pleura mesothelioma

Boron neutron capture therapy (BNCT) is based on the following nuclear reaction: non-radioactive isotope ^{10}B atoms that have absorbed low energy (<0.5 eV) neutrons (thermal neutrons) disintegrate into alpha (^{4}He) particles and recoiled lithium nuclei (^{7}Li), [$^{10}B(n,\alpha)\,^{7}Li$] [1]. These particles deposit large amounts of energy along their very short paths (<10 μm). In BNCT, patients are irradiated with thermal neutrons following administration of ^{10}B-containing agents, which have the characteristics of accumulating selectively in tumors. If a sufficient number of ^{10}B atoms accumulate in tumor cells with a large gradient of ^{10}B concentration between the tumor cells and normal tissue cells, subsequent thermal neutron irradiation provides selective killing of tumor cells with the sparing of normal tissue cells. Therefore, BNCT has the possibility to deliver a curative dose to tumors diffusely spreading in radiosensitive organs, such as lung or liver, without causing fatal adverse effects [2–4]. In this article, we describe the treatment procedure used, its feasibility and the clinical results in two patients with diffuse or multiple pleural tumors treated with BNCT.

Case reports

The BNCT procedures were as follows: boronophenylalanine (BPA), which has been used as a boron compound in clinical trials, was administered at a dose of 250 or 500 mg/kg in a BPA-fructose (BPA-f) solution for 1.5–3.0 h through an intravenous route. Immediate neutron irradiation was applied within 15 min of finishing administration of the BPA-f solution. The details of the BNCT procedure on the treatment day are described in the presentation of each case below.

Treatment plans were constructed using the Simulation Environment for Radiotherapy Applications (SERA) system and JAERI Computational Dosimetry System (JCDS), which are currently available BNCT treatment planning systems [5,6]. The total biologically absorbed dose (Gy-Eq) was calculated as the sum of physical dose components multiplied by the relative biological effectiveness (RBE) and compound biological effectiveness (CBE) of each dose component using the following equation:

$$D_{\text{total}}(\text{Gy-Eq}) = D_{B10}(\text{Gy}) \times \text{CBE}_{\text{BPA}} + D_{\text{proton}}(\text{Gy}) \times \text{RBE}_{\text{proton}} + D_{\gamma\text{-ray}}(\text{Gy}) \times \text{RBE}_{\gamma\text{-ray}}$$

where D is the physical absorbed dose (Gy), $\text{CBE}_{\text{BPA}} = 3.8$ for tumor, $\text{CBE}_{\text{BPA}} = 1.35$ for lung, $\text{RBE}_{\text{proton}} = 2.5$ and $\text{RBE}_{\gamma\text{-ray}} = 1.0$.

To evaluate the D_{B10}, the ^{10}B concentrations in normal and tumor tissues were estimated. The ^{10}B concentrations in normal tissue were assumed to be equal to blood ^{10}B concentrations during irradiation. The ^{10}B concentration in tumors during irradiation was estimated by multiplying the ^{10}B concentration in blood by the ratio of tumor to blood

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concentrations (T/B ratio). The ^{10}B concentrations in blood during irradiation were calculated as the mean of ^{10}B concentrations in the blood sampled just before and after irradiation, since ^{10}B concentrations in blood should decrease after the finish of injection of BPA. The T/B ratio was quantified by analyzing *p*-boronophenylalanine positron emission tomography (^{18}F-BPA PET) images. The procedure used for the 18F-BPA PET study was described in our previous report [7].

The doses reported in the following sections included some uncertainties inevitable in BNCT, ascribed to the following reasons: (1) the blood was not sampled during irradiation to estimate the ^{10}B concentration in the blood; and (2) T/B ratios estimated on the basis of ^{18}F-BPA PET studies performed before BNCT are not guaranteed to be applicable to dose estimation in BNCT, since the schedule for the administration of ^{18}F-BPA in the PET study was different from that in BNCT on the treatment day.

The feasibility of the treatment in both cases was reviewed and approved by the Institutional Review Board, Kyoto University Research Reactor Institute (KURRI) or Japan Atomic Energy Agency (JAEA). The patients gave written informed consent to all the activities performed at the KURRI and JAEA.

Patient 1

A 59-year-old man was presented with a left pleural effusion in March 2002. He had an experience of occupational exposure to asbestos. In January 2005, he was represented with a large left pleural effusion and a subcutaneous tumor at the drainage site of the left chest wall and was admitted to hospital for further study. Biopsy of the subcutaneous tumor revealed malignant pleural mesothelioma (MPM; epithelial type). He had received radiotherapy (RT) (2 Gy × 25) for the chest wall tumor. However, a repeat CT scan showed progressive disease spreading in the left pleural cavity, and he suffered from left chest pain. Since he had received renal dialysis, application of chemotherapy was not planned. He was referred to our center for further treatment of MPM by BNCT. A ^{18}F-BPA PET study performed before BNCT showed good accumulation of BPA in the tumor with a T/B ratio of 3.0.

In the first BNCT, the upper portion of the tumor was treated with anterior and posterior epithermal neutron beams at KUR in November, 2005. A 20-cm circle collimator, which encompassed the upper thoracic portion, was used to collimate both beams. Following the administration of BPA at a dose of 250 mg/kg, 40-min irradiation with each beam was performed. The dose was calculated under the assumption that the ^{10}B concentration in the blood during irradiation was 16 ppm and that in the tumor was 48 ppm, according to the T/B ratio of 3.0. The doses delivered to the tumor volume, which was encompassed in the treatment field, ranged from 10 to 30 Gy-Eq. The maximum dose delivered to the left lung was 6.5 Gy-Eq.

One month after the 1st BNCT, a 2nd BNCT was performed to treat the lower portion of the tumor. In the 2nd BNCT, three-port irradiations with anterior, posterior and left epithermal neutron beams collimated using a 20-cm collimator were carried out following the administration of BPA at a dose of 500 mg/kg. The ^{10}B concentration in the blood was estimated at 29 ppm. The dose delivered to the tumor volume, which was encompassed in the treatment field, ranged from 10 to 60 Gy. The left lung volumes receiving $\geqslant$7 Gy-Eq (V_7) and $\geqslant$10 Gy-Eq (V_{10}) were 29.0% and <1.0%, respectively.

In the post-treatment course, chest pain disappeared the day after BNCT. Follow-up computed tomography (CT) at 1 and 6 months after the 2nd BNCT confirmed partial regression (PR) of the tumor (Fig. 1). No adverse effect was observed during irradiation. As grade 1 acute adverse effects, non-hematotoxic adverse effects, including chill, fatigue, anorexia and diarrhea, and a decrease in platelets (89,000/mm^3), were observed. No acute adverse effect higher than grade 2 was experienced. Consolidation in the left lower lung irradiated with the 2nd BNCT appeared 1 month after the 2nd BNCT and lasted for 6 months. The patient had fever and chest pain, which were evaluated as grade 2 toxicity according to the Radiation Therapy Oncology Group (RTOG) scoring system [8]. Radiographic findings suggested radiation pneumonitis in the region where a dose greater than 4 Gy-Eq was delivered. No steroid therapy was applied to treat the radiation pneumonitis. In the upper portion of the left lung field treated with the 1st BNCT, no sign of radiation pneumonitis was observed. The patient died of local extension of MPM 12 months after the 1st BNCT.

Patient 2

A 43-year-old man was presented with a 7-cm diameter lung tumor in the left lung in August 2003. Since, in 2000, he had received treatment for left seminoma, the lung tumor was suspected to be a metastatic lung tumor from the seminoma. He received surgical resection of the tumor and histological examination revealed a malignant short spindle cell tumor. After the operation, he experienced local recurrences of tumors, which were treated with surgical resection and chemotherapy. In February, 2007, he was referred to our center for further treatment by BNCT for recurrent multiple tumors spreading in the left plural space. A ^{18}F-BPA PET study before BNCT revealed a T/B ratio of 2.0.

The first BNCT was performed at the JRR-4 research reactor in JAEA in June, 2006. Three tumors located in the left lower lung were defined as gross tumor volume (GTV) and treated with BNCT. Since multi-port irradiation is not possible during a single session of BNCT, due to a limitation of the equipment in the irradiation room at JRR4, a single posterior beam collimated by a 15-cm collimator was applied to the patient following the administration of BPA at a dose of 500 mg/kg. The irradiation time was 24 min. The ^{10}B concentration in the tumor during irradiation was estimated to be 33 ppm. The mean and maximum doses of radiation delivered to the tumors ranged from 16.2 to 32.7 Gy-Eq, and from 25.1 to 44.7 Gy-Eq, respectively. The maximum dose delivered to the left lung was 11.4 Gy-Eq. The left lung volumes receiving $\geqslant$7 Gy-Eq (V_7) and $\geqslant$10 Gy-Eq (V_{10}) were 3.4% and <1.0%, respectively.

In August, 2006, three tumors located in the upper portion of the left lung were treated with a 2nd round of BNCT. According to the positions of the tumors, a posterior beam

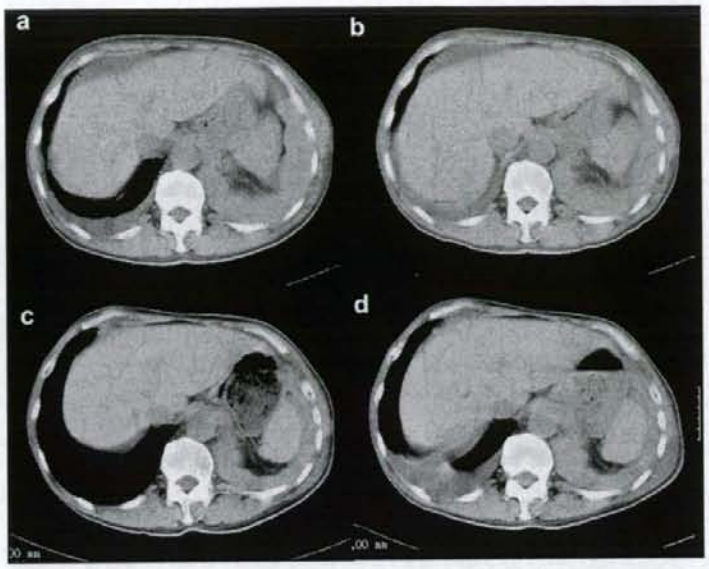

Fig. 1. (a) Pretreatment CT images. (b) Follow-up CT after 1 month showing slight regression of tumors. (c) Follow-up CT after 6 months showing regression of tumors judged as PR. (d) Follow-up CT after 7 months showing enlargement of the tumors abutting the thoracic spine.

collimated with a 15-cm collimator was selected. Twenty minute irradiation was carried out following administration of BPA at a dose of 500 mg/kg. The ^{10}B concentrations in the blood and tumor during irradiation were estimated to be 25.3 and 51 ppm, respectively. The mean and maximum doses in the tumors ranged from 5.8 to 13.3 Gy-Eq, and from 8.2 to 32.7 Gy-Eq, respectively. The maximum dose delivered to the left lung was 5.6 Gy-Eq.

Left back pain, a chief complaint before BNCT, disappeared within a few days of the 1st BNCT. Follow-up CTs at 1 and 3 months after the 1st BNCT revealed regression of the tumors located in the lower portion of the left lung (Fig. 2). The tumors in the upper portion, treated during the 2nd BNCT, remained stable in size at 3 months after the 2nd BNCT. All tumors were enlarged within 7 months of BNCT. One month after the 1st BNCT, Grade 1 radiation dermatitis was detected on the left back skin. No radiation pneumonitis or other late adverse effects were observed during the post-treatment course for 16 months. Although he received proton therapy and chemotherapy for recurrent tumors, he died of extension of the tumors 18 months after the 1st BNCT.

Discussion

In this pilot study, our main concern was the occurrence of lung toxicity. The second BNCT in Patient 1 caused Grade 2 lung toxicity. A focal lung reaction in the lower lung field was observed 1 month after the 2nd BNCT. Since V_{20}, the lung volume irradiated with greater than 20 Gy, has been adapted as the parameter for normal tissue complication probability in many studies using conventional fractionate RT [8,9], V_7 was assessed as the equivalent parameter for evaluating lung toxicity in a single-dose treatment in this

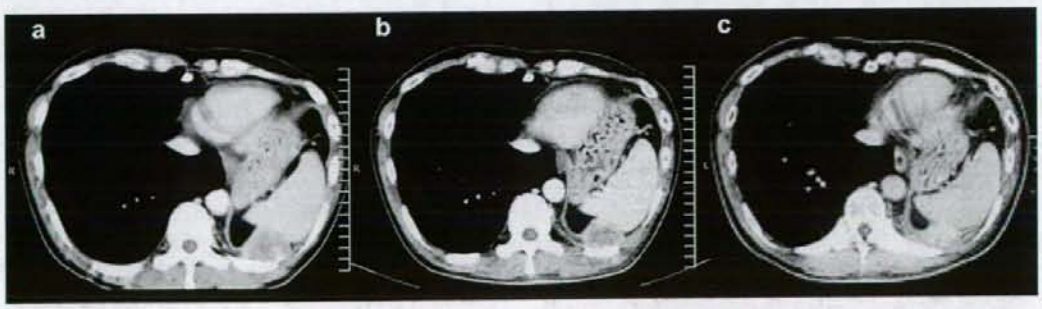

Fig. 2. (a) Pretreatment CT images. (b) Follow-up CT after 1 month showing slight regression of the tumors behind the spleen. (c) Follow-up CT after 3 months showing regression of the tumors judged as PR.

pilot study, assuming an α/β coefficient of 3.0 for normal lung tissues according to the linear–quadratic model. In the 2nd BNCT in Patient 1, the V_7 was 29.0%. In the other three BNCTs, in which radiation pneumonitis was not experienced, the V_7 ranged from 0 to 3.4%. It is impossible to draw any conclusions on the provability of lung toxicity in BNCT from only two cases. Therefore, to reveal the relationship between lung dose delivered by BNCT and the probability of lung toxicity, we are preparing for a phase 1 study treating MPM with BNCT.

The prognosis of MPM has been dismal, and the median survival length is 9–12 months without intervention [10]. Trimodality therapy, surgical resection followed by chemotherapy and radiotherapy, has been applied to MPM patients with curative intent [11,12]. However, unfortunately, the proportion of patients capable of surgery is assessed as fewer than 25% due to medical illness or advanced stage of MPM [10]. Recently, a new chemotherapeutic regimen for MPM, pemetrexed plus cisplatin, provided a 41.3% response rate [13]. However, patients are required to receive chemotherapy every 21 days until the tumor shows regrowth. Although it is not certain that BNCT surpasses the response rate of the new chemotherapy regimen, BNCT has the possibility to be a very effective treatment modality to palliate the symptoms of MPM patients, as suggested in the present cases. In the two cases in this pilot study, palliation of the symptoms, chest or back pain, disappeared within a few days of BNCT. According to the report by de Graaf-Strukowska et al. [14], RT provides local palliation in at least 50% of patients with MPM who were treated using a 4-Gy/fraction scheme to a median dose of 36 Gy. BNCT can deliver an adequate dose for palliation in single or two-fractionated BNCT on 1 or 2 days as demonstrated in the present cases, which seems more beneficial for patients suffering from various symptoms compared with chemotherapy or conventional radiotherapy. Since no severe adverse effects were observed in the two cases, dose escalation may be possible for controlling the tumor. Further clinical study of BNCT is warranted to shed new light on the best way to treat inoperable diffuse pleural tumors such as MPM or pleuritis carcinomatosis.

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Comparison of Postoperative Morphological Changes in Remnant Pancreas Between Pancreaticojejunostomy and Pancreaticogastrostomy After Pancreaticoduodenectomy

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Objectives: The aim of this study was to compare postoperative morphological changes in remnant pancreas between pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG) after pancreaticoduodenectomy (PD).

Methods: The study subjects were 28 patients with PJ and 14 with PG. The diameter of the main pancreatic duct (MPD) and pancreatic parenchymal thickness 2 years after PD were measured on computed tomography scans and compared between the 2 groups.

Results: The preoperative and postoperative MPD diameter was 5.2 mm (SD, 2.4 mm) and 4.2 mm (SD, 2.0 mm) in the PJ group ($P = 0.0422$) and 4.8 mm (SD, 3.2 mm) and 5.7 mm (SD, 1.8 mm) ($P = 0.1494$) in the PG group, respectively. In those patients with preoperatively normal-size MPD, MPD after surgery tended to become dilated relative to before surgery in the PJ group ($P = 0.0931$), and the MPD measured postoperatively was significantly larger than preoperatively in the PG group ($P = 0.0009$). A significant atrophy of the pancreatic parenchyma was noted postoperatively in both groups ($P < 0.0001$), but these changes were more severe in the PG group than the PJ group ($P = 0.0018$).

Conclusions: Considering the above postoperative morphological changes, PJ seems to be preferable to PG after pancreaticoduodenectomy.

Key Words: pancreaticoduodenectomy, pancreaticogastrostomy, pancreaticojejunostomy, morphology, atrophy, duct dilatation

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Pancreaticoduodenectomy (PD) is the standard procedure for neoplasms of periampullary lesions.[1] In this procedure, the cut end of the pancreas is usually anastomosed to either the jejunum (pancreaticojejunostomy [PJ]) or the stomach (pancreaticogastrostomy [PG]). Many previous authors have long compared these 2 types of anastomoses with regard to the incidence of pancreatic leakage, which is the leading cause of complication after PD in the early postoperative period.[2–5] With regard to the incidence of pancreatic leakage, some prospective randomized trials reported that there was no difference between PJ and PG.[6–8]

In addition to the incidence of pancreatic leakage, the exocrine and endocrine functions of the remnant pancreas have been compared. There is no significant difference between PJ and PG in terms of pancreatic endocrine function, whereas PG is associated with more severe or equal pancreatic exocrine insufficiency than PJ.[9–12] In these previous comparative studies, fasting blood glucose level, glycohemoglobin A_{1c}, oral glucose tolerance testing, and the status of diabetes mellitus were used for evaluation of pancreatic endocrine function, and the presence of steatorrhea, fecal elastase-1 test, and nutritional status were used for the evaluation of pancreatic exocrine function. When comparing the functions of the remnant pancreas, morphological evaluation of the remnant pancreas is necessary, in addition to the above parameters, because such function depends on the volume of pancreatic parenchymal tissue. However, there is limited information on the morphology of the remnant pancreas after PD.[13,14] In this study, we evaluated postoperative morphological changes in the remnant pancreas between PJ and PG after PD.

MATERIALS AND METHODS

Between 1999 and 2007, 156 patients who had benign and malignant neoplasms of periampullary lesions underwent PD without hepatic resection in the Department of Surgery, Osaka University Hospital. Among the 156 patients, 17 patients underwent PD including distal gastrectomy, 96 patients underwent subtotal stomach-preserving PD, and the remaining 43 patients underwent pylorus-preserving PD. To exclude the influence of differences in surgical procedures, only patients who underwent subtotal stomach-preserving PD and reconstruction by invagination method were included in this study.

The reconstruction procedure of PJ and PG was chosen based on surgeons' preference. In the PJ group, the pancreatic stump was anastomosed and invaginated end-to-end into the jejunum with interrupted 2-layer sutures: 4–0 absorbable monofilament for outer layer between the remnant pancreatic capsule and jejunal seromuscular layer and for inner layer between the cut edge of the pancreas and the full thickness of the jejunum. In the PG group, a gastrostomy of 2 to 3 cm in length was made in the posterior wall of the stomach, and the pancreatic stump was anastomosed and invaginated with the same interrupted 2-layer method as PJ. In both groups, a stenting tube was placed in the main pancreatic duct (MPD) and exteriorized through the abdominal wall via the wall of the jejunum or stomach. The tube was removed within 1 postoperative month.

In this study, the morphology of the remnant pancreas was evaluated 2 years after the surgery. Patients with intraductal papillary mucinous neoplasm of pancreas were excluded in this study because their preoperative MPD may be dilated for the disease itself. Thus, only patients who had survived 2 years or more without cancer recurrence were included in this study: 28 PJ patients (PJ group) and 14 patients (PG group).

The morphology of the remnant pancreas was examined using computed tomography.

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TABLE 1. Comparison of Clinical Background Between the PJ and PG Groups

	PJ	PG	*P*
No. patients	28	14	
Age, mean (SD), yrs	64 [8]	62 [9]	0.3379
Sex (male/female)	13/15	5/9	0.5083
Origin of tumor			
Pancreas	23	11	
Bile duct	3	1	0.5439
Papilla Vater	2	1	
Duodenum	0	1	
Fibrosis (−/+)	9/19	5/9	>0.9999

The MPD diameter was measured manually in the region where the maximum MPD diameter was identified. The MPD was considered dilated if the diameter exceeded 3 mm.[11,13–15] The pancreatic parenchymal thickness was defined as the anterior-posterior width of the entire gland minus MPD diameter and was measured manually in the region of the pancreas where the maximum MPD diameter was identified. The following equations were used for our calculations:

Rate of reduction of MPD diameter = (preoperative MPD diameter − postoperative MPD diameter) / preoperative MPD diameter

Rate of reduction of pancreatic parenchymal thickness = (preoperative pancreatic parenchymal thickness − postoperative pancreatic parenchymal thickness) / preoperative pancreatic parenchymal thickness

Postoperatively, the degree of fibrosis in pancreatic parenchyma was microscopically examined by a pathologist who had no information on the clinical course of any patient. Then, patients included in this study were divided into 2 groups: fibrosis and no fibrosis.

Abdominal computed tomography scans were performed for postoperative follow-up at regular intervals of 3 to 6 months in patients with malignancy and 12 to 24 months in those with benign tumor.

Data were expressed as mean (SD). Differences between groups were examined for statistical significance using the χ^2, Fisher exact test, Mann-Whitney *U* test, or Wilcoxon signed rank test. $P < 0.05$ denoted the presence of a statistically significant difference. Statistical analyses were performed using StatView (version 5.0; SAS Institute Inc, Cary, NC). This study protocol was approved by the human ethics review committee of Osaka University Hospital, and a signed consent form was obtained from each patient.

RESULTS

Table 1 summarizes the clinical profile of patients of the PJ and PG groups. Patients of the 2 groups were similar with regard to age, sex, and origin of tumor. Most tumors in our cohort were malignant (PJ group: 28/28 [100%], PG group: 13/14 [93%]). The incidence of short-time postoperative complications including pancreatic leakage did not differ between the 2 groups. Fibrosis in pancreatic parenchymal was found in 19 cases (68%) in the PJ group and 9 cases (64%) in the PG group ($P > 0.9999$). Figure 1 shows the preoperative and postoperative values of MPD diameter, and Figure 2 depicts the respective values of pancreatic parenchymal thickness. Table 2 compares the morphological changes between the PJ and PG groups.

In more than half of the patients, the MPD was dilated before surgery (PJ group: 20/28 [71%], PG group: 9/14 [64%]). Among 8 patients of the PJ group who showed no preoperative MPD dilatation, 2 (25%) developed MPD dilatation after surgery. On the other hand, among 5 patients free of preoperative MPD dilatation in the PG group, all patients (100%) showed MPD dilatation after surgery.

The preoperative MPD diameter of the PJ group (5.2 mm [SD, 2.4 mm]) was not significantly different from that of the PG group (4.8 mm [SD, 3.2 mm], $P = 0.7079$). On the other hand, the postoperative MPD diameter of the PJ group (4.2 mm [SD, 2.2 mm]) was significantly smaller than that of the PG

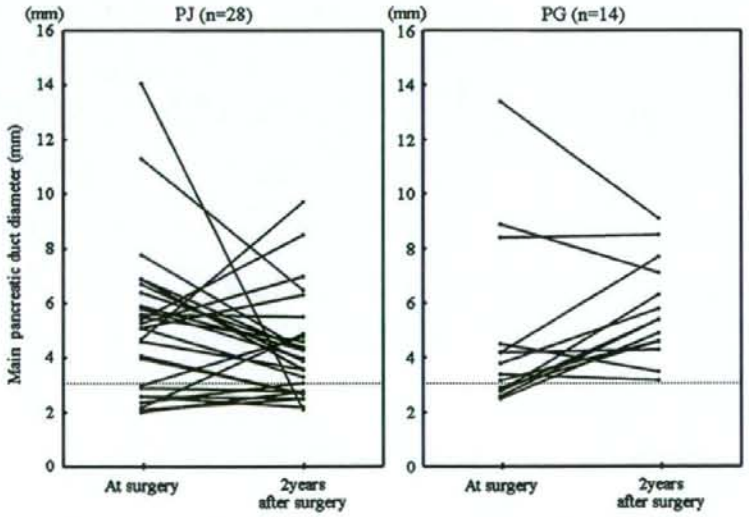

FIGURE 1. Individual data of diameter of the MPD at the time of surgery and 2 years after the surgery.

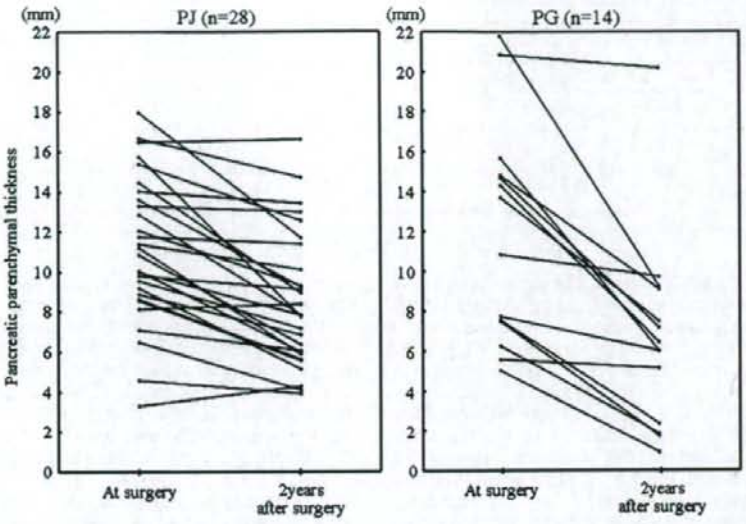

FIGURE 2. Individual data of pancreatic parenchymal thickness at the time of surgery and 2 years after the surgery.

group (5.7 mm [SD, 1.8 mm], $P = 0.0149$). In the PJ group, the MPD diameter after surgery was significantly smaller than that before surgery ($P = 0.0422$). On the other hand, the change in MPD diameter after surgery was not significant in the PG group ($P = 0.1494$). Finally, the rate of reduction of MPD diameter was significantly larger in the PJ (5.1% [SD, 48.3%]) than in the PG groups (−41.6% [SD, 53.9%], $P = 0.0070$).

The preoperative pancreatic parenchymal thickness was similar in the 2 groups (PJ: 11.1 mm [SD, 3.7 mm], PG: 11.8 mm [SD, 5.5 mm], $P = 0.58489$), and decreased significantly in both groups after surgery (PJ: $P < 0.0001$, PG: $P < 0.0001$), although the mean values were not different between the 2 groups (PJ: 8.4 mm [SD, 3.4 mm], PG: 6.7 mm [SD, 4.8 mm], $P = 0.1770$). However, the rate of reduction of pancreatic parenchymal thickness was significantly larger in the PG group (46.0% [SD, 25.9%]) than in the PJ group (22.4% [SD, 19.1%], $P = 0.0018$).

Next, we compared the MPD diameter in those patients of the PJ and PG groups who had a normal-size MPD preoperatively (PJ: n = 8, PG: n = 5) (Table 3). In these patients, the preoperative MPD diameter was similar (PJ: 2.5 mm [SD, 0.4], PG: 2.7 mm [SD, 0.2 mm], $P = 0.3421$). Postoperatively, the MPD diameter increased in the PJ group (3.1 mm [SD, 1.1 mm]), although insignificantly ($P = 0.0931$), whereas it became significantly larger in the PG group (5.3 mm [SD, 0.6 mm], $P = 0.0009$). In addition, the postoperative MPD diameter in the PJ group was significantly smaller than that in the PG group ($P = 0.0015$). The rate of reduction of MPD diameter was significantly larger in the PJ (−27.7% mm [SD, 45.0%]) than in the PG groups (−96.0% mm [SD, 24.4%], $P = 0.0070$).

Only in patients who had survived 3 years or more without cancer recurrence, the postoperative temporal changes in MPD diameter and pancreatic parenchymal thickness were compared (PJ: n = 8, PG: n = 7) (Fig. 3). In both groups, the postoperative changes of MPD diameter and pancreatic parenchymal thickness started just after the surgery and almost finished by 1 year after the operation.

DISCUSSION

The results of the present study showed that the postoperative MPD diameter was significantly smaller than the preoperative MPD only in the PJ group. However, because MPD was dilated preoperatively in more than half of patients enrolled in this study, we also examined the change in MPD diameter in those patients without preoperative MPD dilatation. Such

TABLE 2. Comparison of Morphological Changes Between the PJ and PG Groups

	PJ (n = 28)		PG (n = 14)		
	Mean (SD)	*P*	Mean (SD)	*P*	*P*
Diameter of the MPD, mean (SD)					
Before surgery, mm	5.2 [2.4]	0.0422	4.8 [3.2]	0.1494	0.7097
After surgery, mm	4.2 [2.0]		5.7 [1.8]		0.0149
Reduction rate, %	5.1 [48.3]		−41.6 [53.9]		0.0070
Parenchymal thickness, mean (SD)					
Before surgery, mm	11.1 [3.7]	<0.0001	11.8 [5.5]	<0.0001	0.5849
After surgery, mm	8.4 [3.4]		6.7 [4.8]		0.1770
Reduction rate, %	22.4 [19.1]		46.0 [25.9]		0.0018

TABLE 3. Comparison of Morphological Changes Between the PJ and PG Groups in a Subgroup With Nondilated MPD Preoperatively

	PJ (n = 8)		PG (n = 5)		
	Mean (SD)	*P*	Mean (SD)	*P*	*P*
Diameter of the MPD					
Before surgery, mm	2.5 [0.4]	0.0931	2.7 [0.2]	0.0009	0.3421
After surgery, mm	3.1 [1.1]		5.3 [0.6]		0.0015
Reduction rate, %	−27.7 [45.0]		−96.0 [24.4]		0.0106

analysis found that the MPD diameter after surgery tended to be larger than before surgery in the PJ group, and significantly larger in the PG group. To date, few studies have measured MPD diameter after PD, and their results suggested no significant difference in the rate of change of MPD diameter between the PJ and PG groups.[9,12] On the other hand, Sato et al[13] reported that among 19 patients with PJ, 8 (42%) demonstrated a decline in MPD diameter, 9 (47%) showed no change, and 2 (11%) developed MPD dilatation. Furthermore, Lemaire et al[14] reported that postoperative MPD was significantly dilated in patients with PG. The results of these previous studies are not necessarily compatible. The different results were probably due to patient selection, that is, the enrollment of patients with preoperative MPD dilatation. In fact, the proportion of patients with dilated MPD preoperatively has not been reported, and the change in MPD diameter has been examined only in patients with nondilated MPD preoperatively.[12–15] Thus, had the patients with preoperative MPD dilatation been excluded in the above studies, the results of the present study could have been similar.

The present study also showed that significant atrophy of the pancreatic parenchyma occurred after surgery in both groups. Few studies have examined this issue previously, although there has been no comparative study of pancreatic parenchymal atrophy between PJ and PG. Sato et al[13] reported that parenchymal atrophy of the remnant pancreas occurred in 9 (56%) of 16 patients with PJ. Lemaire et al[14] reported that pancreatic atrophy assessed by subtracting the MPD diameter from the total parenchymal thickness tended to develop in patients with PG, although the study was not comparative. Our results are consistent with those of the above studies. In addition, our study showed that the parenchymal atrophic changes in the PG group were significantly more severe than those in the PJ group.

The current study also revealed the temporal change in MPD diameter and pancreatic parenchymal thickness. To date, there have also been no studies of this issue.

The postoperative MPD dilatation and parenchymal atrophy are thought to result from obstruction or stenosis of the anastomosis.[13,14] However, to date, there have been few reports on pancreatic duct patency after PG. For example, Telford et al[16] showed that total obstruction of the pancreatic duct after PG occurred in 90% of animals in which the duct had been implanted into the stomach. On the other hand, Amano et al[17] reported that in 1 patient among 5 with PG who were followed up postoperatively for more than 9 years, the anastomotic site was not detected by gastroscopy because of overhealing by

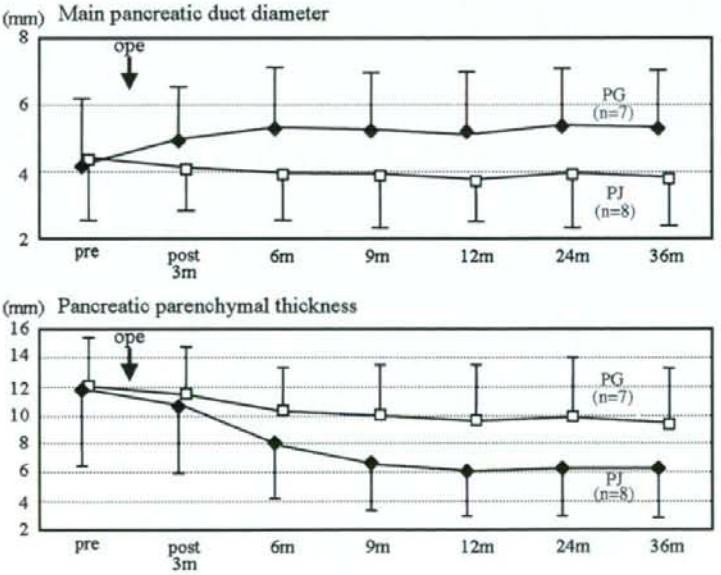

FIGURE 3. The temporal change in the diameter of the MPD and pancreatic parenchymal thickness during 3 postoperative years.

gastric mucosa. Unfortunately, the anastomotic patency was not examined in our study. However, taking into consideration that the anastomosis was performed by the invagination method in all patients, the patency may depend on different environment of the anastomosed remnant pancreas in both groups. The postoperative MPD dilatation and parenchymal atrophy, which was predominant in the PG group relative to the PJ group, could be due to the reflux of gastric juice or ingested food into the remnant pancreatic duct or coverage of the anastomotic orifice by gastric mucosa, which might induce chronic inflammation, stenosis, or obstruction of the anastomotic site.

Postoperative pancreatic function was not examined in this study. Previous studies indicated no significant differences in early postoperative complications and pancreatic endocrine function between PJ and PG, although patients who underwent PG showed more severe or equal pancreatic exocrine insufficiency than that of those who underwent PJ.[3–12] The difference in exocrine function may be natural, considering the postoperative morphological changes in this study.

In summary, only in PJ patients with preoperatively normal-size MPD the MPD after surgery tended to become dilated after surgery, whereas the MPD was significantly larger after surgery than before surgery in the PG group. Furthermore, significant atrophic changes were noted postoperatively in the pancreatic parenchyma in both groups, and these changes were significantly more severe in the PG group than the PJ group. Considering these postoperative morphological changes in the remnant pancreas, PJ may be preferable to PG after PD.

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Original article

Impact of accelerator-based boron neutron capture therapy (AB-BNCT) on the treatment of multiple liver tumors and malignant pleural mesothelioma

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ABSTRACT

Background and purpose: To confirm the feasibility of accelerator-based BNCT (AB-BNCT) for treatment of multiple liver tumors and malignant pleural mesothelioma (MPM), we compared dose distribution and irradiation time between AB-BNCT and reactor-based BNCT (RB-BNCT).
Material and methods: We constructed treatment plans for AB-BNCT and RB-BNCT of four multiple liver tumors and six MPM. The neutron beam data on RB-BNCT were those from the research reactor at Kyoto University Research Reactor Institute (KURRI). The irradiation time and dose–volume histogram data were assessed for each BNCT system.
Results: In BNCT for multiple liver tumors, when the 5 Gy-Eq dose as the mean dose was delivered to the healthy liver tissues, the mean dose delivered to the liver tumors by AB-BNCT and RB-BNCT was 68.1 and 65.1 Gy-Eq, respectively. In BNCT for MPM, when the mean lung dose to the normal ipsilateral lung was 5 Gy-Eq, the mean dose delivered to the MPM tumor by AB-BNCT and RB-BNCT was 20.2 and 19.9 Gy-Eq, respectively. Dose distribution analysis revealed that AB-BNCT is superior to RB-BNCT for treatment of deep-seated tumors.
Conclusions: The feasibility of the AB-BNCT system under construction at our institute was confirmed from a clinical viewpoint in BNCT for multiple liver tumors and MPM.

Boron neutron capture therapy (BNCT) is based on a nuclear reaction: non-radioactive isotope ^{10}B atoms that have absorbed low energy (<0.5 eV) neutrons disintegrate into alpha (^{4}He) particles and recoiled lithium nuclei (^{7}Li). These particles deposit large energy along their very short paths (<10 μm), whose lengths are equal to or shorter than a typical cell size [1,2]. Malignant cells with ^{10}B are thus destroyed following thermal neutron irradiation by these high linear energy (LET) particles. If a sufficient number of ^{10}B atoms accumulate in the tumor cells and the gradient of the ^{10}B concentrations between the tumor and the surrounding normal tissues is large, then boron neutron capture irradiation will be selectively delivered to the tumor.

Selective high LET particle irradiation to cancer cells is a unique property of BNCT, which is an advantage over other radiotherapy modalities. For the use of this unique property, we have continued preclinical studies on application of BNCT to tumors located in radiosensitive organs, such as liver and lung [3,4]. In our previous studies, the feasibility of BNCT for treating multiple liver tumors and inoperable malignant pleural mesothelioma (MPM) was confirmed from the viewpoint of dose distribution [5,6]. Based on these preclinical studies, we have carried out clinical BNCT for multiple liver tumors and MPM since 2005 at Kyoto University Research Reactor Institute (KURRI). One patient with asbestos-induced MPM and three cases of multiple liver tumors have already been treated with BNCT [7,8].

To deal with the increasing number of candidates for BNCT, development of an accelerator-based BNCT (AB-BNCT) system is a prerequisite. Construction of an AB-BNCT system at KURRI was started in June 2008 and was finished in December 2008. To prepare the protocol for clinical studies using the AB-BNCT system, comparison of the parameters for dose distribution and irradiation time between Kyoto University reactor (KUR)-based BNCT (RB-BNCT) and the AB-BNCT is needed. The aim of the present study was to investigate the advantages of AB-BNCT over RB-BNCT for multiple liver tumors and MPM.

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